Effectiveness of tumor necrosis factor inhibitors in patients with psoriatic arthritis and axial spondyloarthritis – treatment response, drug retention and predictors thereof

Results from the nationwide DANBIO registry

Copenhagen Center for Arthritis Research (COPECARE)
Center for Rheumatology and Spine Diseases
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Doctoral thesis

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2018

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Center for Rheumatology and Spine Diseases
Centre of Head and Orthopedics
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The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation, which consists of the already published dissertations listed below, for public defence for the doctoral degree in Medicine.

Copenhagen, 17 October 2018.

Ulla Wewer, Head of Faculty

The defence will take place at Rigshospitalet, Glostrup, Auditorium C, 23 November 2018
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Preface

The writing of this doctoral thesis is the result of several years of hard work and research. Dedicated stubbornness and a wish to prove that it is possible are obligatory elements. But first and foremost, the thesis is the result of a fruitful and positive collaboration with colleagues and experienced researchers.

There is no doubt that this doctoral thesis would not have happened if it was not for professor Merete Lund Hetland and professor Mikkel Østergaard. We first met when I was in the beginning of my rheumatology specialist training in 2008. I was totally inexperienced within the field of rheumatology, but they guided me patiently and introduced me to the epidemiological research methodology, outcome measures and of course the DANBIO registry. They trusted me to analyze the first DANBIO data on patients with ankylosing spondylitis – until then the registry had mainly published within rheumatoid arthritis.

Since then Merete has continuously been my guide and mentor, she has willingly shared her time, her experience, ideas and network, and she has encouraged and inspired me to do research for more than a decade. She was the main initiator behind the Danish Rheumatologic Biobank and she facilitated my employment as a national clinical project leader. This gave me the opportunity to do research during the daytime in parallel with the implementation of the biobank and my employment as a senior consultant at department of rheumatology at Gentofte University Hospital.

Thanks to Head of Department, Henrik Røgind and Senior Nurse, Tine Lundbak, Center for Rheumatology and Spine Diseases for their support and willingness to provide time for my research. Without their flexibility it would not have been possible to combine research with my employment at Gentofte.

Furthermore, I would like to thank senior consultant Annette Hansen who I first met at Herlev Hospital in 2008 where she taught me how to treat and diagnose within the field of rheumatology. She encouraged me to apply for the job as senior consultant at department of rheumatology at Gentofte when I reached the last year of my specialist training. Since then she has patiently accepted my requests to get more time for research and less time to see patients in the clinic. It has not been easy to get a functioning work schedule with me as an employee, but she has always been supportive.

Thanks to senior consultant Lene Dreyer, who has excellent knowledge within epidemiological research and who has been my colleague for several years. She has always been there for advice and scientific discussions. And thank you to all my other good friends and colleagues at the departments of rheumatology at Gentofte and Glostrup (none mentioned none forgotten). It is a major privilege to have continuous clinical work and research anchored at two such inspiring departments. Thank you to all the co-authors from the local departments of rheumatology who willingly have agreed to validate their data in DANBIO. More and more departments have been interested to participate in the research
process during the later years, and I take this as a sign that you find the research projects (nearly) as
interesting as I do. Thank you to all the other collaborators, professor Björn Guðbjörnsson from Iceland,

There would be no DANBIO and there would be no thesis if it was not for Niels Steen Krogh, Zitelab. I have not fully understood his time-optimistic approach to deadlines and data delivery dates. But Niels never rejects an idea or says that something is impossible – and we have always somehow succeeded to comply with the deadlines in the end.

My deepest appreciation for my mother, Sonja – who brought two ambitious twin daughters into this world so many years ago, and my father, Meiner who although he died before I finished medical school would have been ever so proud if he could have experienced this.

The best and most important of all is saved for last: My ever-understanding husband Henrik who has encouraged and accepted that I spend time in front of the computer during yet another evening and who has supported me repeatedly during the writing of this thesis. Without you this would not have been possible. And to the two sweet blondes, Mille and Kalle – you are more important than any registry and any research in the world.

Bente Glintborg
Winter 2017

Post scriptum, Fall 2018
I would like to thank the assessment committee, Professor Axel Finckh, University of Geneva, Switzerland, Professor Oliver Fitzgerald, University College Dublin, Ireland and Professor Søren Jacobsen, University of Copenhagen, Denmark.
**Abbreviations**

ACR: American College of Rheumatology  
ADA: Anti-drug antibodies  
AE: Adverse Event  
Anti-CCP: anti-cyclic citrullinated peptide  
AS: Ankylosing Spondylitis  
ASAS: Assessment of SpondyloArthritis  
ASDAS: Ankylosing Spondylitis Disease Activity Score  
AxSpA: Axial Spondyloarthritis  
BAS: Bath Ankylosing Spondylitis  
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index  
BASFI: Bath Ankylosing Spondylitis Function Index  
BASMI: Bath Ankylosing Spondylitis Metrology Index  
bDMARDs: biologic Disease Modifying Antirheumatic Drugs  
BMI: Body Mass Index  
CRP: C-reactive protein  
csDMARD: conventional synthetic Disease Modifying Antirheumatic Drugs  
DAPSI: Disease activity in Psoriatic Arthritis  
DAS28: Disease Activity Score (28 joints)  
EULAR: European League of Rheumatology  
HAQ: Health Assessment Questionnaire  
HLA-B27: Human Leukocyte Antigen – B27  
HR: Hazard Ratio  
IBD: Inflammatory Bowel Disease  
IgM-RF: Immunoglobin M-Rheumatoid Factor  
IL: Interleukin  
IQR: Inter-Quartile Ranges  
LOE: Lack Of Effect  
MDA: Minimal Disease Activity  
MOA: Mode Of Action  
MRI: Magnetic Resonance Imaging  
MTX: Methotrexate  
NNT: Numbers Needed to Treat
Nr-axSpA: Non radiographic axial Spondyloarthritis
NSAIDs: Non Steroid Anti-Inflammatory Drugs
PsA: Psoriatic Arthritis
PsO: Psoriasis
RADS: Rådet for Anvendelsen af Dyr Sygehusmedicin
RCT: Randomized Controlled Trial
SI-joints: Sacroiliac joints
SpA: Spondyloarthritis
TNF: Tumor Necrosis Factor
TNFi: Tumor Necrosis Factor Inhibitor
US: Ultrasound
VAS: Visual Analogue Scale
Publications

The present doctoral thesis is based on the following 9 publications which in the following are cited as Paper 1, Paper 2 etc. The papers are available as appendices.

**Paper 1**
Bente Glintborg, Mikkel Østergaard, Lene Dreyer, Niels Steen Krogh, Ulrik Tarp, Michael Sejer Hansen, Signe Rifbjerg-Madsen, Tove Lorenzen, Merete Lund Hetland

*Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry.*
Arthritis & Rheumatology 2011 Feb;63(2):382-90

**Paper 2**
Bente Glintborg, Mikkel Østergaard, Niels Steen Krogh, Martin Dehn Andersen, Ulrik Tarp, Anne Gitte Loft, Hanne M. Lindegaard, Mette Holland-Fischer, Henrik Nordin, Dorte Vendelbo Jensen, Christian Holkmann Olsen, Merete Lund Hetland

*Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry*
Arthritis & Rheumatology 2013 May;65(5):1213-23

**Paper 3**
Bente Glintborg, Bjorn Gudbjörnsson, Niels Steen Krogh, Emina Omerovic, Natalia Manilo, Mette Holland-Fischer, Hanne M. Lindegaard, Anne Gitte Loft, Henrik Nordin, Laura Johnsen, Sussi Flejsborg Oeftiger, Annette Hansen, Claus Rasmussen, Gerdur Grondal, Arni Jon Geirsson, Merete Lund Hetland

*Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: results from the nationwide registries DANBIO and ICEBIO*

**Paper 4**
Pil Højgaard/Bente Glintborg, Merete Lund Hetland, Torben Højland Hansen, Philip Rask Lage-Hansen, Martin H. Petersen, Mette Holland-Fischer, Christine Nilsson, Anne Gitte Loft, Bjarne Nesgaard Andersen, Thomas Adelsten, Jørgen Jensen, Emina Omerovic, Regitse Christensen, Ulrik Tarp, René Østgård, Lene Dreyer

*Association between tobacco smoking and response to tumour necrosis factor α inhibitor treatment in psoriatic arthritis: results from the DANBIO registry*
Annals of the Rheumatic Diseases 2015 Dec;74(12):2130-6

Paper 5
Bente Glintborg, Mikkel Østergaard, Niels Steen Krogh, Lene Dreyer, Hanne Lene Kristensen, Merete Lund Hetland
Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years’ surveillance in the Danish nationwide DANBIO registry

Paper 6
Bente Glintborg, Mikkel Østergaard, Niels Steen Krogh, Ulrik Tarp, Natalia Manilo, Anne Gitte Loft, Annette Hansen, Annette Schlemmer, Victoria Fana, Hanne M. Lindegaard, Henrik Nordin, Claus Rasmussen, Leif Ejstrup, Dorte Vendelbo Jensen, Peter Mosborg Petersen, Merete Lund Hetland
Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry

Paper 7
Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry
Rheumatology (Oxford) 2016 Apr;55(4):659-68

Paper 8
Bente Glintborg, Inge Juul Sørensen, Mikkel Østergaard, Lene Dreyer, Abdiweli Awil Mahamoud, Niels Steen Krogh, Oliver Hendricks, Lis Smedegaard Andersen, Johnny Lillelund Raun, Marcin R. Kowalski, Laura Danielsen, Randi Pelck, Henrik Nordin, Jens Kristian Pedersen, Dorte Gunver Adersen Kraus, Susan Ringskær Christensen, Inge Marie Jensen Hansen, Jakob Esbesen, Annette Schlemmer, Anne Gitte Loft, Nabil al Chaer, Lone Salomonsen, Merete Lund Hetland

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Ankylosing Spondylitis versus Nonradiographic Axial Spondyloarthritis: Comparison of Tumor Necrosis Factor Inhibitor Effectiveness and Effect of HLA-B27 Status. An Observational Cohort Study from the Nationwide DANBIO Registry
J Rheumatol 2017 Jan;44(1):59-69

Paper 9
Bente Glintborg, Inge Juul Sørensen, Anne Gitte Loft, Hanne Lindegaard, Asta Linauskas, Oliver Hendricks, Inger Marie Jensen Hansen, Dorte Vendelbo Jensen, Natalia Manilo, Jakob Espesen, Mette Klarlund, Jolanta Grydehøj, Sabine Sparre Dieperink, Salome Kristensen, Jimmi Sloth Olsen, Henrik Nordin, Stavros Chrysidis, Dorte Dalsgaard Pedersen, Michael Veedfald Sørensen, Lis Smedegaard Andersen, Kathrine Lederballe Grøn, Niels Steen Krogh, Lars Pedersen, Merete Lund Hetland
A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis - one year clinical outcomes from the DANBIO registry
Annals of the Rheumatic Diseases, 2017;76(8):1426-143
1. Introduction

The disease spectrum of spondyloarthritis (SpA) includes heterogeneous diseases such as psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) and ankylosing spondylitis (AS). During the last 1-2 decades, treatment with tumor necrosis factor inhibitors (TNFi) has substantially improved patient outcomes in these diseases. The frequency of SpA in Europe is estimated to be 1.2% \(^{10,11}\) and the diseases within the spectrum are associated with chronic pain, poorer quality of life and decreased work productivity.\(^{12,13}\)

When a drug is marketed, treatment effects and safety have been studied in randomized clinical trials (RCTs). The strict inclusion and exclusion criteria and the focus on short term outcomes applied in RCTs is different from the routine care situation where heterogeneous patient groups are treated for long periods of time and the monitoring is less tight. This gap between the RCT and routine care is increasingly acknowledged and emphasizes the need for studies of treatment effectiveness: how does the drug perform when applied in daily routine care? Thus, real world evidence through post-marketing monitoring of safety and long-term outcomes in nationwide registries with prospective follow-up in routine care is increasingly acknowledged as a valuable supplement to RCTs.\(^{14-17}\)

In clinical settings, TNFi treatment failure due to insufficient treatment response or adverse events is frequent and occurs in up to 30-40% of patients.\(^{18-20}\) Valid tools to predict outcomes and pin-point the patients most likely to benefit from treatment are still very limited and personalized treatment strategies addressing specific patient characteristics are practically non-existing. Treatment strategies follow a schematic algorithm where all patients are approached similarly and treated according to disease severity.\(^{21,22}\) Whenever one treatment fails, the clinician has very limited options to predict whether the next treatment will be successful, and treatments are administered according to a trial-and-error rationale.

The introduction of the expensive biological treatments has facilitated the need for clinical registries that could be used for monitoring of treatment outcomes within the rheumatologic diseases. In addition to being a tool on the individual patient level, these registries may also provide research data regarding e.g. treatment effectiveness and long term safety. Lately, marketing of the biosimiar biological drugs has highlighted the need for post-marketing observational research.\(^{23}\) In Denmark, patients with inflammatory arthritis are followed prospectively in the DANBIO registry, which enables research on real-life effectiveness, switching and predictors of response.
2. Aims

2.1. Overall aim

The aim of the present thesis was to investigate long-term TNFi treatment effectiveness in patients with axSpA and PsA based on data from the nationwide DANBIO registry, and to identify clinical characteristics and other factors associated with outcomes. Paper 9 also included patients with RA, but it is beyond the scope of this thesis to describe this patient subgroup in further details.

The overall aim involved the following specific aims (with corresponding paper in parentheses):

2.2. Specific aims

To investigate treatment response and drug retention rate in patients with PsA who:

1. Initiated first TNFi treatment course (Paper 1)
2. Switched from the first to a subsequent bDMARD (Paper 2)

In patients with PsA initiating their first TNFi treatment course to investigate the impact of

3. Infliximab dose regimens (Paper 3)
4. Tobacco smoking (Paper 4)

To investigate treatment response and retention in patients with AS who:

5. Initiated first TNFi treatment course (Paper 5)
6. Switched from the first to a subsequent bDMARD (Paper 6)

In patients with AS initiating their first TNFi treatment course

7. To investigate the impact of tobacco smoking (Paper 7)

In patients with axSpA initiating their first TNFi treatment course in routine care to investigate:

8. The impact of axSpA sub-diagnosis (AS versus non-radiographic axial SpA (nr-axSpA)) on treatment response and treatment retention (Paper 8)

In patients with inflammatory arthritis who switched from originator to biosimilar infliximab (CT-P13) to investigate

9. The impact of the switch on disease activity and one-year treatment retention (Paper 9)
3. Background

3.1. Spondyloarthritis

The disease spectrum of spondyloarthritis (SpA) consists of a group of diseases with common clinical and genetic characteristics. The main disease entities are PsA, AS, reactive arthritis and arthritis related to inflammatory bowel disease. Since the concept of related seronegative spondyloarthritides was initially suggested several decades ago, the nomenclature of these diseases has evolved. Depending on the clinical disease presentation, SpA can be sub-divided into axial SpA (axSpA) and peripheral SpA (Figure 1). Clinical features include inflammatory back pain and sacroiliitis, peripheral arthritis, enthesitis, dactyliitis, anterior uveitis, psoriasis, inflammatory bowel disease and presence of the HLA-B27 antigen.

In the following, focus will be on the disease entities PsA and axSpA (including AS).

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**Figure 1**

The disease spectrum of SpA, adapted from reference 27
Schematic diagram showing the main diagnoses within the SpA spectrum
3.1.1. PsA, disease manifestations and classification criteria
PsA is a heterogeneous disease with various disease manifestations such as involvement of skin, peripheral joints, entheses, nails and axial joints. Various classification criteria have been suggested of which the criteria by Moll and Wright (1973) and the CASPAR classification criteria (2006) are most widely used. Where the Moll and Wright criteria are very simple (inflammatory arthritis, psoriasis and IgM rheumatoid factor sero-negativity), the CASPAR criteria include both dermatologic, rheumatologic and radiographic features. Current RCTs mainly use the CASPAR criteria due to their high sensitivity and specificity.

It has been attempted to group the patients according to classical disease presentations. Moll and Wright suggested 5 subgroups: predominant distal interphalangeal joint disease, asymmetric oligoarthritis, polyarthritis, spondylitis and arthritis mutilans. Some classical disease features may be seen in PsA: Enthesitis is characterized by inflammation at the site of attachments of tendons, ligaments and joint capsule fibers. Enthesitis is frequent in PsA but only rarely seen in RA and may affect e.g. the Achilles tendon and fascia plantaris. Dactylitis – inflammation of an entire digit due to tenosynovitis, synovitis and subcutaneous swelling is another classical feature. However, it remains a challenge to correctly establish the PsA diagnosis in routine care due to overlapping patterns to other SpA related diseases, to RA, fibromyalgia and osteoarthritis.

3.1.2. PsA, outcome measures and response criteria
PsA may cause arthritis, enthesitis, dactylitis, spondylitis, psoriasis and nail disease, and measures for each of these clinical domains have been developed (reviewed in ). Measures of peripheral arthritis are reported as 28 swollen/tender joint count similar to what is done in patients with RA – or the 68/66 tender/swollen joint count. Patient reported outcomes are patient’s global score measured on a visual analog scale, fatigue and pain, whereas the Health Assessment Questionnaire (HAQ) may be applied as a measurement of functional status. The composite tool DAS28 includes the 28 joint count (swollen/tender), CRP and patient’s global score, whereas the disease score DAPSA (Disease activity in PsA) includes a 66/68 joint count, patient’s scores of pain and global and the CRP value.

In routine care, the DAS28 score is the composite disease activity score most frequently applied. DAS28 was initially developed and validated for RA, but studies have reported DAS28 to be an acceptable measure of disease activity in PsA. Similarly, the ACR20/50/70 response and the EULAR good/moderate response may be applied for changes in disease activity, although these measures are also adapted from RA. A major disadvantage is that these measures only include the 28 joint-count and thus e.g. the distal interphalangeal joints, which are often affected in PsA, are not included.

It is increasingly acknowledged that PsA in some ways is a more complex disease than RA. Several efforts have been made to construct multidimensional scores able to further capture disease
manifestations of the skin, enthesitis, dactylitis and spinal disease (e.g. the composite psoriatic disease activity index (CPDAI), Minimal Disease Activity (MDA), the PsA Disease Activity Score (PASDAS))(reviewed in 41). These efforts are mainly driven by the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) and the Outcome Measures in Rheumatology (OMERACT).35,42,43

3.1.3. AxSpA, classification criteria and disease manifestations

The classical disease within axSpA is AS, which is characterized by back pain, stiffness and limited range of movement combined with radiographic changes in the sacroiliac joints according to the modified New York criteria (1984).44 However, acknowledging that early inflammatory disease is not captured by the New York criteria, the Amor criteria (1990) and the European Spondylarthropathy Study Group (ESSG) criteria (1991)45 were developed.46,47 In year 2009, the ASAS (Assessment of Spondyloarthritis International Society) classification criteria for axSpA were published.47,48 The ASAS criteria illustrate an emphasis on diagnosing disease early before the development of radiographic changes. The criteria may be applied to patients with back pain (≥3 months) and age ≤45 years at onset. Sacroiliitis on imaging (MRI or radiographs) or HLA-B27 positivity combined with ≥1 or ≥2 SpA features, respectively, are necessary to fulfil the criteria.47 SpA features are arthritis, enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, response to NSAIDs, SpA family history, HLA-B27 positivity and elevated CRP.47,49 Thus, the disease spectrum of axSpA includes patients with radiographic axSpA, who fulfil the modified New York criteria for AS, and patients with nonradiographic axial SpA (nr-axSpA) who have either sacroiliitis on MRI with one additional SpA feature or who are HLA-B27 positives with two additional features.

3.1.4. AxSpA, outcome measures and response criteria

The Bath Ankylosing Spondylitis Disease Activity score (BASDAI) was introduced in year 1994 and is the most widely used measure of patient reported disease activity in axSpA.50 The BASDAI consists of six 10 cm horizontal VAS scales that measures fatigue, spinal and peripheral joint pain, tenderness and morning stiffness. The final score ranges from 0-10 cm (best-worst).50

The BAS Function Index (BASFI) constitutes a patient self-reported measurement of function (0-10, best-worst),51 and the BAS Metrology Index (BASMI) is five clinical measures that reflect axial mobility (final score 0-10, best-worst).52

The ASAS group has suggested core sets on how to monitor axSpA patients in routine care (reviewed in 47) – and besides the three BAS scores, routine monitoring of CRP, evaluation of joints and entheses (44-joint count and validated enthesitis scores) and patient’s VAS global, pain and fatigue are included.53 The ASAS group has endorsed response criteria based on relative changes in the BASDAI score:
ASAS20 and ASAS40 improvement and ASAS 5/6 improvement criteria or achievement of a low absolute score (ASAS partial remission criteria). In year 2009, the ASDAS score was developed which is calculated based on measures of CRP (alternatively erythrocyte sedimentation reaction), back pain, peripheral pain, patient’s global score, and morning stiffness. The cut off values are suggested to be 1.3, 2.1 and 3.5 units for inactive, moderate, high and very high disease activity, respectively.

In routine care, it is convenient to apply the BASDAI50%/20mm response criteria (a 50% relative or 20 mm absolute reduction in the BASDAI score), which solely relies on the change in the BASDAI score.

3.1.5. Treatment strategies in PsA and AxSpA

In 2003, treatment with bDMARDs was approved for the treatment of PsA and AS. Until the 1990’es and the beginning of the 2000’s, the main treatment option in PsA had been conventional synthetic disease modifying antirheumatic drugs (csDMARDs) whereas it was physiotherapy and non-steroid anti-inflammatory drugs (NSAIDs) in axSpA. The first bDMARD available was infliximab followed by etanercept and adalimumab, later came golimumab and certolizumab pegol. These drugs are all inhibitors of the tumor necrosis factor (TNF) pathway. Lately, drugs with other modes of action (MOA) have been introduced e.g. secukinumab (Interleukin (IL)17A blocker), ustekinumab (IL12/23 inhibition), apremilast (phosphodiesterase 4 inhibition) – and several treatments targeting other immune-pathways are expected.

As patents on the originator bDMARDs expire, the cheaper biosimilars are developed. A biosimilar may be defined as a ’biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference product’. Due to the complexity of the molecules, a biosimilar is never completely identical to the originator product. Extensive regulations have evolved to ensure comparable efficacy and safety of the biosimilar and the reference product. In year 2015, the first biosimilar bDMARD was marketed in Denmark, namely CT-P13 (biosimilar infliximab) which was followed by biosimilar etanercept, SB4, in 2015. Numerous biosimilars are expected in the coming years.

Treatment algorithms and guidelines for bDMARD treatment (including biosimilars) in PsA and axSpA are available from ASAS/EULAR and the Danish Society of Rheumatology. Within both disease entities, bDMARDs are administered in patients with progressive inflammatory disease and insufficient response to conventional treatment. Several treatment options are available and new treatments are emerging, and the guidelines are thus updated regularly.

There is no doubt that the availability of bDMARDs differs between countries and that political and health economic factors have an impact on the penetration of these expensive drugs. In Denmark, bDMARDs for rheumatic diseases can only be prescribed and administered at hospital
departments of rheumatology and not by private practitioners. The drugs are fully reimbursed and of no
cost to the individual patient. Thus, social factors and economic status should have minimal impact on
which patients receive treatment.

Until year 2012, it was the responsibility of the treating physician to choose between the
bDMARDs. Since 2012, the council for the use of expensive hospital medicines (Rådet For Anvendelse af Dyr
Sygehusmedicin, RADS – now Medicinerrådet) has provided treatment guidelines regarding first and
second line bDMARD treatment. This has had a major impact on the bDMARD prescription patterns in
Danish routine care.

3.2. How to study bDMARD treatment outcomes, efficacy versus effectiveness
When a drug is marketed, experience mainly stems from randomized controlled clinical trials (RCTs) which
study the safety and efficacy of the drug under controlled conditions. Thus, these trials are characterized
by strict inclusion criteria, exclusion of patients with comorbidities or disease complications resulting in a
homogeneous and motivated patient group, use of many resources and expert staff, and close adherence
to a study protocol. Due to this strict standardization of the setting combined with randomization and
blinding of treatment, any positive or negative result is attributed to the intervention.

The therapeutic benefits of bDMARDs in AS and PsA have been documented in RCTs.
(reviewed in 19;78) However, when the drug subsequently is used in routine care, the patient group is large
and heterogeneous with higher age and various comorbidities, risk of non-adherence to treatment, less
stringent administration of drug (dose, interval) and use of routine care staff which may influence
outcomes. It has previously been demonstrated that the majority of patients treated in routine care would
not comply with RCT inclusion criteria.17;79 The extent to which a drug achieves its intended effect and
tolerability in the usual clinical setting may be defined as treatment effectiveness.77 Treatment retention is
the extent to which the patients remain on treatment. Retention is a proxy outcome parameter expressing
both effectiveness and safety and may be perceived as a combination of benefits and risks of the
treatment.80

Observational studies and RCTs are thus complementary methods with each their strengths
and weaknesses.81;82 An obvious advantage of the observational study design is that patients treated in
routine care irrespective of disease severity, age and comorbid disease are included. Furthermore,
observational data allows longer follow up periods of a large number of patients and research questions
not addressed in RCTs may be investigated e.g. switching and comparison of treatment effects according to
drug type. Disadvantages include lack of randomization and risks of bias or confounding.

A bias is ‘a systematic error in the design, recruitment, data collection or analysis that results
in mistaken estimation of the true effect of exposure on outcome’.83 Examples of bias include selection bias
(systematic error in the selection and retention of patients) and misclassification/information bias (inaccurate classification of disease or exposure or other variables e.g. misdiagnosis and missing data). A confounder is a variable, which distorts the measure of the association between exposure and outcome.\textsuperscript{83} Thus, a confounder wholly or partially accounts for the observed effect of a risk factor on disease status. The following applies to a confounder: It is an independent risk factor for the outcome, it is associated with the risk factor, and it is not on the causal pathway between exposure and disease.\textsuperscript{83} Examples of bias and confounding in the papers included in the present thesis are further discussed below (results Section 5.2. and methodological considerations Section 6.2.).

### 3.3. Predictors of treatment effectiveness in PsA and axSpA

Although treatment with bDMARDs has revolutionized the treatment of PsA and axSpA, many patients do not benefit from treatment due to adverse events or insufficient treatment response. The treatments are expensive and patients may potentially be harmed due to risk of adverse events. Therefore, it is important to correctly identify the patients most likely to benefit from treatment early during the treatment course or even before the treatment commences. As discussed above, the extrapolation from RCTs to routine care is a challenge as the patients who actually receive treatment with a specific drug may differ from the patients who were included in the original trials.

Various factors are potentially associated with treatment effectiveness. Some factors apply to patient demographics or biological factors that could influence drug pharmacokinetics, dynamics and/or immunogenecity (e.g. body mass index, gender, age, co-medication with csDMARDs, comorbidities). Others relate to disease status and potential for reversibility (disease duration, radiographic changes) whereas some factors are of a strategic (or political) character. For example, the marketing of more bDMARDs might encourage faster bDMARD switching in case of lack of effect. Similarly, introduction of biosimilars might potentially facilitate treatment initiation at an earlier time point during the disease course due to lower price. Treatment guidelines and time trends (patient/physician demands of a certain treatment, pricing, availability of drug) are other factors that might have an impact on disease duration and disease status at the time of treatment initiation and thereby affect effectiveness.\textsuperscript{82}

Clinical factors potentially associated with treatment effectiveness are shown in Table 1.\textsuperscript{84,85}
Table 1 Baseline factors potentially associated with treatment outcomes

| Demographic features | Gender  
|                      | Age  
|                      | Disease duration  
|                      | Smoking  
|                      | Body mass index  
|                      | Comorbidities  
|                      | Socioeconomic status  
| Disease characteristics | Classification criteria (e.g. HLA-B27 in ax-SpA)  
|                      | Disease activity (e.g. CRP, patient reported outcomes)  
|                      | Disease status (functional status, radiographic changes, early/late disease)  
|                      | Disease phenotype (e.g. peripheral/axial)  
| Treatment strategy | bDMARD drug type  
|                      | Originator bDMARD versus biosimilar  
|                      | bDMARD dose regimen  
|                      | Co-medication with csDMARDs  
|                      | Number of previous bDMARD treatment courses  
|                      | Reason for stop of previous bDMARD  
| Other* | Biomarkers measured in biological material (blood)  
|                      | Imaging results (MRI, US etc.)  

* It is beyond the scope of the present theses to discuss biomarkers measured in blood/biological material in further detail. Furthermore, imaging will not be addressed.

3.4. Real world registries

Registries may be defined as ‘longitudinal observational cohorts, typically prospective, which enroll patients with a specific purpose; it could either be drug- or disease-based or both’. Registries represent an excellent source of information regarding medication use and treatment effectiveness in routine care. Furthermore, several of the factors potentially associated with treatment outcomes mentioned above may be identified in registries.

In order to ensure external validity and generalizability, the registry should have high completeness and should include and follow patients who are representative of the typical patient. Thus regarding bDMARDs, (almost) all users of the drug should be included in the registry – or at least a random patient sample in order to avoid selection during recruitment of patients. Furthermore, the patients should be monitored with close intervals in order to capture changes in disease activity, concomitant treatment with csDMARD or other signs of bDMARD failure/response.

The marketing of the bDMARDs has encouraged the establishing of registries within rheumatology in several European countries, including the Danish DANBIO registry, in the Unites States and across the world. Whereas several focus on RA, others include patients with axSpA and PsA, e.g. the SCQM of Switzerland, the BIOBADASER of Spain, the LORHEN of Italy, the BSRBR-AS of UK, the SRQ, ARTIS and SwePsA of Sweden, just to mention examples from European countries. The registries are often
initiated in collaboration with the national societies of rheumatology aiming to improve pharmacovigilance and knowledge on treatment effectiveness and long term safety.\textsuperscript{14} Pharmacovigilance is by the World Health Organization defined as ‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem’.\textsuperscript{92} However, it also lies within the responsibilities of the registries to investigate long term disease outcomes, quality of life and to perform independent research.\textsuperscript{14}

DANBIO is a Danish nationwide rheumatologic registry that was initiated in year 2000.\textsuperscript{93,94} The registry is approved by the Danish Board of Health and the Danish Data Protection Agency. In the early years, data were submitted to DANBIO by paper formulas. Since 2006, all data entry has occurred prospectively by an online system (www.danbio-online.dk). Patient report outcomes and data regarding comorbidities, smoking and lifestyle by touch screens in the waiting area.\textsuperscript{95} It is mandatory to include the following patient groups in DANBIO: 1) all rheumatic patients treated with bDMARDs (irrespective of diagnosis) and 2) all newly referred RA patients irrespective of treatment.\textsuperscript{94}

DANBIO includes data on (reviewed in \textsuperscript{94}):

- patient characteristics: social security number, age, gender, disease duration, symptom duration, BMI
- disease characteristics: serology (antiCCP, IgM-RF), which classification criteria the patient fulfills upon diagnosis (voluntary and not uniformly available, e.g. HLAB27 status), year of diagnosis, year of symptom start, radiographic data (MRI in axSpA, X-ray status hand/feet)
- disease activity, patient reported outcomes: VAS global/fatigue/pain, BASDAI and BASFI-scores (axSpA), HAQ
- disease activity, objective measures: tender and swollen 28-joint count (68 joint count only available in a minority of patients), enthesitis count (only available in a minority of patients), BASMI, CRP
- composite measures of disease activity: DAS28, ASDAS (since year 2010)
- current and previous treatment with csDMARDS and bDMARDs (name, administration route, dose regimen, start/stop date, reason for withdrawal)
- health behavioral factors: smoking, alcohol consumption, physical activity, EQ-5D

DANBIO coverage is audited yearly by the DANBIO secretariat and coverage is >90\% for patients treated with bDMARDs in routine care.\textsuperscript{76,93} It is recommended that clinical data are registered at least 1-2 times yearly and whenever the patient starts or stops treatment with a DMARD.

The ICEBIO registry was established in year 2008 and includes data regarding Icelandic patients with inflammatory arthritis. Data are collected prospectively on the same IT-platform as DANBIO.\textsuperscript{3,96}
4. Patients and methods

The current thesis is based on data retrieved from the DANBIO registry. In paper 3, ICEBIO data from Iceland were also included (Icelandic data will not be explored further in the thesis).

4.1. Cohorts and study design

All cohorts were identified in the DANBIO registry. The criteria for patient inclusion and –exclusion, the patient cohorts and methods for data validation are briefly described below. For more details please see enclosed papers (Appendix 1-9).

4.1.1. Patient inclusion

The time periods for patient inclusion into the cohorts were in most papers from the start of DANBIO (year 2000) until specific censoring dates. All Danish departments of rheumatology were invited to participate in the studies. Table 2 shows participating departments and inclusion time intervals for the 9 papers/cohorts.

<table>
<thead>
<tr>
<th>Publication year</th>
<th>Paper no.</th>
<th>Number</th>
<th>Participating departments</th>
<th>Inclusion time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>6</td>
<td>13</td>
<td>Gentofte, Glostrup, Aarhus, Frederiksberg, Vejle, Aalborg, Køge, Odense, Rigshospitalet, Hjørring, Esbjerg, Helsingør, Randers</td>
<td>2000 – 2011 (Jan)</td>
</tr>
<tr>
<td>2013</td>
<td>2</td>
<td>9</td>
<td>Gentofte, Glostrup, Frederiksberg, Aarhus, Vejle, Odense, Aalborg, Rigshospitalet, Helsingør</td>
<td>2000 – 2012 (Jan)</td>
</tr>
<tr>
<td>2015</td>
<td>4</td>
<td>14</td>
<td>Gentofte, Frederiksberg, Glostrup, Holbæk, Esbjerg, Svendborg, Aalborg, Odense, Vejle, Rigshospitalet, Helsingør/Hillerød, Køge, Aarhus, Silkeborg</td>
<td>2000 – 2012 (Jan)</td>
</tr>
</tbody>
</table>

* For details, see Paper 9.
Patients were included in the cohorts according to the diagnosis registered in DANBIO i.e. the diagnosis according to the expert opinion of the treating rheumatologist.

The main inclusion criteria and the number of patients included in the 9 cohorts are shown in Table 3.

<table>
<thead>
<tr>
<th>Paper no.</th>
<th>Diagnosis</th>
<th>Main inclusion criteria</th>
<th>Patients included, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PsA</td>
<td>≥1 TNFi treatment courses</td>
<td>764</td>
</tr>
<tr>
<td>2</td>
<td>PsA</td>
<td>≥2 bDMARD treatment courses</td>
<td>548</td>
</tr>
<tr>
<td>3</td>
<td>PsA</td>
<td>Infliximab the first TNFi treatment course</td>
<td>462</td>
</tr>
<tr>
<td>4</td>
<td>PsA</td>
<td>≥1 TNFi treatment course</td>
<td>1388</td>
</tr>
<tr>
<td>5</td>
<td>AS</td>
<td>≥1 TNFi treatment courses</td>
<td>842</td>
</tr>
<tr>
<td>6</td>
<td>AS</td>
<td>≥2 bDMARD treatment courses</td>
<td>432</td>
</tr>
<tr>
<td>7</td>
<td>AS</td>
<td>≥1 TNFi treatment course</td>
<td>1576</td>
</tr>
<tr>
<td>8</td>
<td>AxSpA</td>
<td>≥1 TNFi treatment course</td>
<td>1250</td>
</tr>
<tr>
<td>9</td>
<td>PsA, AxSpA, RA</td>
<td>Switch from originator to biosimilar infliximab</td>
<td>802</td>
</tr>
</tbody>
</table>

The cohorts were partly overlapping (Figure 2A and B). The patients included in paper 9 were not characterized by TNFi treatment start year but according to biosimilar switching and are hence not included in the figures. Further data regarding the RA patients included in paper 9 will not be presented in this thesis.

In the following, tables and figures refer to data from the original papers except Figure 5B and Figure 8 which are based on an update of the data originally presented (DANBIO per May 1st 2017).
Figure 2
Number of patients (y-axis) in DANBIO starting first and second TNFi according to year of treatment start (x-axis). Arrows along x-axis indicate time intervals for patient inclusion according to paper number. A: patients with PsA, B: patients with AS. (Data-source: Paper 8 and Paper 3 dataset)

**Figure 2A** Psoriatic arthritis

**Figure 2B** Ankylosing spondylitis
4.1.2. Patient exclusion

In all papers, patients were excluded if they

- had not been followed in DANBIO since commencement of the first TNFi
- received their bDMARD treatment from non-rheumatologic departments and hence were not systematically registered in DANBIO (e.g. departments of dermatology or gastroenterology)
- received a first bDMARD that was not a TNFi - or that was a TNFi not indicated for the relevant rheumatologic disease in the given time period (e.g. certolizumab pegol for AS before year 2014, golimumab for PsA before year 2013)
- participated in clinical studies/trials and e.g. received blinded project bDMARD treatment
- had contra-intuitive registrations (e.g. negative bDMARD treatment duration etc.)

4.2. Validation of data in DANBIO

The data in DANBIO are entered prospectively by an online system. The IT solution minimizes the risk of errors compared to paper formats and uses a standardized format for the collection of variables. Examples of prospective data validation are: 1) min-max boundaries of patient reported outcomes e.g. VAS, and 2) that a new bDMARD cannot be prescribed before the previous bDMARD has been withdrawn - including registration of the reason for withdrawal. These solutions have however been implemented gradually and were not available in the earlier years.

Retrospective data validation occurs annually when the local departments of rheumatology are requested to assess coverage of bDMARD treated patients. Furthermore, hospital patient records may be used to update missing data (e.g. CRP) before the evaluation of quality indicators that are reported in the DANBIO Annual Clinical Quality Report.94

As part of research projects, further retrospective data validation may lead to even higher data completeness regarding specific covariates or outcomes. Thus, as part of the data collection process of the 9 papers included in this thesis, all Danish department of rheumatology were invited to participate and to verify the data entered in DANBIO specifically regarding:

- Treatment duration of bDMARDs including exact date for starting the drug and the date of the first missed dose/stop date
- In case of withdrawal to enter reason for withdrawal
- If bDMARD treated patients with lack of follow-up for >6 months were still treated or had withdrawn

Furthermore, in specific papers, focus was on entering data regarding:
• Infliximab treated patients’ body height/weight/BMI (including Landspitali University Hospital, Reykjavik) (Paper 3)
• Which classification criteria individual patients fulfilled upon start of the first TNFi (Paper 8). These data were only available in a limited number of patients treated in routine care. Thus, patients were only included in study 8 if their local department of rheumatology entered the required information
• The exact switch date from originator to biosimilar infliximab. If the biosimilar treatment had stopped to enter the reason for withdrawal (Paper 9)

4.3. Baseline characteristics, measures of disease activity and outcomes

An overview of the included baseline patient characteristics, measures of disease activity, function and clinical response to treatment is shown in Table 4 for PsA and Table 5 for axSpA. It is beyond the scope of this thesis to report further data on RA (Paper 9). All the reported variables were identified in DANBIO except comorbidities (Paper 9, see next Section 4.4.).

Disease activity was evaluated according to the available clinical data in DANBIO (‘visits’) and captured according to the following time windows: The baseline visit was defined as the time of TNFi treatment start. The time window applied for the baseline visit (bDMARD start date) varied across the papers. Thus, the baseline visit included data from 5 days before until 6 days after treatment start (Paper 1, 2, 4, 5, 6), or from 30 days before until 6 days after treatment (Paper 3), or from 60 days before until 6 days after treatment start (Paper 7, 8). In Paper 9, which included patients on long-time treatment with infliximab, a longer time interval of 90 days before baseline was defined. The time windows for the visits after 2 weeks (1-4 weeks), 6 weeks (5-9 weeks), 6 months (18-32 weeks), 2 years (91-117 weeks), 3 years (143-182 weeks), 4 years (183-233 weeks) and 5 years (234-285 weeks) was identical in all papers. In Paper 9, additional time windows covering before the baseline visit were applied: 3 months’ window: 0-25 weeks, 6 months’ window: 25-32 weeks before start of CT-P13.

Treatment retention was defined as the number of days during which individual patients maintained treatment with the bDMARD. Stop date was the date of the first missed treatment dose. Temporary treatment interruptions of < 3 months durations were allowed.

Reasons for stopping treatment were categorized as LOE, AE (side effects, infection, death, cancer) or other (pregnancy, surgery, loss to follow-up, remission, several reasons for discontinuation). Patients were classified as having achieved a clinical response according to the 3 and 6 months’ visits. Definition of response varied across papers: In Paper 1 and 5, patients with at least one registration of clinical response at either of the two time points were considered a responder. In Paper 2, 3, 4, 6, 7, 8,
patients were required to have a clinical response at both visits in order to be considered a responder. In case of missing data, one registration of response was sufficient to categorize the patient as responder. No response measures were applied in Paper 9.

| Table 4 Overview of reported baseline characteristics, measures of disease activity, function and clinical response in PsA according to paper number |
|---------------------------------|---|---|---|---|---|
| PsA Baseline characteristics | Gender, age | + | + | + | + |
| | Disease/symptom duration | + | + | + | + |
| | Concomitant MTX | + | + | + | + |
| | Concomitant oral prednisolone | + | + | + | + |
| | Height/weight/BMI | + | + | + | + |
| | Smoking status | + | + | + | + |
| | TNFi type | + | + | + | + |
| | TNFi dose regimen | + | + | + | + |
| | TNFi start year | + | + | + | + |
| | Previous csDMARDs | + | + | + | + |
| | Number of comorbidities (10 years back)** | + | + | + | + |
| | Disease activity and function | CRP | + | + | + | + |
| | DAS28 | + | + | + | + |
| | 28 swollen and tender joint count | + | + | + | + |
| | VAS pain/global/fatigue | + | + | + | + |
| | VAS physician | + | + | + | + |
| | BASDAI/BASMI/BASMI | + | + | + | + |
| | HAQ | + | + | + | + |
| | Outcome measures | bDMARD treatment duration | + | + | + | + |
| | Reason for treatment withdrawal | + | + | + | + |
| | EULAR good response | + | + | + | + |
| | ACR20/50/70 | + | + | + | + |
| | DAS28 remission | + | + | + | + |
| | Changes in disease activity (baseline vs. 3-6 mths) | + | + | + | + |
| | NNT | + | + | + | + |

*Only VAS fatigue, ** identified in the Danish National Patient Registry
Table 5 Overview of reported baseline characteristics, measures of disease activity, function and clinical response in axSpA according to paper number

<table>
<thead>
<tr>
<th>AxSpA</th>
<th>Paper no.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
</tr>
<tr>
<td>Gender, age</td>
<td>+</td>
</tr>
<tr>
<td>Disease/symptom duration</td>
<td>+</td>
</tr>
<tr>
<td>Concomitant MTX</td>
<td>+</td>
</tr>
<tr>
<td>Concomitant prednisolone</td>
<td></td>
</tr>
<tr>
<td>Height/weight/BMI</td>
<td>+</td>
</tr>
<tr>
<td>Smoking status</td>
<td>+</td>
</tr>
<tr>
<td>TNFi type</td>
<td>+</td>
</tr>
<tr>
<td>TNFi start year</td>
<td>+</td>
</tr>
<tr>
<td>HLA B27 status</td>
<td></td>
</tr>
<tr>
<td>Classification criteria</td>
<td></td>
</tr>
<tr>
<td>Number of comorbidities (10 years back)**</td>
<td></td>
</tr>
<tr>
<td>Disease activity, function</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>+</td>
</tr>
<tr>
<td>VAS pain/global/fatigue</td>
<td>+</td>
</tr>
<tr>
<td>VAS physician</td>
<td>+</td>
</tr>
<tr>
<td>BASDAI</td>
<td>+</td>
</tr>
<tr>
<td>BASMI/BASFI</td>
<td>+</td>
</tr>
<tr>
<td>Thorax excursion range</td>
<td>+</td>
</tr>
<tr>
<td>ASDAS</td>
<td>+</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
</tr>
<tr>
<td>bDMARD treatment duration</td>
<td>+</td>
</tr>
<tr>
<td>Reason for treatment withdrawal</td>
<td>+</td>
</tr>
<tr>
<td>BASDAI50%/20mm response</td>
<td>+</td>
</tr>
<tr>
<td>BASDAI&lt;40mm</td>
<td>+</td>
</tr>
<tr>
<td>ASAS40, ASAS remission</td>
<td>+</td>
</tr>
<tr>
<td>ASDAS inactive disease</td>
<td>+</td>
</tr>
<tr>
<td>ASDAS clinically important improvement</td>
<td>+</td>
</tr>
<tr>
<td>Changes in disease activity (baseline vs. 3-6 mths)</td>
<td>+</td>
</tr>
<tr>
<td>NNT</td>
<td></td>
</tr>
</tbody>
</table>

*Only VAS fatigue, **Identified in the Danish National Patient Registry

4.4. Comorbidities

Comorbidities (previous cancer, infections, cardiovascular disease etc.) may have an impact on bDMARD prescription patterns and are suspected to affect treatment outcomes.¹⁴,⁹⁷ Thus it is of interest to include comorbidities as a potential confounder in analyses of treatment effectiveness. In DANBIO, comorbidities may be included through patient self-report on the touch screen (=‘yearly visit’). However, this is not done routinely and data are not uniformly available.

In paper 9, number of comorbidities according to the Charlson comorbidity index⁹⁸ was identified in the National Patient Register.⁹⁹ This was done by cross linkage by social security numbers. The National Patient Register contains diagnoses from hospitalization-discharges and from in- and out-patient
care and has high completeness. The possibilities of enrichment of DANBIO data with information from national registries are further discussed in Section 7.1. regarding future perspectives.

4.5. Ethics

DANBIO has been approved by the Data Protection Agency since year 2000 (j. nr. 2207-58-0014 and j. nr. 2007-58-0006), and since year 2006 as a national quality registry by the National Board of Health (j. nr. 7-201-03-12/1). Patient registration in DANBIO does not require patient consent. According to Danish Law, publication of registry data does not require approval by Ethics committees.

4.6. Statistical analysis

In all papers, demographics and descriptive data are mainly presented by medians (IQR), and groups are compared by non-parametric testing (Unpaired: Chi square test, Mann-Whitney test. Paired: Wilcoxon’s signed rank test).

Treatment retention and factors associated with retention were investigated with Kaplan-Meier plots, log rank tests and uni- and multivariate Cox regression analyses (hazard ratios). Stratified analyses according to reason for stop of treatment (AE/LOE) were done in paper no 1-6.

In paper 1-8 the response rates were calculated as the proportion of patients who achieved a clinical response at the 3-6 months visits by the algorithm described above. Factors associated with response were investigated with multivariable logistic regression analyses (odds ratios).

Further details on statistical analyses are described in the papers.

Table 6A and Table 6B show which baseline characteristics that were included in the multivariable statistical analyses in each paper, and if they were included as categorical or continuous variables. Variables that were not included in the multivariable analyses were either 1) available but rendered irrelevant for that paper or 2) of relevance but unavailable. The reason for unavailable data could be poor quality in DANBIO and hence need for validation before publication (e.g. smoking status or diagnostic criteria for axSpA in the early publications).
<table>
<thead>
<tr>
<th>Table 6A  Baseline DANBIO characteristics included in multivariable analyses in PsA patients according to paper number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main outcome</strong></td>
</tr>
<tr>
<td>Effectiveness of 1st TNFi</td>
</tr>
<tr>
<td>Effectiveness of 2nd bDMARD</td>
</tr>
<tr>
<td>Impact of infliximab dose regimens on effectiveness</td>
</tr>
<tr>
<td>Impact of smoking on effectiveness of 1st TNFi</td>
</tr>
<tr>
<td>Infliximab non-medical switch</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>TNFi type</td>
</tr>
<tr>
<td>CRP</td>
</tr>
<tr>
<td>Methotrexate</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Disease duration</td>
</tr>
<tr>
<td>Swollen joint count</td>
</tr>
<tr>
<td>Tender joint count</td>
</tr>
<tr>
<td>VAS global</td>
</tr>
<tr>
<td>VAS pain</td>
</tr>
<tr>
<td>VAS fatigue</td>
</tr>
<tr>
<td>HAQ</td>
</tr>
<tr>
<td>DAS28</td>
</tr>
<tr>
<td>Start year</td>
</tr>
<tr>
<td>Stop reason first TNFi</td>
</tr>
<tr>
<td>Time interval between infliximab infusions</td>
</tr>
<tr>
<td>Infliximab dose</td>
</tr>
<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>No. of comorbidities*</td>
</tr>
</tbody>
</table>

*K=categorical, C=continuous, *Identified in the Danish National Patient Registry
Table 6B Baseline characteristics included in multivariable analyses in AS or axSpA patients according to paper number

<table>
<thead>
<tr>
<th>Main outcome</th>
<th>Paper 5</th>
<th>Paper 6</th>
<th>Paper 7</th>
<th>Paper 8</th>
<th>Paper 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>TNFi type</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>K</td>
</tr>
<tr>
<td>CRP</td>
<td>K</td>
<td>C</td>
<td>K</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>K</td>
</tr>
<tr>
<td>Age</td>
<td>C</td>
<td>C</td>
<td>K</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Disease duration</td>
<td>K</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS global</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS pain</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS fatigue</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASDAI</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>BASFI</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASMI</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASDAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Start year</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>K</td>
<td>K</td>
</tr>
<tr>
<td>Stop reason first TNFi</td>
<td>K</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td>K</td>
<td>K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B27</td>
<td>K</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>axSpA subdiagnosis</td>
<td>K</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of comorbidities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
</tbody>
</table>

K=categorical, C=continuous, *identified in the Danish National Patient Registry
5. Summary of results

5.1. Baseline demographics of study cohorts

Table 7A and Table 7B show the main baseline characteristics of patients with PsA and AS (axSpA for paper 8 and 9), respectively. For paper 3, only demographics for Danish and not Icelandic patients are shown. For paper 9, characteristics of patients with RA are not reported.

As shown in Figure 1A and Figure 1B, the cohorts are partly overlapping.

| Table 7A  Baseline demographics in PsA according to paper number |
|-------------|-----------------|--------|--------|--------|--------|
|             | 1               | 2      | 3*     | 4      | 9      |
|             | Non-switchers N=874 | Switchers N=548 |        |        |        |
| Patient number, n | 764 | 1422 | 376 | 1388 | 120 |
| Women, n (%) | 396 (52) | 699 (49) | 204 (54) | 679 (48) | 58 (48) |
| Age, years | 47 (38-56) | 48 (39-56) | 48 (40-56) | 48 (38-56) | 52 (44-61) |
| Type of TNFi, n (%) | | | | | |
| Adalimumab | 320 (42) | 636 (45) | - | 634 (46) | - |
| Etanercept | 184 (24) | 318 (22) | - | 322 (23) | - |
| Infliximab | 260 (34) | 429 (30) | 376 (100) | 432 (31) | 120 (100) |
| Golimumab | - | 39 (3) | - | - | - |
| Concomitant MTX, n (%) | 410 (54) | 482 (55) | 283 (52) | 260 (69) | 746 (53) | 84 (69) |
| Disease duration, years | 5 (2-11) | 4 (1-10) | 3 (1-9) | 7 (3-13) | 4 (1-10) | 12 (9-20) |
| CRP, mg/l | 10 (4-22) | 9 (3-19) | 9 (3-23) | 10 (4-25) | 9 (3-20) | 4 (1-6) |
| DAS28 | 4.8 (3.9-5.5) | 4.4 (3.6-5.2) | 4.8 (4.0-5.7) | 4.7 (3.8-5.5) | 4.6 (3.7-5.4) | 2.3 (1.7-3.1) |
| Patient's global score, mm | 69 (50-81) | 68 (48-83) | 70 (53-85) | 69 (51-84) | 68 (50-83) | 34 (10-67) |
| HAQ | 1.0 (0.6-1.5) | 0.9 (0.5-1.4) | 1.1 (0.6-1.6) | 1.1 (0.8-1.6) | 1.0 (0.5-1.5) | 0.6 (0.1-1.1) |

Numbers are medians (IQR) unless otherwise stated. Not all numbers are shown in original papers

* Only patients in DANBIO are shown (ICEBIO patients excluded)
Table 7B  Baseline demographics in AS (axSpA for paper 8 and 9) according to publication number

<table>
<thead>
<tr>
<th>Paper</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-switchers</td>
<td>Switchers</td>
<td>Non-switchers</td>
<td>Switchers</td>
<td>Non-switchers</td>
</tr>
<tr>
<td>Patient number, n</td>
<td>842</td>
<td>1436</td>
<td>1576</td>
<td>1250</td>
<td>279</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AS</td>
<td>AS</td>
<td>AS</td>
<td>AxSpA</td>
<td>AxSpA</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>239 (28)</td>
<td>360 (25)</td>
<td>442 (28)</td>
<td>458 (37)</td>
<td>73 (26)</td>
</tr>
<tr>
<td>Type of TNFi, n (%)</td>
<td>Adalimumab</td>
<td>247 (29)</td>
<td>532 (37)</td>
<td>625 (40)</td>
<td>519 (41)</td>
</tr>
<tr>
<td></td>
<td>Etanercept</td>
<td>150 (18)</td>
<td>231 (16)</td>
<td>274 (17)</td>
<td>183 (15)</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>445 (53)</td>
<td>653 (45)</td>
<td>547 (34)</td>
<td>294 (24)</td>
</tr>
<tr>
<td></td>
<td>Golimumab</td>
<td>-</td>
<td>20 (1)</td>
<td>130 (8)</td>
<td>246 (20)</td>
</tr>
<tr>
<td>Concomitant MTX, n (%)</td>
<td>343 (41)</td>
<td>262 (26)</td>
<td>157 (36)</td>
<td>407 (26)</td>
<td>222 (18)</td>
</tr>
<tr>
<td>Age, years</td>
<td>41 (32-50)</td>
<td>41 (33-51)</td>
<td>41 (32-49)</td>
<td>41 (32-51)</td>
<td>40 (31-49)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>5 (1-3)</td>
<td>5 (1-4)</td>
<td>3 (1-11)</td>
<td>3 (1-13)</td>
<td>1 (0-6)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>14 (7-27)</td>
<td>13 (5-27)</td>
<td>13 (5-26)</td>
<td>12 (4-24)</td>
<td>9 (3-20)</td>
</tr>
<tr>
<td>BASDAI, mm</td>
<td>59 (44-72)</td>
<td>56 (43-69)</td>
<td>62 (52-76)</td>
<td>59 (45-71)</td>
<td>61 (49-73)</td>
</tr>
<tr>
<td>BASMI, mm</td>
<td>40 (20-50)</td>
<td>40 (20-60)</td>
<td>40 (20-60)</td>
<td>40 (20-50)</td>
<td>30 (10-40)</td>
</tr>
<tr>
<td>BASFI, mm</td>
<td>50 (34-67)</td>
<td>47 (31-65)</td>
<td>54 (39-71)</td>
<td>50 (33-67)</td>
<td>50 (34-68)</td>
</tr>
<tr>
<td>Patient’s global score, mm</td>
<td>67 (48-81)</td>
<td>66 (46-79)</td>
<td>72 (57-85)</td>
<td>69 (50-82)</td>
<td>72 (53-85)</td>
</tr>
</tbody>
</table>

Numbers are medians (IQR) unless otherwise stated. Not all numbers are shown in original papers.

The baseline demographics for paper 1-8 reflect that the patients have high disease activity at start of TNFi therapy illustrated by high patient’s global score, DAS28 (for PsA), BASDAI (for axSpA) and a high level of functional impairment (HAQ for PsA, BASMI and BASFI for axSpA). In contrast, baseline demographics for paper 9 reflect that the cohort included patients on long-lasting stable treatment with infliximab and thus lower disease activity, longer disease duration and higher age.

The disease characteristics and patient demographics that were reported in the papers reflected information that was available from DANBIO. In Paper 9, data were enriched with data from the National Patient Registry regarding number of comorbidities. DANBIO was developed for use in routine care and the collection of data should be feasible in a busy routine care setting. Thus, some disease characteristics are not routinely registered e.g. which classification criteria for the patient fulfills or specifics regarding disease phenotype. For example, in PsA, information regarding enthesitis, dactylitis, psoriatic skin manifestations or disease phenotype (arthritis mutilans, erosive disease, axial disease, etc.) is not available. Thus, all patients are considered as having the same type of disease, and common measures of disease activity and outcome are applied in all patients. In PsA these outcome measures focus on peripheral 28-joint involvement combined with patient reported outcomes and functional status. It is however possible that certain disease characteristics e.g. degree of psoriatic skin involvement might have had an impact on
when to start which drug in which patient – and when to render the treatment effective or ineffective. Similarly in axSpA, the treatment might be driven by mainly peripheral joint involvement, uveitis or other inflammation outside the spine.

5.2. Summary of results and discussion according to specific aims

The main results presented in this section refer to the specific aims stated in Section 2.2. The main focus will be on significant/positive results, for additional results please see the original papers 1-9. Issues of relevance for the specific aim are discussed and should be perceived as a supplement to the discussion available in the original papers. The term Baseline refers to the time point for start of the first TNFi unless otherwise stated.

5.2.1. Treatment response, treatment retention, and predictors thereof during the first TNFi treatment course in PsA (Specific aim 1, Paper 1)

At baseline, women had higher subjective measures of disease activity, higher tender joint count and HAQ score compared to men, whereas swollen joint count was lower. Concomitant use of methotrexate was more frequent among patients treated with infliximab.

The median TNFi treatment retention was 2.9 years and 70% of the patients maintained treatment after 1 year and 57% after 2 years. The main reason for stopping treatment was lack of treatment effect (52% of withdrawals) followed by adverse events (28%). Baseline factors associated with longer retention in multivariable analyses were male gender, increased CRP, use of methotrexate and low patient’s global score. Lower HAQ was only significant in univariate analysis.

There was a significant improvement in disease activity and patient reported outcomes and function during TNFi treatment (2 weeks to 5 years after initiation of treatment). After 6 months’ treatment, the EULAR good response rate was 54% and the ACR20/50/70 rates were 59%/45%/24%, respectively. No adjustments for non-completers were conducted in these analyses.

The baseline factors associated with response were CRP>10mg/L (significant for EULAR good response, ACR20, ACR50 and ACR70 response), male gender (EULAR good response), younger age (EULAR good response), use of methotrexate (ACR20) and higher patient’s global (ACR20). In crude univariable analyses, the NNT in order to achieve an ACR70 response were 7 if the CRP ≤10 mg/L and 3 if CRP >10 mg/L.

When the paper was published in year 2011, only few observational studies regarding TNFi treatment outcomes in routine care were available.97,101-105 Afterwards, several studies have been published which are either prospective registry based e.g. from Italy,106 Norway107,108 and Canada109 whereas others report single-center studies or retrospective evaluations (reviewed in 84,85). Similarly to our study, these
papers found that treatment with TNFi was well tolerated with one-year retention rates ranging between 76-94%, and in case the patient stopped it was mainly due to lack of effect.\textsuperscript{97,101,104,110,111} 

The proportion of patients with response varies across studies partly due to the application of various response measures. Some previous studies applied ACR and EULAR response rates as in our study whereas others calculated disease state e.g. clinical remission or minimal disease activity. Minimal disease activity was achieved in 61-64% of patients\textsuperscript{110,112}, DAS28 remission in 58%\textsuperscript{103}, ACR20 response in 76-79\%\textsuperscript{104} and EULAR good or moderate response in 70-75\%.\textsuperscript{97,102} One study found that the response rate doubled from 4 to 8 months therapy\textsuperscript{110} and another that a subgroup of patients had delayed response not apparent until after one year.\textsuperscript{109} This indicated that efficacy should be evaluated at late time-points and not as early as 3-6 months as recommended in guidelines.\textsuperscript{70} We did not specifically address this issue in our data, but as shown in table 2 of the paper, there seemed to be a further improvement in measures of disease activity between 6-12 months, however patients withdrawn from treatment early and hence not contributing data might bias these results.

A systematic review and meta-analysis regarding predictors of TNFi treatment response in PsA concluded that no uniform predictors could be identified.\textsuperscript{85} However, similar to our study, several publications have found elevated CRP\textsuperscript{102,110,113,114} and male gender\textsuperscript{97,103,106,110,112,114} to be associated with TNFi treatment response.

The role of co-medication with methotrexate has been addressed in several publications\textsuperscript{115} (reviewed in \textsuperscript{85}) as it is of high clinical relevance to establish if combination therapy is superior to monotherapy. Indeed, 54% of the patients in our study received concomitant methotrexate. In randomized trials there does not seem to be any additional effect of adding methotrexate to TNFi treatment.\textsuperscript{116,117} Although some studies have indicated positive impact of co-medication with methotrexate on treatment retention and outcome, the meta-analysis did not find any additional effects of adding methotrexate.\textsuperscript{85} A similar conclusion was made in a GRAPPA treatment guideline.\textsuperscript{22} However differences across TNFi drug types cannot be ruled out.\textsuperscript{118,119} In epidemiological research, confounding by indication is an important consideration and is discussed in Section 6.2. below.

The heterogeneity of studies and the various outcome measures applied across studies might potentially explain the lack of significance of the individual potential predictors in meta-analysis. Within AS it has been attempted to construct matrix models that combine numerous baseline predictors into a model with a maximum capture of which patients respond to treatment,\textsuperscript{120} see discussion for paper 5 below. Similar attempts have not been done in PsA. Thus, in routine care it remains a challenge to correctly identify clinical predictors of bDMARD response in individual patients.
5.2.2. Treatment response, treatment retention, and predictors thereof among PsA patients switching to a subsequent bDMARD (Specific aim 2, Paper 2)

The main baseline demographics according to switch status are summarized in Table 7A. During follow-up (median 2.3 years (IQR 1.0-4.3)) 39% of patients switched treatment to a second bDMARD, 44% maintained treatment and 17% stopped treatment without starting a new bDMARD. Upon start of the first TNFi, the patients who subsequently switched to another bDMARD (= switchers) were more frequently women, had shorter disease duration, had higher HAQ, DAS28, VAS pain, VAS fatigue, swollen and tender joint count compared to the patients who maintained treatment (=non-switchers).

The main reason for switching was lack of treatment effect. The treatment retention decreased after switching and the proportion of patients who maintained treatment after 2 years during the first, second and third treatment course was 52%, 42% and 40 %, respectively.

The factors associated with longer treatment retention during the second bDMARD treatment course were lower VAS fatigue upon start of therapy (multivariable Cox regression analysis). Male gender, fewer tender joints and treatment start during the earlier years were only significant factors in univariable regression analyses.

The disease activity decreased significantly during both the first, second and third bDMARD treatment course. The proportion of patients who achieved a clinical response decreased significantly after switching exemplified by a NNT to achieve an ACR20 response during the first and second and third treatment course of 2 and 5 and 6, respectively.

The factors associated with response to the second TNFi were fewer tender joints (for ACR20 and ACR50, EULAR good response), lower HAQ (ACR50, EULAR good response), higher DAS28 (ACR20, ACR50, ACR70, EULAR good response), no use of methotrexate (ACR20, ACR50) and reasons for stopping the previous TNFi (ACR20, ACR50).

Inhibition of the TNFi pathway was until recently the only available mechanism of action (MOA) for biological treatment in PsA. Thus, if a patient failed treatment with the first TNFi, switching to a second became routine care. The availability of therapies with other MOAs (e.g. secukinumab: Interleukin (IL)17A blocker, ustekinumab: IL12/23 inhibition, apremilast: phosphodiesterase 4 inhibition) has further intensified the debate on effective switch patterns in PsA. The subject is to some degree addressed in RCTs where TNFi failures are subsequently treated with e.g ustekinumab, secukinumab or certolizumab pegol. However, no RCTs have systematically addressed switching in PsA, and the main experience still comes from observational studies (reviewed in ).

Our study illustrated that switching in routine care was a frequent event and occurred in nearly 40% of the patients and that switching was mainly due to lack of effect. Lower switch rates have
been found in other countries (South-Sweden 34%, Great Britain 17%, Norway 15%, Spain 5%), perhaps illustrating differences in the availability of bDMARDs across countries. Overall, lack of effect was the most frequent reason for stopping and switching treatment.

Our results that patients benefitted from switching to a second TNFi although effectiveness was attenuated compared to first line was in agreement with other observational studies. Similarly, available guidelines recommend TNFi switching in PsA.

We saw a tendency toward effects of even a third TNFi. There are very limited data regarding switching beyond a second TNFi and available studies include very few patients (<60). Why one TNFi is efficient when another one is not is unclear and might be due to the formation of anti-drug antibodies (ADA) or other drug specific factors overcome by switching. A recent Swedish study recommended that switching to a third TNFi should not be performed due to poor chances of response. The availability of DMARDs with other MOA available during the recent years is likely to change the patterns of switching in routine care.

We were not able to identify uniform predictors of outcome after switching, and the subject has only been addressed in few previous studies which also found lower HAQ and higher DAS28 to be associated with better response. However, it must be concluded that when it comes to predicting effectiveness of TNFi treatment after the first and second treatment course, options are still very limited.

5.2.3. Impact of different infliximab dose regimens on treatment response and treatment retention during the first TNFi treatment course in PsA (Specific aim 3, Paper 3)

This paper was the result of collaboration between Denmark and Iceland and included data from both DANBIO and ICEBIO. In Denmark and Iceland, there are different guidelines on how to dose infliximab: Danish patients are dosed according to body weight whereas Icelandic patients start treatment with 200 mg (corresponding to 3.3 mg per kilo for a person with weight 60 kg) irrespective of body weight followed by dose up-titration if necessary. According to the Remicade summary of products characteristics, the recommended dose for treatment of PsA is 5 mg/kg bodyweight. Since 2012, guidelines from the Danish Council for the Use of Expensive Hospital Medicines became available recommending a similar dose.

The main aims of this paper were to describe the infliximab dose regimens used in routine care in the two countries and to investigate if the lower start doses used in Iceland affected infliximab effectiveness. The Danish patients received higher infliximab doses compared to the Icelandic patients (3.1 mg/kg versus 2.3 mg/kg) and they had lower BMI, higher DAS28 and higher tender joint count at baseline. The Danish patients who received infliximab >5 mg/kg were more frequently women, started treatment during the later years and had higher VAS physician and lower swollen joint count compared to patients starting lower doses.
During a median follow-up time of 550 days, the majority of patients received sustained doses <5 mg/kg (77% Danish patients, 96% Icelandic patients). Retention rate was significantly shorter among Danish than Icelandic patients (1-year: 58% vs. 66%). Treatment retention was shorter among patients who started treatment during the later years or who did not receive concomitant methotrexate (Kaplan-Meier). Baseline infliximab dose did not influence treatment retention when it was included as a categorical variable in Kaplan-Meier or multivariable Cox regression analysis, but as a continuous variable, Danish patients on lower start doses had poorer treatment retention.

After 1 year’s treatment, Danish and Icelandic patients had similar disease activity, and the baseline infliximab dose had no impact on the disease activity. Similarly, 6 month’s response rates (EULAR good response, ACR20, ACR50 and ACR70 response rates) were not associated with infliximab dose (Danish patients, logistic regression analyses) and the response rates were similar in Danish and Icelandic patients.

The paper showed that treatment guidelines regarding recommended infliximab dose were implemented slowly in Denmark. As illustrated in Figure 3 (based on data from DANBIO used in Paper 9 including year 2016), the average start infliximab dose has steadily increased during the years, but in year 2015 the baseline dose was still below the recommended 5 mg/kg. This probably reflects wide use of the initially recommended RA dose regimen of 3 mg/kg for PsA patients.

Figure 3
Average baseline infliximab dose in Danish PsA patients according to start year of treatment. (Data-source: Paper 9 dataset)
The fact that originator infliximab upon marketing had mainly been tested in 5mg/kg doses illustrates the need for observational post-marketing research to investigate the use of other doses in routine care. The use of bDMARDs in lower doses than recommended in the summary of products characteristics may occur as a part of a step-down strategy among patients in clinical remission or may be due to use of low start doses.\textsuperscript{133,134} On the other hand, if a patient has insufficient response to infliximab, the dose per infusion may be increased - or the interval between infusions reduced in order to maximize effect.\textsuperscript{135} Doses as high as 10 mg/kg might be considered in RA.\textsuperscript{136}

Our study indicated that lower infliximab doses were as effective as the higher doses – both within the Danish patient population but also when Danish patients were compared to Icelandic patients. However, confounding by indication is an important issue to consider in the interpretation of the results (see Section 6.2. below). Although we tried to eliminate such potential confounding in the multivariable analyses, it cannot be ruled out that residual confounding affected the results. For instance the start infliximab dose might be influenced by the patients’ disease presentation (e.g. spinal disease favoring higher doses and which could explain low joint counts), or prescription related factors (e.g. calendar year with start of treatment during earlier years favoring lower doses). These factors might have influenced patient characteristics or treatment effectiveness.

Currently, the adjustment of the infliximab dose regimen or the decision to stop treatment due to LOE in Danish routine care is done according to a clinical evaluation. Several studies have demonstrated an association between higher drug levels, lack of ADA and better treatment effect indicating a benefit of therapeutic drug monitoring.\textsuperscript{137,139} Co-medication with csDMARDs seems to reduce the formation of ADA in a dose dependent manner.\textsuperscript{119,140,141} However, the usefulness of measurements of drug levels and ADA in routine care is still debated\textsuperscript{142} and would require a definition of an optimal therapeutic drug concentration and awareness of the complexity of therapeutic drug monitoring.\textsuperscript{143,145} It is also unclear whether higher infliximab induction dose reduces immunogenicity\textsuperscript{141} – an issue of high relevance e.g. considering the low initial doses used in Iceland.

In conclusion, lower infliximab doses and subsequent dose escalation according to response seems feasible in many patients with PsA. The use of lower doses might potentially reduce medication costs for society. However, RCTs addressing different baseline doses, exploring the occurrence and impact of ADA and appropriate therapeutic drug monitoring algorithms are still lacking. Thus, it seems appropriate for the time being to use infliximab according to available guidelines to ensure uniform treatment of all patients across Denmark.
5.2.4. The impact of smoking on baseline disease activity and outcomes during the first TNFi treatment course in PsA (Specific aim 4, Paper 4)

The main baseline demographics for all included patients are summarized in Table 7A. Among the 1388 included patients, 83% had known smoking status. Of these, 33% were current, 41% were never and 26% were previous smokers. Current smokers had shorter disease duration, lower BMI, higher HAQ, higher VAS fatigue and global score compared to never smokers.

Current smokers had poorer treatment retention than never smokers - but only in univariable and not multivariable analysis. In analyses stratified by TNFi type, current smokers had poorer retention for etanercept and infliximab (multivariable Cox regression analysis). Previous smokers who had stopped smoking >4 years ago had similar treatment retention as never smokers.

Reduction in disease activity after 3 and 6 months’ treatment was similar among current and never smokers. Current smokers had poorer EULAR good response rates, ACR20 and ACR50 response rates than never smokers but mainly in univariable analyses. In multivariable analyses results were only significant for EULAR good response among men.

Our study illustrated that smoking was a very common exposure in patients with PsA and that more than half of the TNFi treated patients were either current or previous smokers. A similar number (62%) was found in a recent cross sectional questionnaire-based survey among Swedish patients with PsA (concurrent DMARD treatment was not reported). The Swedish survey found smokers to report worse health status than non-smokers in accordance with our findings. Thus, it seems important to bear in mind that those PsA patients who smoke might have a different disease presentation than non-smokers although the underlying mechanism is unknown.

Several studies have investigated the impact of smoking on TNFi treatment effects in RA, however data are still sparse in PsA where studies are often small, single-center and/or retrospective with only unadjusted analyses. Five observational studies of baseline predictors associated with TNFi effectiveness in PsA reported smoking to be a negative predictor of treatment retention (univariate analyses) or unassociated whereas the impact on smoking on response was either insignificant or not described.

Thus although there is no doubt that smoking is poor for overall health, data on the impact on TNFi treatment effects are vague and mainly apparent in univariable analysis. Furthermore, our study suggests that smoking cessation improves chances of a better treatment outcome since we found previous smokers who stopped treatment >4 years before start of TNFi to have retention rates similar to never smokers.
5.2.5. Treatment response, treatment retention, and predictors thereof during the first TNFi treatment course in patients with AS (Specific aim 5, paper 5)

Upon start of the first TNFi, women had higher subjective measures of disease activity (BASDAI, BASFI, VAS scores) but lower BASMI and CRP compared to men. Concomitant use of methotrexate was more frequent among patients treated with infliximab.

The median TNFi treatment retention was 4.3 years, and the proportions of patients who remained on treatment after one and two years were 74% and 63%, respectively. The main reason for stopping treatment was lack of treatment effect (48% of withdrawals) followed by adverse events (29%). The baseline factors associated with longer retention were male gender, increased CRP (>14 mg/L) and low VAS fatigue.

There was a significant improvement in disease activity after 2 weeks. After 6 months’ treatment, the BASDAI50%/20mm response rate was 63%. No adjustment for withdrawal was done in this analysis. The baseline factors associated with BASDAI50%/20mm response were CRP>14mg/L, lower BASFI and younger age.

When these results were published, only few observational studies on TNFi treatment effects in AS in routine care were available and none of them had studied factors associated with outcome. Several publications have addressed these aspects during the later years (reviewed in 85;154). There is an overall tendency across RCTs and observational studies towards better response among patients characterized by younger age, male gender and higher CRP. Furthermore, HLAB-27 positivity seems to be associated with better response, however this factor was not included in our analyses due to incomplete data in DANBIO at the time of publication.

Similar to PsA, it is debated whether co-medication with methotrexate improves TNFi effectiveness in AS. 80;155 Indeed, use of methotrexate in routine care is highly prevalent (20-41% of TNFi treated patients).5;155-157 One RCT adding MTX to infliximab therapy found negative results, 158 and a Cochrane review based on 3 RCTs concluded that there was no added benefit of MTX in AS. 159 In observational studies some find a positive impact on treatment retention155;156 others find none107;157;160 or even a negative impact of methotrexate co-medication. 161 Confounding by indication is very likely to affect these results – methotrexate might be prescribed more frequently to patients with peripheral arthritis, patients treated with infliximab, or patients with higher disease activity which are all factors potentially linked to outcome. In two recent studies the authors aimed to address this by propensity score adjusted analyses. 155;157 The study by Sepriano et al 157 found no impact of MTX co-medication on treatment retention whereas response rates were not reported. The study by Ciurea et al 155 found improved drug retention among axSpA patients treated with combination therapy, mainly in non-smokers and patients
treated with infliximab, but response rates were similar. The authors included data on TNFi switch patients along with non-switchers, which might have affected the results.

It is a challenge to apply these observational data obtained on a group level to the individual patient level. Nearly half of the patients treated with TNFi in routine care have normal levels of CRP and 20-25% of the patients are women. And although the chance of response is poorer for a woman with normal CRP, some of these patients respond to treatment – similar to the discussion for PsA above. In year 2011, Vastesaeger et al. proposed an algorithm including several predictive factors in one common model based on data from two RCTs in AS.\textsuperscript{120} The authors suggested that in the lack of good alternatives, expert opinion combined with objective markers of inflammation despite attempted treatment with NSAIDs should warrant treatment with TNFi in AS during a defined trial period.

This latter ‘defined trial period’ is perhaps important to bear in mind – that treatment effects should always be re-evaluated after a specific time period and the treatment should be stopped in case of lack of effect. The use of clinical quality registries such as DANBIO provides optimal conditions for the evaluation of treatment effects because the disease activity upon start of treatment is uniformly available. Implementation of this principle may, however, represent a challenge. Thus, according to Paper 9, a substantial fraction (79%) of axSpA patients treated with originator infliximab for median 6 years were not in remission (ASDAS<1.3) when they switched to the biosimilar CT-P13.

In conclusion, there are still no uniform baseline clinical factors that are able to distinguish a future TNFi responder from a non-responder upon start of therapy in AS or in PsA for that matter. It is possible that addition of imaging results (e.g. active inflammation on MRI of SI joints) or specific biomarkers measured in blood in the future might lead to more precise prediction models in the future.\textsuperscript{162-164}

5.2.6. Treatment response, treatment retention, and predictors thereof among AS patients switching to a subsequent bDMARD (Specific aim 6, paper 6)

The main baseline demographics according to switch status are summarized in Table 7B. During follow-up (median 2.4 years (IQR 1.0-4.8)) 32% of patients switched treatment to a second bDMARD, 53% maintained treatment and 29% stopped treatment without starting a new bDMARD. Upon start of the first TNFi, the patients who later switched to a second bDMARD were more frequently women, treated with methotrexate, had shorter disease duration, higher VAS scores, BASFI and BASDAI compared to non-switchers.

The main reason for switching was insufficient treatment response. The treatment retention decreased after switching and the proportion of patients who maintained treatment after 2 years during the first, second and third treatment course was 58%, 47% and 49 % respectively. The factors associated
with longer treatment retention of the second bDMARD were male gender and low BASFI (upon start of the second bDMARD, multivariable Cox regression analysis) whereas treatment with adalimumab and previous treatment with infliximab were significant factors in univariable regression analyses.

The disease activity decreased significantly during both the first, second and third bDMARD treatment course. However, fewer patients achieved a clinical response after switching, and the NNT to achieve a BASDAI50%/20mm response during the first and second and third treatment course was 2 and 3 and 4, respectively.

The factors associated with BASDAI50%/20mm response during the second TNFi treatment course were higher CRP, lower VAS fatigue and lower BASFI (upon start of the second TNFi).

Our study illustrates that switching occurs in nearly 1 of 3 TNFi treated patients in routine care, which is largely similar to the results from other countries.127,165-167 TNFi’s are still the main MOA for bDMARD treatment in axSpA although secukinumab, an IL17A inhibitor, was recently marketed.168,169 Experience on switching mainly stem from observational studies. These studies have often been retrospective or minor with inclusion of <200 switchers.127,165-167,170-172 It is however agreed across these studies, than whenever treatment with the first TNFi fails in AS – which most often occurs due to lack of effect, switching to a second TNFi should be recommended regardless of the reason for withdrawal of the first (reviewed in 173).

A phase 3 study, Rhapsody, studied treatment with adalimumab among patients who were either bDMARD naïve or had failed treatment with infliximab, etanercept or both.174 The study found that patients were more likely to achieve response if they were biologics naïve or if they had failed the previous TNFi treatment due to secondary lack of effect (and not primary lack of effect). Regarding switching, it seemed more effective to switch infliximab -> adalimumab compared to etanercept ->adalimumab.174 Only few studies have been powered to compare differences in baseline characteristics among switchers versus non-switchers. In a Spanish study including 131 switch patients with mixed spondylopathies, switching occurred mainly among women and patients with higher VAS scores167 – similar to the results found in our study. In a Korean study, 70 switchers more frequently had ankylosis of the SI –joints and were less frequently treated with adalimumab.165

The predictors of treatment effects of the second TNFi treatment course have only been investigated in few studies.170,175,176 It has been speculated that if a patient stops treatment with a TNFi due to secondary LOE this indicates TNFi driven disease. Thus, beneficial effects of a second TNFi should be expected as discussed in the Rhapsody trial.174,176 DANBIO data do not allow a distinction between primary and secondary lack of effect, and several other observational studies have not included these data either.127,171,177 In a recent Swiss study, the authors perceived stop after >6 months due to LOE to be
indicative of secondary LOE. The 12-months ASDAS response after switching among these patients were significantly higher than among patients who had failed the previous TNFi treatment course due to primary LOE. The authors included patients with axSpA according to the ASAS criteria. Patients who stopped due to primary LOE were more often HLAB-27 negative, had normal CRP and did not have radiographic axSpA. This could indicate potential misclassification that might have affected the results.

In conclusion, the current knowledge regarding bDMARD switching is widely similar for axSpA and PsA. As discussed for Paper 2 above, switching is a very frequent event in routine care, but little is still known regarding the most effective TNFi switch patterns and when to switch to a bDMARD with another MOA. The second TNFi treatment course is effective, although not as effective as the first, but no uniform predictive factors exist regarding effectiveness after switching. The reason for stopping the previous TNFi may be of relevance. Among switchers, it may be important to apply predefined schedules for re-evaluation of treatment effects – just as it was discussed for the first bDMARD treatment course above. It must be kept in mind that some patients have e.g. concomitant fibromyalgia, irreversible damage or other comorbid disease causing pain, which is not modifiable to bDMARD treatment.

5.2.7. The impact of smoking on baseline disease activity and outcomes during the first TNFi treatment course in patients with AS (Specific aim 7, paper 7)

The main baseline demographics for all included patients are summarized in Table 7B. Among the 1576 patients, 90% had known smoking status. Among these, 43% were current, 41% were never and 16% were previous smokers. Current smokers were more frequently male, had longer disease duration and had higher BAS scores compared to never smokers.

Current smokers had poorer treatment retention than never smokers both overall and stratified according to gender and TNFi type. Previous smokers who had stopped smoking ≥6 years ago had similar treatment retention as never smokers.

The decline in disease activity after 3 months’ treatment was smaller among current smokers. Current smokers had poorer BASDAI50%/20mm response rates after 6 months than never smokers.

These results mimic those seen for TNFi treated PsA patients: that smoking is common in these patient groups and that smoking is associated with poorer outcomes i.e. higher disease activity at start of therapy, poorer response rates and shorter treatment retention. Interestingly, a similar trend is seen among previous smokers, mainly if smoking cessation occurs in the recent years, indicating a time-dependent positive impact of smoking cessation.
Although some studies fail to demonstrate any negative impact of smoking, the common knowledge across studies in axSpA is that smokers have earlier disease onset, higher disease activity, increased radiographic progression and poorer treatment outcomes.

Among the studies that have investigated how smoking influences TNFi treatment outcomes, an observational study performed in the Swiss SCQM registry demonstrated similar negative impact of current smoking among 698 patients with axSpA, especially in patients with elevated CRP at baseline. The authors found no negative impact of previous smoking, however information regarding years since smoking cessation was not available. A recent study by the same main authors demonstrated that current smoking ameliorated the effect of csDMARD co-medication on TNFi retention rates. This illustrates the importance of including smoking status as a potential confounder in multivariable analyses, as it seems to interact with other covariates.

The causality between smoking and outcomes remains to be established. Apart from any impact on biochemical and inflammatory markers, smoking status is associated to potential confounders such as more comorbidities, depression, decreased physical activity, lower educational level and socioeconomic status. It has been argued that mechanical stress and blue-collar work/occupational activity might be the true causative factor whereas smoking is the confounder of such a relationship.

In conclusion, our study supports the growing evidence of a negative impact of smoking in AS. It also stresses the importance of including smoking status in observational study research – further methodological considerations are discussed below. It is obvious that smoking cessation must be recommended to patients consulting their rheumatologist for health beneficial reasons, but the exact relationship between smoking cessation and reversion of the negative smoking effects remains to be established.

5.2.8. The impact of axSpA sub-diagnosis (AS versus non-radiographic axial SpA (nr-axSpA)) on treatment response and treatment retention during the first TNFi treatment course in patients with AxSpA (Specific aim 8, paper 8)

The main baseline demographics for all included patients are summarized in Table 7B. Among 1250 included patients, 29% had nr-axSpA, 50% had AS and 21% lacked X-rays of the sacroiliac joints at the start of the first TNFi. In the paper, patients with lacking X-rays were defined as having ‘unspecified axSpA’ because the exact sub-diagnosis could not be established.

Patients with nr-axSpA were more frequently women, HLA-B27 negative, had shorter disease duration, higher VAS scores and BASDAI, but lower CRP and BASMI than patients with AS. Patients with nr-axSpA had shorter TNFi treatment duration but only in univariable and multivariable analyses. Response
rates (after 3-6 months) and changes in disease activity (after 3 months) were similar in AS and nr-axSpA. Patients that were HLA-B27 positive had longer treatment retention and better response rates compared to HLA-B27 negative, both overall and stratified by axSpA sub-diagnosis.

HLA-B27 status was available in DANBIO for 84% of the patients. As shown in Figure 4, more HLA-B27 negative patients started TNFi treatment during the later years. The same tendency was seen across sub-diagnoses (not shown). This might be due to a higher emphasis on radiographic imaging and MRI’s during the later years. Thus, it should be kept in mind that the positive impact of HLA-B27 on treatment outcomes at least in part may be due to changes in the case mix over time.

Figure 4
HLA-B27 status among axSpA patients in Paper 8 according to start year of first TNFi. N=1250

![Figure 4](image)

Figure 5A shows the number of patients who started the first TNFi treatment course stratified by diagnosis in DANBIO (AS or nr-axSpA, raw data from DANBIO with no further validation) between year 2000 and 2016. Figure 5B shows the number of patients starting their first TNFi treatment per year according to sub-diagnosis including unclassified patients (lack of radiographic imaging). Please notice that Figure 5A only includes the subgroup of axSpA patients where data have been validated by the local departments of rheumatology (=patients included in Paper 8), and this is also the reason why only data between year 2005 and 2013 are shown. Two points can be made: 1) A substantial number of patients had unspecified ax-SpA due to lacking radiographic imaging of SI joints upon start of TNFi treatment, and the number increased during the later years. This illustrates that MRI is increasingly preferred as the...
diagnostic imaging procedure instead of X-rays in routine care, 2) The overall number of patients with nr-axSpA increased during the period whereas the number of TNFi treated AS patients remained stable.

**Figure 5A**
Annual number of patients starting first TNFi treatment stratified by diagnosis in DANBIO (AS: ICD-10 code M45.9. Nr-axSpA: M46.1, M46.8+M02.9, M46.8+M07.4/M07.5, M46.9).
(Data-source: Updated DANBIO dataset, May 2017)

**Figure 5B**
Annual number of patients starting first TNFi treatment stratified by sub-diagnosis.
(Data-source: Paper 8 dataset)
According to the data presented in Paper 8, there seems to be a time trend towards more patients having nr-axSpA upon start of TNFi treatment. Furthermore, imaging in the form of MRI rather than X-rays is being used for disease classification. This strategy is not in accordance with Danish guidelines, where MRI is recommended as the primary imaging procedure but should be followed by X-rays in cases with positive MRI findings – especially among patients >30 years old. X-rays should be used for classification purposes (AS versus nr-axSpA), but also to correctly rule out differential diagnoses (degenerative disease etc). X-rays could be the primary imaging modality in patients with long standing disease and clinical suspicion of AS. Therefore, there is a potential risk that some patients were incorrectly diagnosed as having nr-axSpA due to lacking X-rays.

It is debated how the ASAS classification criteria should be applied in routine care. Indeed, it is difficult to distinguish between AS versus nr-axSpA due to the challenge of correct interpretation of radiographs and MRIs - and misclassification of radiographs may occur in 20-40% of cases. TNFi’s were initially marketed to treat AS, but have in RCTs been shown to be effective in nr-axSpA as well. However, in USA, TNFi treatment is only recommended in AS and not nr-axSpA according to guidelines from the US Food and Drug Administration (FDA). Similarly, in Denmark, physiotherapy free of charge is only available in AS and not nr-axSpA. For these reasons, classification into AS or nr-axSpA has a major impact for individual patients in some countries. On the other hand, several studies have similarly to our findings shown that patients with nr-axSpA have pain and disability levels similar to patients with AS and that the two patient groups respond equally well to treatment. Recent ACR guidelines suggest that patients with nr-axSpA should be treated with TNFi if they are nonresponsive to NSAIDs and particularly in case of sacroiliitis with bone marrow oedema on MRI and/or elevated CRP. It should also be kept in mind that the ASAS criteria have been developed for classification and not for routine care diagnostic purposes, thus the criteria should always be accompanied by an expert opinion of the rheumatologist including the patient’s symptoms and relevant test results.

In conclusion, the therapeutic and practical implications of a sub-classification within the axial spondyloarthritis disease spectrum in routine care are a matter of debate. It is undoubtedly a challenge to interpret and use treatment guidelines and radiographic findings in routine care. HLA-B27 positivity seems to be an important factor associated with TNFi treatment outcomes.

5.2.9. The impact of switch from originator to biosimilar infliximab on disease activity and one-year treatment retention (Specific aim 9, paper 9)

This paper included 802 patients treated with originator infliximab who switched to the biosimilar drug CT-P13 according to a national Danish treatment guideline that dictated a non-medical switch for economic
reasons. Thus at the time of marketing, biosimilar infliximab costed less than half the price of the originator. The baseline patient demographics are shown in Table 7A and 7B for PsA and axSpA, respectively. For details regarding the sub-group of patients with RA, please see Paper 9. At time of the switch, the previous treatment duration of originator infliximab was >6 years. This is also reflected in the baseline disease activities shown in Tables 7A and B, which were markedly lower than in the other papers illustrating that a large proportion of the patients was in remission at the time of the switch.

Three-months’ disease activity and flare rates were largely unaffected by the switch. The one-year crude retention rate of CT-P13 of 84% was not statistically different from that of originator infliximab in a comparison cohort, and just reached statistical significance in adjusted analysis. The withdrawal rates were similar across diagnoses.

Among the 16% of patients who withdrew from CT-P13 treatment during one year follow-up, withdrawal was mainly due to lack of effect or adverse events. Higher VAS patient global and higher DAS28 (among RA patients) was associated with withdrawal. This illustrated that outcomes might not only be attributable to the drug per se – but might also be due to poor disease control or due to the so called ‘nocebo’ effect. Thus, it has been demonstrated that negative anticipations toward a drug e.g. due to lower price or that it is a generic substitution of the originator drug might facilitate a negative outcome. Due to the observational setting and the non-blinded study design, it was not possible to explore these issues further.

In Denmark, all patients treated with originator infliximab was switched to the biosimilar drug in accordance with the national guideline. This increases the generalizability of the results and minimizes confounding by indication - compared to a situation where only a subgroup was switched. Only few studies have previously explored non-medical infliximab switching. The NOR-Switch RCT was performed in patients with inflammatory diseases, mainly inflammatory bowel disease, but 198 patients had arthritis. In this RCT, long term infliximab treated patients in routine care were switched from the originator to the biosimilar and main outcome was disease worsening within 52 weeks’ treatment. The study was designed as a non-inferiority trial, and the authors found that the flare rate was higher in the biosimilar vs. originator group (26.2 vs. 29.6) but was within the non-inferiority margin. The main conclusion was that treatment with CT-P13 was not inferior to the originator, which is in agreement with our results. Below in Section 7.3.1 regarding future perspectives, biosimilars are discussed in more detail.
6. Methodological considerations

The 9 studies presented in this thesis were all based on observational data from the DANBIO registry. As discussed in the introduction, the use of observational data has methodological challenges that must be considered in the interpretation of data. In the following, some general methodological aspects are discussed including how missing data and misclassification was handled in the studies.

6.1. Data quality and interpretation

6.1.1. Missing data

In all research there is a risk of missing data. In longitudinal observational studies and biologics registries, data are collected as part of routine care and missing data is an inherent challenge. Data may or may not be missing at random. In some cases it is easy to detect that data are incomplete (e.g. lacking registration of diagnosis or of baseline disease activity in a patient followed in the registry) whereas in other cases it is impossible to detect without additional sources of information (e.g. lacking inclusion of patients in the registry, or lacking registration of concomitant use of a csDMARD in bDMARD treated patients - which must be validated from e.g. hospital files).

Data missing at random cause lack of power as some patients or variables are excluded from the statistical analysis. On the other hand, data that are missing not at random give a risk of selection bias. An example of the latter is incomplete data during follow-up caused by early treatment withdrawal due to lack of treatment effect or adverse events – or if patients systematically are included/excluded in DANBIO according to their disease status or disease activity (e.g. only the ill patients are monitored).

Several efforts have been made to reduce missing data in DANBIO. In routine care, audits are performed yearly in order to ensure a continuously high registration percentage, and it has previously been shown that >90% of bDMARD treated patients are registered in DANBIO. This is important in order to ensure generalizability of the results. In the early years, a new bDMARD could be prescribed in DANBIO without necessarily stopping the previous bDMARD therapy, but during the later years this was prevented by the software thus facilitating fewer prescription errors in the system. Furthermore, in all papers an effort was made to enrich the data in DANBIO (e.g. CRP levels, concomitant use of csDMARDs) and to validate the registrations (treatment regimen, start and stop dates of bDMARD therapy, see methods Section 4.2.) based on co-authors’ access to the patient files. Thus, the Danish departments of rheumatology were invited to participate and to validate the registrations in DANBIO before data analysis. As is shown in Table 2, many departments participated and contributed to more complete data.

Missing data may also be handled in the data analysis phase. In case of incomplete registration of disease activity upon start of bDMARD therapy, outcome measures regarding relative
changes in disease activity are not calculable. This results in loss of statistical power. In order to address this, larger time intervals were applied for the baseline visit in the later publications. As shown in Figure 7, approximately 85% of patients had available data if the time window for the baseline visit was defined as 60 days before until 5 days after start of therapy. The fact that more patients during the later years had a baseline visit 6-30 days before start of TNFi (year 2011-16 in Figure 7) might illustrate a lag time between the documentation of the disease status by the doctor preceding the decision to start biological treatment versus date of the first given dose.

In Paper 9, patients with long-lasting infliximab treatment (5-7 years) were included. These patients were followed with less frequent visits in DANBIO (according to the guideline to monitor patients in stable bDMARD treatment with ≥1 visit per year). We did several efforts to minimize missing data 1) As the patients were expected to have stable disease status a larger time interval of 120 days before until 6 days after switch to biosimilar infliximab was applied for the baseline visit, 2) overlapping time intervals
pre-baseline were applied in order to ensure flexibility in the selection of data for a specific time interval (data were only used once), 3) missing follow-up data upon the 3 months’ pre/post switch time intervals were imputed from the 6 months intervals.

Patients withdrawn from therapy pose a problem in the analysis of treatment outcomes: patients who stop treatment early do not provide data regarding follow-up disease activity and may thus cause an overestimation of treatment effects. This was addressed by considering a patient who stopped therapy within the first three months as a non-responder (non responder imputation, Paper 3, 4, 7, 8, 9). Another possibility would have been to apply the Lundex correction where the estimates of treatment effects are adjusted for the proportion of patients withdrawn.212

The numbers of patients/observations that were available for each variable of interest were more rigorously reported in the later publications in order to comply with the STROBE guidelines.213,214 In paper 8 we furthermore applied supplementary statistical methods (multiple imputation of missing data) to test the robustness of the results. Furthermore, patients with unspecific axSpA (and lacking x-rays of the SI joints) were included as either AS or nr-axSpA in the statistical tests.

Thus, several efforts are done prospectively and retrospectively in order to achieve as high data completes in DANBIO as possible in routine care as well as for research purposes. In the analytical phase and during the reporting of data, transparency regarding missing data and how these were handled increases the credibility of results.

6.1.2. Misclassification
In all publications, diagnoses were according to the treating physician and misclassification cannot be ruled out. Furthermore, 21% of patients with axSpA in paper 8 had no available X-rays of the SI-joints upon start of TNFi therapy. Thus, it was not possible to conclude whether these patients fulfilled the classification criteria for AS or not. If patients with nr-axSpA were included in the AS group this might potentially have affected the results of Paper 5-7.

Another potential misclassification error is use/no use of concomitant csDMARDs (including prednisolone, tablets and intraarticular injections). Lacking information on prednisolone use might explain why a small part of the patient group had low disease activity upon start of bDMARDs. The participating departments of rheumatology were asked to validate data regarding concomitant use of csDMARDs in order to minimize such misclassification.

6.1.3. Outcome data
In all papers outcome measures were reported for certain time points as both 1) relative improvements compared to baseline (PsA: ACR20/50/70, EULAR good response, axSpA: BASDAI50%/20mm response,
ASAS40, ASDAS clinically important improvement) and 2) the current disease state (PsA: DAS28 remission. AxSpA: BASDAI<40mm, ASAS remission, ASDAS inactive disease) and disability (HAQ). Patients with high disease activity upon start of treatment have a higher chance of a relative improvement without necessarily having experienced a satisfactory end point. It is therefore beneficial to use the outcome measures in combination.

In DANBIO, DAS28 is frequently used as an outcome measure in PsA and only a minority of patients has available 66/68-joint counts. Due to the fact that the DAS28 score does not include the distal interphalangeal joints of the hand and feet it is ‘easier’ to achieve a low disease state. Thus, it has been demonstrated that use of the DAS28 in PsA results in higher response rates compared to other response measures e.g. minimal disease activity and other definitions of remission. Furthermore, enthesitis, dactylitis and skin involvement are important disease domains not captured through routine care use of DANBIO.

During the last decade, introduction of more sensitive CRP analyses has occurred stepwise in several departments. Details regarding the analytical method are not registered in DANBIO but might potentially have an impact on results. In all papers, a CRP value <10mg/L was interpreted as being within the normal range. If the CRP level was included as a continuous variable in a statistical analysis, it is of importance if a value of CRP ≤5 mg/l (the detection limit in many laboratories) was interpreted as ‘5 mg/L’ or ‘0 mg/L’. In publication 1, 5, 8, baseline CRP levels were included in the multivariable statistical models as a categorical value to address that it might be more important to consider above/below a certain threshold instead of expecting a linear effect.

### 6.2. Confounders included in multivariable analyses

As mentioned in the introduction Section 3.2., one of the risks in observational studies is the inclusion of a heterogeneous mix of patients and an uneven distribution of confounders across treatment groups. A confounder may be defined as an extraneous variable that wholly or partially accounts for the observed effect of a risk factor on outcomes. Presence of confounders may cause incorrect assessment of the relationship between exposure (here: treatment with bDMARDs) and outcomes (treatment effectiveness).

This may be exemplified by confounding by indication where e.g. concomitant use of csDMARDs or baseline dose of bDMARD may be linked to specific disease characteristics which again may be potentially linked to outcomes. For instance, concomitant use of csDMARD (methotrexate) may be associated with TNFi drug type (higher methotrexate use among patients treated with infliximab) or may be associated with certain disease characteristics (peripheral arthritis in axSpA). Similarly, a higher baseline
dose of infliximab could be linked to disease presentation (axial symptoms in axSpA thereby facilitating 5mg/kg bodyweight) or start year of treatment (higher doses in PsA and axSpA used during the later years due to national guidelines recommending use of 5 mg/kg). Confounding may be addressed by multivariable confounder adjusted analyses, but still the risk of residual confounding exists.\textsuperscript{80}

As shown in Table 6A and 6B, the variables included in the multivariable models varied across papers. In the methods’ sections of the respective papers, the confounders included in the multivariable regression models are discussed. In general, when several factors were closely intercorrelated only one was included in the model (e.g. VAS scores). In the papers where the impact of a specific factor on outcomes was investigated (smoking in paper 4 and 7, axSpA sub-diagnosis in paper 8), it was important to thoroughly consider which variables should be included in the multivariable analyses as potential confounders due to the risk of over-correction. Thus, if smokers for instance were more frequently men and gender was included in the statistical model together with smoking, a potential effect of smoking might be overlooked. We found patients to have clinically important differences in disease activity at baseline according to the variables we were looking at (smoking status in paper 4 and 7, axSpA sub-diagnosis in paper 8). Thus in paper 4 and 7, we rendered measures of disease activity (DAS28 etc.) to be intermediate factors that were hence not included in the multivariable model. In paper 8, BASDAI was included in the multivariable model due to the consideration that it is important to correct for this variable because higher BASDAI at baseline increased the chance of a relative improvement.\textsuperscript{215}

In the following, examples of specific confounders included (or not included) in the 9 papers are discussed.

\textbf{Start year of TNFi treatment:} As shown in paper 3, year of starting treatment was strongly associated with treatment retention rates. In paper 3, start year was considered an intermediate variable (part of the causal pathway between exposure and outcome) and hence not included in multivariable analyses. In the earlier papers (no. 1, 5, 6), start year of treatment was not included in the multivariable model and this may have affected the results. Similarly, other previous studies within the subject have not included calendar year.\textsuperscript{160,216,217}

The impact of calendar year on outcomes may be due to changes in the treatment paradigm of the rheumatic diseases.\textsuperscript{218} During the later years, early and aggressive medical treatment with treat to target strategies and adherence to international treatment algorithms\textsuperscript{68,69} has resulted in increased anti-rheumatic drug use,\textsuperscript{219,220} start of bDMARDS earlier in the disease course\textsuperscript{221} and more frequent switching.\textsuperscript{219,222} In other words, the perception of disease activity (and when it is considered intolerable) has changed over the years.\textsuperscript{82} This is illustrated in Figure 8A and Figure 8B which show the disease activity in DANBIO upon start of the first TNFi (exemplified with DAS28 in PsA and BASMI in axSpA). According to
**Figure 8A**  
First TNFi treatment course in PsA, baseline DAS28 by year of treatment start.  
Boxplot showing median, interquartile ranges, and 5 and 95% percentiles.  
Data censored in May 2017

![Boxplot of DAS28 by year of treatment start.](image1)

**Figure 8B**  
First TNFi treatment course in AxSpA. Baseline BASMI by treatment start year.  
Boxplot showing median, interquartile ranges, and 5 and 95% percentiles  
Data censored in May 2017

![Boxplot of BASMI by year of treatment start.](image2)
the figures, disease activity tended to be lower during recent years compared to former years. This is in accordance with findings by others.220

Smoking: As shown in paper 4 and 7, current smokers had poorer outcomes. However smoking status was not included as a potential confounder in paper 1, 2, 3, 5, 6 due to limited data regarding smoking status in DANBIO during the earlier years.

Diagnosis (nr-axSpa versus AS): During the later years, the disease spectrum of axial spondyloarthritis has changed and an increasing number of patients has been diagnosed according to the ASAS classification criteria (see section 5.2.8 above). These criteria include patients with nr-axSpA who does not fulfill the modified New York criteria for AS (see introduction Section 3.1.3.). In paper 8, we found patients with nr-axSpa versus AS to differ in baseline disease activity and also to some degree in treatment outcomes. Any erroneous classification of patients with nr-axSpA as having AS in the publications 5, 6, 7 might potentially have affected the results.

HLA-B27: As shown in paper 8, HLA-B27 positivity was strongly associated with better outcomes in both AS and nr-axSpA. HLA-B27 was not included as a potential confounder in paper 5, 6, 7 due to limited data.

Comorbidities: As mentioned in the introduction, information regarding comorbidities are not routinely available in DANBIO. However, through cross linkage by social security numbers to national patient registries, diagnosis from in-hospital and out-patient care may be identified (ICD-10 codes). According to paper 9, approximately 20% of the infliximab treated patients had at least one comorbidity. Furthermore, there was a tendency towards poorer treatment retention after switch from originator to biosimilar infliximab among patients with more comorbidities. Thus, the lack of correction for comorbidities in the former publications might have affected the results.82,97,223 There is also the possibility that patients with comorbid disease are prescribed other bDMARDs or are monitored more tightly – which might affect the outcomes.

In conclusion, it is sometimes difficult to decide whether a specific factor is a confounder or an intermediate factor. There is no ultimate right and wrong in how data are analysed but careful consideration is needed and additional sensitivity analyses might explore the robustness of the data. Furthermore, when the study results are compared to those of other cohorts, it is important to consider methodological issues and how potential confounders were adjusted for.

A variety of other potential confounders would have been of relevance but are not routinely available in DANBIO. Examples include concomitant use of NSAIDs in axSpA224,225, disease phenotype in PsA (e.g. axial disease) and axSpA (peripheral joint involvement),160 socioeconomic status and the presence of fibromyalgia.179,180
6.3. Other methodological considerations

In all publications the baseline variables potentially associated to outcomes were included in the statistical model (e.g. disease activity). However, in order to evaluate in details how a specific factor correlates to outcome, it might be of relevance to include the covariates as time-varying variables. For instance, covariates such as DAS28 or ASDAS change dynamically during treatment and this might influence the results. On the other hand, when we wish to identify factors associated to outcomes even before the treatment starts, it seems of higher relevance to include only the baseline value.
7. Discussion of future perspectives

Prospectively collected data regarding bDMARD treated patients in routine care provides a unique possibility to explore research questions that are difficult to address in RCTs e.g. rare outcomes, rare exposures or patient groups not routinely included in randomized trials. In the following paragraphs, aspects regarding the future perspectives for biologics registries including DANBIO for research within bDMARD treatment effectiveness are discussed.

7.1. Data enrichment

DANBIO contains extensive data on patient demographics, treatment and treatment outcomes. For research purposes, these data may be enriched by additional information regarding the patient’s history or outcomes identified through external sources i.e. other registries. The papers included in this thesis present results that are mainly based on data from DANBIO. However, paper 9 includes data on number of previous comorbidities identified in the National Patient Registry (NPR=Landspatientregisteret).99;100

Comorbidities have been demonstrated to have an impact on disease activity and bDMARD treatment duration in PsA,226 and comorbidities (e.g. previous cancers) may influence bDMARD prescription patterns.227 Therefore, it may be of importance to include comorbidity as a potential confounder in multivariable analyses of treatment effectiveness and safety.228;229 It is possible for patients to enter information on comorbid disease history in DANBIO by the touch screens in the waiting area.94 However, these data are currently not uniformly available. Thus, another method to obtain information regarding comorbidities is through linkage by social security numbers to NPR. NPR contains data on previous hospital contacts (hospitalizations and outpatient care) coded according to the international classification of diseases (IC-8, ICD-10 from 1994 onward) including date of admission and discharge, type of admission, chemotherapy and surgical procedures.100

NPR may, according to the scientific question, also provide information regarding the outcome of interest e.g. rare safety signals.230-233 Upon marketing, a drug has only been tested in a limited number of highly selected patients during the trial phase. Thus, rare safety events may not be detected until post marketing. Although adverse events may be reported by the health care personnel or the patients themselves (in Denmark by www.laegemiddlestyrelsen.dk), underreporting is likely to occur. Through linkage to national registries it is possible to link exposure (treatment) to adverse outcome (hospital contact/ambulatory care).

Apart from the NPR, information from other Danish national registries may also be retrieved through linkage. The Danish Prescription database contains information on prescribed drugs including package size, drug name, indication for use and dosing schedule.234 The civil registration system includes
civil status, place of residence and vital status, IDA (Integrerede Database for Arbejdsmarkedsforskning) information regarding education, occupation, sick leave and disability compensation (1980-), and DREAM contains occupational and socio-economic data (1991-).

Several publications have already explored research questions regarding bDMARD safety, bDMARD effectiveness, rare outcomes and socioeconomics taking advantage of this methodology where detailed information from biologic registries is linked to national registries. These publications often originate from Scandinavian countries - which apart from a similar tradition of biologic registries share the opportunity of data linkage. The majority of publications have been within RA. In the coming years, research within PsA and axSpA will be a valuable supplement to knowledge from randomized clinical trials and for post marketing pharmcovigilance.

7.2. Collaboration across countries

Collaboration across countries may increase statistical power to answer scientific questions regarding rare outcomes, rare exposures or treatment strategies. A classic example of a rare outcome is cancer risk during bDMARD treatment. Furthermore, collaboration may provide knowledge regarding bDMARD prescription patterns – which has an interest in its own right, but is also of relevance in order to evaluate heterogeneity between treated patients in different countries.

Different prescription patterns across countries may occur for several reasons. Although there are international guidelines regarding treatment strategies, these may be overruled by national guidelines. In Denmark, The Danish Society of Rheumatology (Dansk Reumatologisk Selskab) has issued guidelines regarding the diagnosis and treatment strategies whereas The Council for use of expensive Drugs (RADS) (now: Medicinerrådet) has published instructions on first line bDMARD drug and subsequent drug choice after failure. Examples of different treatment strategies according to national guidelines are:

1) use of biosimilars including non-medical switching as discussed below
2) in some countries patients with nr-axSpA are obliged to have elevated CRP or signs of active inflammation on MRI in order to be candidates for treatment with bDMARDs,
3) differences in infliximab start dose and step up strategy exemplified by Denmark versus Iceland as discussed in Paper 3.

Across European countries there are huge inequities in access to bDMARD treatment due to unaffordability in lower income countries. This results in differences in the baseline disease activity and patient characteristics upon treatment initiation - which might affect the generalizability of the results. Patients from high availability bDMARD areas potentially have other treatment outcomes than patients from low availability areas. Lower disease activity and less structural damage upon treatment initiation might facilitate better outcomes (=window of opportunity). Previous studies in RA have indicated
higher response rates if treatment is initiated early in the disease course\textsuperscript{218,242} whereas the concept is less acknowledged in PsA and axSpA.\textsuperscript{243-245}

Denmark along with the other Nordic countries have high access to bDMARDs, and treatment is fully reimbursed and provided free of charge to the patient.\textsuperscript{73} However, even in these similar countries there are differences in patient demographics and baseline disease activity upon start of bDMARD treatment illustrating different treatment strategies and availability of treatment.\textsuperscript{246}

This heterogeneity across countries provides opportunities and challenges. Differences in access to treatment, baseline disease activity, prescription pattern, use of biosimilars etc. may be an opportunity for research that explores the impact of these differences – but on the other hand illustrates that pooling of data across countries should be done with caution. A proper statistical approach depending on the data at hand and the scientific question is important.\textsuperscript{87} The impact of these differences should be explored by collaboration during the data-analysis phase – and not only by comparing the published response rates across papers. Initiatives within the Scandinavian and European countries are on the way regarding PsA and axSpA.\textsuperscript{247-249}

7.3. Important research questions for future registry research

7.3.1. The biosimilar drugs
The marketing of the cheaper biosimilar drugs is expected to have a major impact on access to bDMARDs – especially in countries with low availability of biologic treatment.\textsuperscript{66,73,240,250} The biosimilars have already affected the prescription and switch patterns in many countries. Denmark, Norway and Holland are among countries where large numbers of patients in remission on treatment with the originator drug have been switched to the biosimilar.\textsuperscript{251,252} In Sweden, for instance, the uptake of the biosimilars has been much slower.\textsuperscript{205,247} By 2017 in Denmark, two rounds of non-medical switching had occurred namely upon marketing of biosimilar infliximab (CT-P13)\textsuperscript{9} and etanercept (SB4).\textsuperscript{253} Several hundred biosimilars are expected in the coming years,\textsuperscript{66} and it will be of interest to explore how the availability of cheaper bDMARDs affect prescription patterns and if a tendency towards earlier prescription of bDMARDs in the disease course is seen. This is a question that may be addressed by use of observational registry data.

The biosimilars are required to have comparable safety and efficacy and similar immunogenicity compared to the originator drug. This must be demonstrated in a pharmacokinetic and – dynamic study performed in humans and ≥1 RCT before approval by the regulatory authorities.\textsuperscript{66} It has been argued that the risk of adverse events of the biosimilar is similar to the risk associated with the small changes that have occurred during the years of the manufacturing of the originator drug.\textsuperscript{254} However, even minor differences in the formulation, purity or packaging of a drug may potentially affect the
immunogenicity and the formation of ADA resulting in lower drug concentrations and poorer long-term efficacy and safety. Although the RCTs have found no relevant differences in the immunogenicity profiles, it might be speculated if the same results would be found in patients treated in routine care (higher age, comorbidity, co-medication). Upon marketing, the biosimilars have often only been tested in few indications – for CT-P13 in axSpA and RA. However, in routine care extrapolation across diagnoses is often performed and the biosimilars are used in e.g. PsA and inflammatory bowel disease. This may theoretically be of importance since age, genetics, co-medication with csDMARDs and drug dose differ across diseases and as these are all factors that might affect immunogenicity. This stresses the importance of prospective follow-up of patients treated with biosimilars in clinical registries such as DANBIO.

Previous RCTs and observational studies have only investigated single-way transition from originator to biosimilar (= one switch episode). In the future, multiple switches may be seen in the same patient due to cheaper biosimilars/bDMARDs continuously becoming available. This will pose a challenge to the monitoring of pharmacovigilance - but must however be addressed by real world observational clinical data as this type of drug interchangeability is difficult to assess in RCT studies.

7.3.2. Treatment strategy, switching and prediction of response

As discussed for Paper 2 and 6 above, bDMARD treatment failure followed by switching to another bDMARD occurs often in routine care. However, little is known regarding the most effective switch patterns. More and more treatments are becoming available and the switching patterns are becoming increasingly complex. Until recently, TNFi were the only mode of action for biological treatment in PsA and AS. However, the introduction of IL17A and IL12/IL23 inhibitors has further raised the need to explore optimal treatment strategies and when to switch to a bDMARD with other mode of action.

Currently, secukinumab is not recommended as first line treatment in Denmark, and only few patients have received treatment with the drug. In Sweden the prescription rate is higher – but mainly as second line treatment. In the placebo controlled RCT MEASURE 2, secukinumab treatment was given to AS patients with active disease despite treatment with NSAIDs. In a subgroup analysis, efficacy was investigated among patients with previous TNFi failure. Response rates were lower than in TNFi naïve patients, but still significant and sustained clinical response was observed. The study was not powered to subgroup according to reasons for failure of previous TNFi or by bDMARD treatment number. Issues regarding effectiveness of various switch strategies may be addressed through observational registry data. Collaboration across registries as discussed above will improve power and enable earlier post-marketing studies of newly introduced drugs.
The concept of tailored or personalized medicine has become increasingly acknowledged within treatment of certain diseases e.g. cancer— and a similar concept seem appealing within inflammatory rheumatic diseases. To predict bDMARD treatment effectiveness in routine care based on clinical and simple biochemical measures has been attempted within RA.\textsuperscript{261,262} In the future, it is possible that more advanced prediction models aiming at personalized medicine will include biomarker analyses, imaging results (MRI, ultrasound), etc.\textsuperscript{263} The Danish Rheumatologic Biobank was established in year 2015 and is funded by the Danish Regions and the Danish Rheumatism Association. The Biobank provides an infrastructure for nationwide collection of biologic material for research of diagnostic, predictive and prognostic biomarkers within inflammatory arthritis.\textsuperscript{264,265} In parallel to the collection of biologic material (mainly blood samples), high quality clinical data are registered in DANBIO. Standardized operating procedures ensure that the material is of high quality - this provides optimal conditions for collaboration across different departments. Currently, >2000 samples are collected each year in Danish patients with inflammatory arthritis. Hopefully, the prospectively collected clinical data combined with biological material will facilitate research within personalized medicine and treatment effectiveness among patients with inflammatory arthritis.
8. Conclusion

The nine papers and the results presented in this thesis demonstrate that observational registry data from DANBIO may answer research questions regarding bDMARD effectiveness in patients with PsA and axSpA/AS which only to a limited degree have been addressed in previous RCT studies. Examples are long term treatment effectiveness, baseline variables associated with treatment response and withdrawal, switching outcomes - including impact of non-medical biosimilar switching.

Also in the future, DANBIO and other clinical rheumatology registries will be important data sources that enable research within questions that are difficult or impossible to investigate in a randomized setting. Methodologies regarding confounder adjustment, inclusion of external data from national registries and international collaboration will refine the observational research method even further.
9. Danish summary

De biologiske lægemidler har de seneste 10-20 år forbedret behandlingsmulighederne indenfor rygsøjlegigt og psoriasisigt ganske betydeligt. I den kliniske hverdag må op mod halvdelen af patienterne dog afbryde behandlingen pga. bivirkninger eller manglende effekt. Dette er en uhensigtsmæssig situation for patienten og for samfundet. Der er således et stort ønske om forbedrede muligheder for at forudse behandlingseffekter og bivirkninger hos patienterne - og for i det hele taget at forstå, hvorledes disse potente lægemidler anvendes optimalt i klinikken.

Når de biologiske lægemidler markedsføres, er deres effekt og bivirkningsprofil afprøvet i randomiserede kliniske studier. Det er dog tiltagende anerkendt, at praktiske kliniske erfaringer, hvor lægemidlerne anvendes hos for eksempel ældre patienter med konkurrerende sygdomme og en mindre klassisk sygdomspræsentation, er et vigtigt supplement til de randomiserede studier. Den landsdækkende danske kliniske kvalitetsdatabase, DANBIO, blev etableret parallelt med markedsføringen af de biologiske lægemidler og indeholder nu prospektive data vedrørende >40.000 voksne patienter med inflammatorisk ledssygdom i Danmark. I databasen registreres oplysninger om de enkelte patienters sygdomskarakteristika, hvilken gigtbehandling patienten får, og hvilken effekt behandlingen har – målt som patient rapporterede data, objektive mål som for eksempel antal hævede og ømme led, udvalgte radiografiske data samt eventuelle årsager til stop af behandlingen, bivirkninger og lignende.

I denne doktorafhandling præsenteres 9 artikler inden for sygdomsgrupperne rygsøjlegigt og psoriasisigt. Alle artikler er publicerede i internationale reumatologiske tidsskrifter og tager udgangspunkt i data fra DANBIO. Artiklerne undersøger hvilke faktorer, som har betydning for langtids effekt og tolerabilitet af biologisk behandling. Inden for psoriasisartrit beskrives biologisk behandlingseffekt og -varighed blandt patienter, der 1) starter deres første biologiske behandlingsforløb, 2) skifter fra deres første til et efterfølgende biologisk behandlingsforløb, og 3) anvender forskellige startdoser af lægemidlet infliximab (i samarbejde med det islandske ICEBIO register). Derudover 4) undersøges effekten af tobaksrygning. På lignende måde beskrives ved rygsøjlegigt behandlingseffekt og -varighed blandt patienter, der 1) starter deres første biologiske behandlingsforløb, 2) skifter fra deres første til et efterfølgende behandlingsforløb, 3) har/har ikke radiografiske forandringer på røntgen optagelser af korsbensled, eller som 4) er rygere versus ikke-rygere. Sluttelig beskrives konsekvenser af det landsdækkende danske skift fra original til biosimilært infliximab på tværs af reumatologiske diagnoser.


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10. English summary

The introduction of the biologic disease modifying antirheumatic drugs (bDMARDs) has during the last 1-2 decades significantly improved treatment outcomes among patients with axial spondyloarthritis and psoriatic arthritis. However, in a routine care setting, up to 50% of patients experience treatment failure due to side effects or lack of effect – with a negative impact on patient and on society. There is still an unmet need to fully understand the optimal treatment algorithms for the use of biologics in the clinic, and the ability to select the right treatment for the right patient (personalized medicine) is practically non-existing.

Upon marketing, the beneficial effect and the safety profile of the biological drugs have been investigated in randomized clinical trials (RCTs). The extrapolation from RCTs to routine care is, however, a challenge as the patients who actually receive treatment with a specific drug may differ from the patients who were included in the original trials. This is due to higher age, less classical disease presentations, comorbid disease and treatment with co-medications. Thus, knowledge from observational registries is increasingly acknowledged as a valuable supplement to the randomised studies.

The nationwide Danish DANBIO registry was initially established with the aim to monitor use of biological therapies. DANBIO now includes >40.000 adult patients with inflammatory arthritis treated with conventional synthetic or biologic DMARDs. Data are collected prospectively in routine care by an online solution and includes information on patient reported outcomes, objective disease measures, radiographic data, treatment regimen, reason for withdrawal and adverse events.

This doctoral thesis presents 9 papers within axial spondyloarthritis (including ankylosing spondylitis) and psoriatic arthritis which all have been published in peer-reviewed high-impact journals and present data from the DANBIO registry. The papers all aim to investigate treatment response and long-term drug retention rates and predictors thereof in biologically treated patients. Within psoriatic arthritis, treatment effectiveness is investigated in 1) patients who initiate first TNFi treatment course, 2) patients who switch from the first to a subsequent bDMARD, 3) patients treated with different infliximab dose regimens (collaboration with Icelandic ICEBIO registry), 4) smokers versus non-smokers. In ankylosing spondylitis, treatment response and –retention is investigated 1) during the first TNFi treatment course, 2) after switching to a subsequent bDMARD, 3) according to tobacco smoking. In patients with axSpA initiating their first TNFi treatment course the impact of axSpA sub-diagnosis on treatment effectiveness is investigated. Finally, the impact of a non-medical switch from originator to biosimilar infliximab is described across diagnoses.
The thesis contains a summary and discussion of the 9 papers and a general description of the epidemiologic methodology applied across all manuscripts. Furthermore, the future perspectives of research within DANBIO and other clinical registries within rheumatology are discussed.
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12. Papers 1-9
Treatment Response, Drug Survival, and Predictors Thereof in 764 Patients With Psoriatic Arthritis Treated With Anti–Tumor Necrosis Factor α Therapy

Results From the Nationwide Danish DANBIO Registry

Bente Glintborg,1 Mikkel Østergaard,2 Lene Dreyer,3 Niels Steen Krogh,4 Ulrik Tarp,5 Michael Sejer Hansen,1 Signe Rifbjerg-Madsen,6 Tove Lorenzen,7 and Merete Lund Hetland8

Objective. To investigate disease activity, treatment response, and drug survival, and predictors thereof, among Danish patients with psoriatic arthritis (PsA) receiving their first treatment series with a tumor necrosis factor α (TNFα) inhibitor.

Methods. Patients with PsA were identified from a prospective nationwide rheumatologic database, the Danish biologics registry DANBIO, using data registered from 2000–2009. Information was obtained on the patients’ clinical response to anti-TNFα treatment (defined as achievement of the American College of Rheumatology 20% [ACR20], ACR50, and ACR70 improvement criteria or a European League Against Rheumatism [EULAR] good response at least once during the first 6 months of treatment) and duration and rate of drug adherence (referred to as drug survival), as well as predictors thereof.

Results. Of 764 patients with PsA, 320 received adalimumab, 260 infliximab, and 184 etanercept. Median drug survival was 2.9 years, and 1-year and 2-year drug survival rates were 70% and 57%, respectively. Clinical parameters that showed improvement over 6 months were the C-reactive protein (CRP) level, Health Assessment Questionnaire score, and 28-joint Disease Activity Score. Male sex, CRP level >10 mg/liter, concomitant methotrexate use, and low patient health visual analog scale score at baseline were associated with longer drug survival. Improvement was achieved by 59%, 45%, 24%, and 54% of patients according to the ACR20, ACR50, ACR70 response criteria and EULAR good response, respectively. A CRP level >10 mg/liter was predictive of the improvement responses (odds ratio [OR] 2.6 for ACR20, OR 3.0 for ACR50, OR 3.6 for ACR70, and OR 2.2 for EULAR good response).

Conclusion. In these patients with PsA treated with their first TNFα inhibitor in clinical practice, high drug adherence and responder rates were observed. Moreover, increased levels of CRP at baseline were associated with both good treatment responses and continued treatment, which may be of clinical value in selecting the patients most likely to benefit from treatment with TNFα inhibitors.
The prevalence of psoriatic arthritis (PsA) among Caucasians is 0.1–0.2%, with an estimated incidence of 6 per 100,000 person-years (1). PsA covers a wide spectrum of disease manifestations, including peripheral and axial arthritis, enthesitis, and dactylitis (2,3).

The wide range of disease manifestations in PsA warrants individualized treatment and presents a challenge to the treating physician (4). Similar to rheumatoid arthritis (RA), disease-modifying antirheumatic drugs (DMARDs) are often the first line of treatment in PsA. However, the experience with DMARDs has mainly been obtained in RA patients, and only a few randomized clinical trials have been performed in patients with PsA (4). In the past decade, several placebo-controlled clinical trials have described the effect of tumor necrosis factor α (TNFα)-inhibiting therapy in PsA (2,4,5). Until recently, 3 TNFα inhibitors, infliximab, adalimumab, and etanercept, were available for the treatment of PsA (4,6).

National registries that include followup data on patients treated with biologic drugs have been established in several countries (5,7–9). These real-life data allow for the investigation of long-term drug effects among a heterogeneous group of patients, including elderly patients who may experience comorbid diseases. Such data provide a valuable supplement to results from randomized clinical trials, which often include a limited number of patients who fulfilled a strict set of inclusion criteria and who were studied for a limited time span (5,10,11).

The rheumatologic database of the Danish biologics registry DANBIO currently includes up to 8 years of followup data. It is mandatory for the treating clinicians to prospectively report treatment and disease activity among patients being treated with biologic agents for a rheumatic disease (12,13). Our aims, based on the DANBIO data, were to report drug efficacy and drug survival (defined as duration and rate of adherence to anti-TNFα treatment), as well as to identify predictors thereof, among Danish patients with PsA who were receiving their first treatment course with a TNFα inhibitor in routine care.

**PATIENTS AND METHODS**

**Identification of patients.** DANBIO is a nationwide Danish rheumatologic registry that was initiated in 2000 and covers ~90% of patients treated with a biologic drug in routine clinical care (12,13). Each year, all departments of rheumatology in Denmark (25 in total) are asked to report the personal identification code of all patients receiving biologic treatment. When the codes in the registry were compared with these reports, coverage was calculated to be 88% in 2008 and 93% in 2009. By November 1, 2009, 1,237 patients with PsA, diagnosed according to specialists in rheumatology, had been registered in DANBIO. Of these patients, 432 were not included in the present study, because they were only treated with DMARDs and had never received biologic treatment. Another 41 patients were treated with biologic agents but participated in clinical studies, and therefore were also excluded. Thus, 764 patients were included in the present study (Table 1). Patients treated by dermatologists are not included in the database.

In Denmark, biologic treatments of rheumatic diseases can only be prescribed and administered at hospital departments of rheumatology and not by private practitioners. The drugs are fully reimbursed by the health care system and are of no cost to the individual patient. Therefore, the selection of

| Table 1. Characteristics of the 764 patients with psoriatic arthritis* |
|-------------------------|------------------|
| Demographic variables at baseline | |
| Women, no. (%) | 396 (52) |
| Age, median (IQR) years | 47 (38–56) |
| Disease duration, median (IQR) years | 5 (2–11) |
| Symptom duration, median (IQR) years | 7 (4–14) |
| MTX use, no. (%) | 410 (54) |
| Previous DMARDs, no. (%)† | |
| Sulfasalazine | 391 (51) |
| MTX | 288 (38) |
| Glucocorticoids | 147 (19) |
| Cyclosporine | 67 (9) |
| Azathioprine | 51 (7) |
| Gold | 47 (6) |
| Leflunomide | 38 (5) |
| Not stated | 97 (13) |
| TNFα inhibitor, no. (%) | |
| Adalimumab | 320 (42) |
| Etanercept | 184 (24) |
| Infliximab | 260 (34) |
| Year of treatment initiation, no. (%) | |
| 2000 | 2 (0.3) |
| 2001 | 7 (1) |
| 2002 | 8 (1) |
| 2003 | 41 (5) |
| 2004 | 65 (8) |
| 2005 | 113 (15) |
| 2006 | 118 (16) |
| 2007 | 128 (17) |
| 2008 | 161 (21) |
| 2009 (January–November) | 121 (16) |
| Reason for drug discontinuation, no. (%) | |
| Lack of efficacy | 175 (23) |
| Adverse effects | 95 (12) |
| Disease remission | 9 (1) |
| Psoriatic skin flare | 7 (1) |
| Planning pregnancy | 6 (1) |
| Cancer (suspected/verified) | 5 (1) |
| Lost to followup | 4 (1) |
| Other reasons | 20 (3) |
| Not stated | 15 (2) |
| Total discontinuations | 336 (44) |

* IQR = interquartile range; MTX = methotrexate; TNFα = tumor necrosis factor α.
† Some patients previously received >1 disease-modifying antirheumatic drug (DMARD), and therefore the percentages do not add up to 100%.
patients for treatment is not influenced by factors such as social status. According to national clinical guidelines, patients who are considered for treatment should have continuously active disease and must have experienced treatment failure with at least 1 DMARD. The decision to start and stop treatment is made locally by a rheumatologist.

Baseline demographic and clinical variables included in the registry are age, sex, disease duration, and previous or current treatment with methotrexate (MTX) or other DMARDs. In addition, disease activity parameters are prospectively reported to DANBIO through an online system (available at http://www.danbio-online.dk) (14). Data collection occurs, at a minimum, biannually.

The DANBIO database has been approved by the Danish Board of Health and the Danish Data Registry. The registration of data on patients treated with biologic agents does not require patient consent. Publication of data does not require approval by the Registry Ethics Committee.

### Measures of disease activity and clinical response

Levels of disease activity were monitored with the use of Health Assessment Questionnaire (HAQ) scores (15), the 28-joint Disease Activity Score (DAS28) (16), and visual analog scale (VAS) scores for pain, patient’s global assessment of health, and fatigue. In cases of clinical signs and/or symptoms of axial involvement, the treating rheumatologist was encouraged to additionally monitor axial disease activity, using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Functional Index (BASFI), and Metrology Index (BASMI) (introduced in 2003) (17–19). In addition, disease activity and outcomes were evaluated using the C-reactive protein (CRP) level and the swollen and tender joint counts. All of these measures were determined at 0, 2, and 6 weeks, 6 months, and 1, 2, 3, 4, and 5 years after initiation of the anti-TNF therapy (Table 2).

The clinical response to anti-TNF therapy was evaluated as achievement of the American College of Rheumatology 20% (ACR20), ACR50, and ACR70 improvement criteria (20) or a European League Against Rheumatism (EULAR) good response (21). Arbitrarily, we classified patients as responders if they achieved a clinical response (determined as yes versus no) at least once during the first 6 months of treatment. Complete baseline and outcome data for the calculations of the ACR and EULAR responses were available from 426 patients (56%) and 483 patients (63%), respectively.

### Treatment duration

Duration of drug survival was calculated as the number of days during which individual

### Table 2. Disease activity in patients with psoriatic arthritis at baseline and during followup

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 weeks</th>
<th>6 weeks</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of swollen joints</td>
<td>3 (1–7)</td>
<td>1 (0–4)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td></td>
</tr>
<tr>
<td>HAO score, mm†</td>
<td>1.0 (0.6–1.5)</td>
<td>0.75 (0.25–1.25)</td>
<td>0.6 (0.1–1.1)</td>
<td>0.6 (0.0–1.0)</td>
<td>0.4 (0.0–1.0)</td>
<td>0.3 (0.0–1.0)</td>
<td>0.3 (0.0–0.9)</td>
<td>0.5 (0.0–1.0)</td>
<td></td>
</tr>
<tr>
<td>No. of tender joints‡</td>
<td>7 (3–13)</td>
<td>3 (1–8)</td>
<td>2 (0–6)</td>
<td>1 (0–5)</td>
<td>1 (0–3)</td>
<td>0 (0–2)</td>
<td>0 (0–3)</td>
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<tr>
<td>DAS28†</td>
<td>4.8 (3.9–5.5)</td>
<td>3.4 (2.6–4.3)</td>
<td>3.0 (2.1–4.0)</td>
<td>2.8 (1.9–3.9)</td>
<td>2.6 (1.8–3.6)</td>
<td>2.3 (1.7–3.1)</td>
<td>2.1 (1.7–3.2)</td>
<td>2.0 (1.5–2.9)</td>
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<tr>
<td>VAS pain score, mm†</td>
<td>63 (45–75)</td>
<td>36 (20–60)</td>
<td>27 (13–52)</td>
<td>21 (10–47)</td>
<td>20 (8–48)</td>
<td>20 (8–38)</td>
<td>21 (8–40)</td>
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<td></td>
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<tr>
<td>VAS fatigue score, mm‡</td>
<td>65 (49–79)</td>
<td>51 (29–75)</td>
<td>44 (22–71)</td>
<td>35 (14–59)</td>
<td>37 (10–62)</td>
<td>31 (10–52)</td>
<td>19 (8–53)</td>
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<tr>
<td>VAS global score, mm†</td>
<td>69 (50–81)</td>
<td>46 (21–68)</td>
<td>31 (15–58)</td>
<td>27 (10–52)</td>
<td>23 (9–51)</td>
<td>21 (10–45)</td>
<td>21 (8–48)</td>
<td>20 (7–43)</td>
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<tr>
<td>BASDAI, mm‡</td>
<td>62 (46–75)</td>
<td>49 (28–68)</td>
<td>34 (22–52)</td>
<td>25 (11–47)</td>
<td>25 (9–49)</td>
<td>17 (10–47)</td>
<td>16 (7–47)</td>
<td>16 (6–26)</td>
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</tr>
<tr>
<td>BASFI, mm‡</td>
<td>52 (35–68)</td>
<td>47 (26–62)</td>
<td>38 (21–55)</td>
<td>26 (6–47)</td>
<td>27 (7–46)</td>
<td>18 (6–57)</td>
<td>22 (5–57)</td>
<td>23 (5–48)</td>
<td></td>
</tr>
<tr>
<td>BASMI, mm</td>
<td>20 (10–40)</td>
<td>20 (10–30)§ 10 (10–20)§ 10 (0–20)§ 10 (0–30)§ 20 (0–30)§ 10 (0–30) 20 (10–50) 15 (0–40)</td>
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<tr>
<td>No. of patients treated¶</td>
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<td>749</td>
<td>732</td>
<td>615</td>
<td>432</td>
<td>293</td>
<td>181</td>
<td>130</td>
<td>68</td>
</tr>
<tr>
<td>No. of patients with visit registered¶</td>
<td>658</td>
<td>275</td>
<td>366</td>
<td>406</td>
<td>318</td>
<td>229</td>
<td>127</td>
<td>104</td>
<td>45</td>
</tr>
</tbody>
</table>

* Except where indicated otherwise, values are the median (interquartile range). The baseline visit was the time point at which the patient received his or her first dose of tumor necrosis factor α inhibitor. Outcome data were reported according to the registrations in the DANBIO registry at the following time points: 2 weeks of treatment (time interval 1–4 weeks), 6 weeks (time interval 5–9 weeks), 6 months (time interval 18–32 weeks), 1 year (time interval 46–64 weeks), 2 years (time interval 91–117 weeks), 3 years (time interval 143–182 weeks), 4 years (time interval 183–233 weeks), 5 years (time interval 234–285 weeks), and 6 years (time interval 286–338 weeks). If more DANBIO registrations occurred within a given time interval, the one closest to the given time point was selected. If a patient had no registrations within a given time interval, data were registered as missing for the given time point. CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index.

† P < 0.001 by paired comparison of followup data at all time points versus baseline.

‡ P < 0.05 by paired comparison of followup data at all time points versus baseline.

§ P < 0.05 at this time point versus baseline.

¶ Among patients with incomplete followup data, the followup time was estimated according to the latest visit registered in the DANBIO.

### Treatment duration

Duration of drug survival was calculated as the number of days during which individual
patients continued their treatment with the first TNFα inhibitor. The start date was the date at which the first dose was administered, and the stop date was the date of the first missed dose. Temporary treatment interruptions (e.g., due to infections or surgery) of <3 months’ duration were allowed. All observations were censored at November 1, 2009. Reasons for drug discontinuation were registered.

Queries were sent to the hospitals with regard to 133 patients for whom no followup data were available since July 1, 2009 and for whom no treatment stop date was registered. Subsequently, data on treatment duration were complete for 741 (97%) of the 764 patients. For the remaining 23 patients whose followup data were incomplete, data were censored according to the last visit registered in DANBIO.

Statistical analysis. Analyses of the data were performed using SPSS software (version 16.0) and SAS software (version 9.0). Demographic and descriptive data are expressed as the median and interquartile range (IQR). Groups were compared by nonparametric testing (for unpaired data, chi-square and Mann-Whitney tests; for paired data, Wilcoxon’s signed rank test). Efficacy was analyzed as described above, per protocol. In all statistical tests, \( P \) values less than 0.05 were considered statistically significant.

Kaplan-Meier plots, log rank tests, and multivariate Cox regression analyses were used for drug survival analyses. Logistic regression analysis was used for the identification of factors associated with clinical response. In order to visualize stratified Kaplan-Meier drug survival curves, baseline VAS scores for global health status were converted into quartiles, and baseline CRP levels were converted into a binary variable (below versus above 10 mg/liter, according to the detection limit of the CRP level in most centers). For the analysis of time to discontinuation of treatment due to adverse events, discontinuations due to ineffectiveness were treated as censored observations. Similarly, discontinuations due to adverse events were handled as censored observations in the analysis of time to discontinuation due to ineffectiveness.

In the Cox and logistic regression analyses, sex, type of TNFα inhibitor, baseline CRP level (below or equal to 10 mg/liter versus above 10 mg/liter), and baseline MTX use (yes versus no) were included as categorical variables, whereas patient age, disease duration, swollen and tender joint counts, VAS scores, HAQ scores, and DAS28 scores were continuous variables. The variables with least significance were excluded stepwise (backward selection), leaving only statistically significant variables in the model. The Bath Ankylosing Spondylitis data were excluded from the analysis, because only a limited number of patients had data on axial disease at baseline (for the BASDAI \( n = 159 \), for the BASFI \( n = 157 \), and for the BASMI \( n = 122 \)). Baseline MTX use was defined as any concurrent use of MTX at baseline, irrespective of dose, and did not include former or later use of the drug.

In the logistic regression analysis, all interactions involving sex, patient age, disease duration, MTX use, drug type, baseline HAQ scores, and DAS28 scores were tested. Each interaction pair was included in the overall statistical model, and was thereafter excluded in the backward selection process if the interaction was statistically nonsignificant. We found no statistically significant interactions.

RESULTS

Patient characteristics. The number of patients with PsA who initiated their first treatment series with a TNFα inhibitor increased over the years of the registry. The majority of patients received adalimumab (42%) (Table 1). A total of 336 patients (44%) had withdrawn from TNFα inhibitor treatment by November 1, 2009. As shown in Table 1, the most prevalent reasons for drug discontinuation included lack of efficacy (in 175 of 336 patients; 52% of withdrawals) and adverse effects (in 95 of 336 patients; 28% of withdrawals). Adverse effects were infections in 33 patients, allergic reactions in 5 patients, infliximab infusion reactions in 5 patients, skin rash in 12 patients, nausea/fatigue in 8 patients, neutropenia in 3 patients, elevated liver enzyme levels in 2 patients, chest pain in 2 patients, polyneuropathy in 2 patients, and other/unspecified effects in 23 patients. One of the 5 patients who experienced infliximab infusion reactions was receiving concomitant MTX at the time of the reaction.

At baseline, 410 patients (54%) were receiving concomitant MTX. Baseline MTX use was more prevalent among patients receiving infliximab (70%) compared with those receiving adalimumab (49%) or etanercept (39%) \( (P < 0.001) \). After 3 months, 329 (80%) of these patients continued to receive concomitant MTX, 44 patients (11%) had stopped receiving MTX but continued to receive TNFα inhibitor treatment, and 37 patients (9%) had stopped receiving the TNFα inhibitor.

When we compared the baseline data between women and men, we found that women had significantly higher HAQ scores (median 1.13 versus 0.88), VAS global health scores (median 72 mm versus 66 mm), VAS fatigue scores (median 70 mm versus 62 mm), VAS pain scores (median 65 mm versus 62 mm), and tender joint counts (median 7 versus 6), whereas women had lower swollen joint counts (median 3 versus 4) \( (P < 0.05 \) by Mann-Whitney test). Age (median 48 years versus 46 years), disease duration (median 4 years versus 6 years), DAS28 scores (median 4.8 for both), and baseline CRP levels (median 10 mg/liter for both) were similar between women and men \( (P > 0.05) \).

Therapeutic effect. All outcome parameters improved during followup (all \( P < 0.05 \) versus baseline, by Wilcoxon’s signed rank test) (Table 2). Among the 483 patients with available EULAR response data, 259 patients (54%) achieved a EULAR good response at least once during the first 6 months of treatment, 131 (27%) achieved a moderate response, and 93 (19%) had no response. ACR improvement responses were avail-
able for 426 patients, among whom 253 (59%) achieved a response at the ACR20 level, 190 (45%) achieved ACR50, and 104 (24%) achieved ACR70.

**Drug survival.** The total treatment period was 2,135 person-years. The median duration of drug survival was 2.9 years, and 1- and 2-year drug survival rates were 70% and 57%, respectively.

The crude retention rates were similar among patients receiving infliximab, those receiving adalimumab, and those receiving etanercept ($P > 0.05$). As shown in Figure 1, male sex ($P < 0.001$ by log rank test), a CRP level $>10 \text{ mg/liter}$ at baseline ($P = 0.006$), and a low VAS score for global health at baseline ($P = 0.005$) were associated with improved drug survival. Concomitant use of MTX at baseline did not affect drug survival ($P > 0.05$).

Baseline disease parameters and patient characteristics were included in a Cox regression analysis in order to identify the baseline factors associated with subsequent discontinuation of TNFα inhibitor treatment. In all patients, the VAS pain scores correlated strongly with VAS global health scores (Spearman’s rho = 0.81, $P < 0.001$). Therefore, the VAS pain score was excluded from the multivariate Cox regression analysis. In the final model, female sex, a high VAS global health score at baseline, a low CRP level at baseline, and lack of concomitant MTX use were associated with shorter drug survival, whereas patient age, type of biologic drug, DAS28 score, HAQ score, tender and swollen joint counts, and VAS fatigue score were not associated with drug survival (Table 3).

In a stratified multivariate Cox regression analysis that included only adverse effects as the event causing drug termination, female sex (hazard ratio [HR] 1.8, 95% confidence interval [95% CI] 1.3–1.9; $P = 0.01$), use of infliximab (HR versus adalimumab 0.49, 95% CI 0.29–0.84 [$P = 0.01$]; HR versus etanercept 0.46, 95% CI 0.25–0.85 [$P = 0.01$]), lack of concomitant use of MTX (HR 1.67, 95% CI 1.02–2.70; $P = 0.04$), and a high number of tender joints (HR 1.03/joint, 95% CI 1.01–1.06; $P = 0.02$) at baseline were statistically significant predictors of shorter drug survival. Similarly, including only lack of efficacy as the event causing drug termination, a CRP level $\leq 10 \text{ mg/liter}$ (HR 2.11, 95% CI 1.49–3.00; $P < 0.001$) and a higher baseline VAS score for global health (HR 1.18/cm, 95% CI 1.09–1.29; $P < 0.001$) were statistically significant factors associated with shorter drug survival.

**Prediction of clinical response.** In a multiple logistic regression analysis (backward stepwise selection) with EULAR good response as the dependent variable, a CRP level of $>10 \text{ mg/liter}$ (odds ratio [OR] 2.2 for high versus low, 95% CI 1.5–3.2; $P < 0.001$), male sex (OR 1.5 for male versus female, 95% CI 1.0–2.2; $P = 0.04$), and younger age (OR 0.98/year increase, 95% CI 0.97–1.0; $P = 0.01$) were associated with a EULAR good clinical response, whereas type of biologic drug, disease duration, DAS28 scores, HAQ scores, VAS global
health scores, and concomitant use of MTX at baseline showed no statistically significant association with a EULAR good clinical response (all $P/\leq0.05$).

In a similar analysis using the ACR20 response as the dependent variable, concomitant use of MTX (OR 1.7 for use versus nonuse, 95% CI 1.1–2.6; $P = 0.03$), a high VAS score for global health (OR 1.01/cm increase, 95% CI 1.00–1.02; $P = 0.01$), and a CRP level $>10$ mg/liter (OR 2.4 for high versus low, 95% CI 1.7–3.9; $P < 0.001$) were associated with clinical response. The unadjusted effect of a high CRP level was an OR of 2.6 (95% CI 1.7–3.9; $P < 0.001$).

In a multiple logistic regression analysis with ACR50 as the dependent variable, a CRP level $\geq10$ mg/liter was the only variable associated with clinical response (OR 3.0, 95% CI 2.0–4.5; $P < 0.001$). A similar result was found in the model using ACR70 as the measure of clinical response (for high CRP, OR 3.6, 95% CI 2.2–5.9; $P < 0.001$). Sex, age, type of biologic drug, disease duration, DAS28 scores, HAQ scores, VAS global health scores, and concomitant MTX use were not associated with ACR50 or ACR70 improvement responses.

When patients were stratified according to their baseline level of CRP ($\leq10$ mg/liter versus $>10$ mg/liter), the percentages of patients achieving a clinical response within 6 months of treatment were as follows: 51% versus 73% achieving ACR20, 33% versus 60% achieving ACR50, 14% versus 37% achieving ACR70, and 47% versus 65% achieving a EULAR good response. Thus, 1 in 7 patients achieved clinical improvement according to the ACR70 if their CRP level was in the normal range at treatment start, whereas 1 in 3 patients whose CRP level was elevated at treatment start achieved an ACR70 improvement response.

**DISCUSSION**

TNFα inhibitors are efficacious in the treatment of patients with PsA in randomized clinical trials (22–26). Data from clinical practice are needed to complement the trials and to assess their external validity (27). Published studies on patients with PsA treated with biologic drugs are, however, few (4,8,9,28,29). The present nationwide study of 764 patients with PsA followed up prospectively for up to 8 years in routine care represents the largest cohort and the longest observation time published to date. Three findings of this study are of importance for clinical practice: approximately half of the patients with PsA who received their

<table>
<thead>
<tr>
<th>Table 3. Baseline statistical predictors of discontinuing treatment with tumor necrosis factor α inhibitors, as determined by multivariate Cox regression analysis*</th>
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<tr>
<td>Unadjusted analysis</td>
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<tr>
<td>----------------------</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Female</td>
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<td><strong>No. of swollen joints</strong></td>
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<td><strong>DAS28</strong></td>
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<td>Etanercept</td>
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<td><strong>Age</strong></td>
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* Values are the hazard ratio (HR) with 95% confidence interval (95% CI) determined in 764 patients with psoriatic arthritis. VAS = visual analog scale; HAQ = Health Assessment Questionnaire; DAS28 = Disease Activity Score in 28 joints; CRP = C-reactive protein; MTX = methotrexate.
first treatment series with a TNFα inhibitor achieved a clinical response (ACR50 or EULAR good response) within 6 months. The number needed to treat (NNT) to achieve an ACR70 response was much higher in patients whose baseline CRP level was in the normal range (NNT = 7) than in patients whose baseline CRP level was elevated (>10 mg/liter) (NNT = 3). CRP was the only baseline variable that was predictive of both longer treatment continuation and good treatment response.

Carmona et al reported a 1-year drug survival rate of 88% among 570 patients with PsA registered in the Spanish national registry, although no efficacy data were reported (8). Similarly, 76% of British patients with PsA followed up for more than 1 year were continuing to receive treatment with their first TNFα inhibitor, according to British registry data (5). A report based on data from the South Swedish register did not explicitly present the drug survival rates, but a EULAR good response rate of 55% was reported among 261 patients with PsA (9), a rate that was very similar to the 54% found in our study. These findings are difficult to compare with the results from randomized controlled trials, as those trials have often focused on ACR20 clinical responses or shorter observation periods, but the 6-month ACR50 response rate of 45% in our study is similar to the rates of 40–45% previously reported in randomized trials (22–26).

An increased CRP level at baseline was the sole factor most uniformly linked to clinical response and treatment continuation. Similar results have been reported by other authors among patients with PsA as well as patients with RA and patients with spondylarthropathies (9,30–37). The CRP level is probably linked to systemic inflammation in patients with rheumatic disease, and thus it might be used to distinguish those patients who mainly experience chronic irreversible damage from those with active inflammatory disease. In contrast, some authors have found high baseline HAQ or VAS scores to be predictive of drug discontinuation, perhaps because of an association with chronic irreversible disease (31). It would be of great value to select the patients most likely to benefit from biologic treatment at early stages of the decision process; in this aspect, CRP levels seem to be a promising candidate.

We found that MTX use was associated with treatment continuation, a tendency that has been previously described by others (5,9,38) but only in analyses that were adjusted for other baseline variables. MTX use was not a uniform predictor of clinical response in our study, since it was only a predictor of the ACR20 response and not the EULAR response or the ACR50 or ACR70 response. These discrepancies may be explained, at least in part, by the concept of bias by indication with regard to concomitant MTX treatment. No data were available on the reasons for addition of MTX to the biologic treatment regimen in some patients and not in others. Absence of concomitant MTX use might be associated with the presence of a comorbidity of importance for drug continuation (9). MTX use was linked to use of infliximab, but it is currently unknown whether MTX has any effect on the formation of immunopathogenic antibodies in PsA during anti-TNFα therapy (39). Randomized controlled trials of anti-TNF medications in PsA have not shown any beneficial effect associated with the use of MTX as a concomitant treatment in patients with PsA (23,24).

In the present study, men had a longer treatment duration and better EULAR response than did women (5,28,36,38). Shorter treatment duration and poorer treatment response among women treated with TNFα inhibitors have also been described in patients with RA and in those with ankylosing spondylitis (37,38,40,41). Similarly, the tendency toward higher VAS and HAQ scores in women has previously been observed (41,42). However, any linkage between musculoskeletal performance, sex hormones, or other sex-related factors and anti-TNFα therapy has not been established (41).

The main reason for drug discontinuation was lack of treatment effect, whereas only a few patients stopped treatment due to adverse events. Discontinuation of infliximab use was related to adverse events. A similar tendency has been described previously (5,43), but, due to the observational study design and lack of randomization of drug therapy, such data must be interpreted with caution.

The DANBIO data in our study can be considered of high quality. According to previous reports, >90% of Danish patients treated with biologic agents are registered in the DANBIO database, probably due to the fact that registration is mandatory irrespective of patient’s consent (13). This is supported by the fact that coverage is much lower in databases using voluntary registration and requiring patient consent (8). In the DANBIO registry, similar to that in most clinical trials, the type of arthritis, peripheral or axial, is not registered. Since the disease entities are treated differently (44), this may have influenced the results. Similarly, smoking status and comorbid disease are other factors that might influence treatment outcomes (5). However, these data were only recently introduced in the registry and are still not uniformly available.

This analysis of 764 patients with PsA in a
nationwide prospective registry documents that TNFα inhibitors decrease the disease activity in patients with PsA in clinical practice. Overall, half of the patients achieved a good clinical response, but the response rate and duration of drug survival were significantly higher in patients with an elevated CRP level at baseline. Male sex was predictive of longer treatment continuation and a EULAR good response. The effect of concomitant MTX use was weak but seemed to have some beneficial effect on drug survival and achievement of the ACR20 response. Other parameters, including the type of biologic drug, HAQ score, DAS28 score, VAS score, and disease duration, did not significantly affect drug survival or treatment efficacy. Among these Danish patients with PsA, the TNFα-inhibiting treatments were well tolerated, and only a few patients stopped treatment due to adverse effects.

ACKNOWLEDGMENTS

We thank all of the rheumatology departments in Denmark for reporting patient data to the DANBIO registry.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Glintborg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Glintborg, Østergaard, Tarp, Hetland.

Acquisition of data. Glintborg, Dreyer, Tarp, Røjbjerg-Madsen, Lorenzen, Hetland.

Analysis and interpretation of data. Glintborg, Østergaard, Dreyer, Krogh, Tarp, Hansen, Hetland.

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Clinical Response, Drug Survival, and Predictors Thereof Among 548 Patients With Psoriatic Arthritis Who Switched Tumor Necrosis Factor \(\alpha\) Inhibitor Therapy

Results from the Danish Nationwide DANBIO Registry

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**Objective.** To describe the frequency of treatment switching and outcomes among patients with psoriatic arthritis (PsA) who switched tumor necrosis factor \(\alpha\) inhibitor (TNFi) agents in routine care.

**Methods.** We conducted an observational cohort study based on the Danish nationwide DANBIO registry. Treatment outcomes were evaluated using the American College of Rheumatology criteria for 20% improvement (ACR20)/ACR50/ACR70, European League Against Rheumatism (EULAR) response criteria for good response, and the 28-joint count Disease Activity Score (DAS28) (remission). Kaplan-Meier and regression analyses were used for drug survival analyses and to identify predictors of outcome after treatment switching.

**Results.** Of 1,422 patients starting TNFi agents, 548 patients (39%) switched to a second biologic drug during up to 10 years of followup. Median followup was 2.3 years (interquartile range [IQR] 1.0–4.3 years). Switchers were more frequently women (56% versus 45%), had a shorter disease duration (3 versus 4 years), a higher median Health Assessment Questionnaire (HAQ) score (1.1 [IQR 0.6–1.6] versus 0.9 [IQR 0.5–1.4]), HAQ, DAS28, and VAS scores and C-reactive protein levels had decreased after 6 months (all \(P < 0.05\)), and median drug survival was 2.2 versus 1.3 years (\(P < 0.001\)). Lower fatigue score increased survival of the second TNFi. After switching, the proportions of patients achieving a sustained ACR20, ACR50, ACR70, EULAR good response, and DAS28 remission after 3–6 months were 22% (number needed to treat [NNT] 4.5),...
Psoriatic arthritis (PsA) covers a wide spectrum of disease manifestations, including arthritis, enthesitis, dactylitis, and axial spondylitis. This diversity in symptoms warrants individualized treatment and presents a challenge to the treating physician. Methotrexate (MTX) and other synthetic disease-modifying antirheumatic drugs (DMARDs) are often the first-line treatment in PsA (1–4). Upon treatment failure, tumor necrosis factor α inhibitors (TNFi) have proven effective in several randomized clinical trials, with 40–60% of patients achieving response according to the American College of Rheumatology criteria for 20% improvement (ACR20) (5–12).

Currently, 4 TNFi agents with different chemical structures and pharmacokinetics are marketed to treat PsA in Denmark: infliximab, adalimumab, etanercept, and golimumab. Among patients who experience TNFi treatment failure due to insufficient response or adverse events (AEs), switching to a second TNFi seems appealing. However, evidence on the effect of TNFi switching in PsA is scarce and mainly originates from smaller observational studies that include ≤30 switch episodes (13–17). The British Society for Rheumatology Biologics Register reported a 1-year drug survival rate of 74% among 178 switchers with PsA. However, no outcome data or predictors among switchers were reported (18). No randomized trials on treatment switching in PsA have been performed.

The Danish nationwide DANBIO registry now includes >10 years of prospective followup of patients with inflammatory arthritis treated with biologic agents in routine care (19). We have previously described treatment response and predictors of TNFi treatment in patients with PsA who had not received biologic agents (20). In the present study, we aimed to investigate frequencies and reasons for switching, treatment responses, duration and rates of drug adherence (referred to as drug survival), and predictors thereof in patients with PsA who switched TNFi agents in routine clinical care.

PATIENTS AND METHODS

DANBIO registry. The nationwide Danish DANBIO registry was started in 2000 and was approved by the Danish Health and Medicines Authority as a clinical quality registry in 2006. DANBIO covers >90% of adults with rheumatic disease who are treated with biologic agents in routine care (21–23). According to Danish legislation, the registration and publication of data from clinical registries do not require patient consent or approval by ethics committees.

In this observational cohort study based on data from the DANBIO registry, we included patients who were diagnosed as having PsA according to the treating rheumatologist. All treatment courses initiated before January 1, 2012 were evaluated. Patients were excluded if they received only DMARDs, if they received biologic agents as part of clinical trials, if they were not followed up in the registry since start of their first TNFi, or if they did not receive a biologic drug marketed to treat PsA as the first biologic agent.

In DANBIO, baseline data collected include age, sex, disease duration, and previous or current treatment with MTX or other DMARDs. Disease activity parameters are prospectively reported in an online system (www.danbio-online.dk) (24). Functional status is monitored using the Health Assessment Questionnaire (HAQ) (25), and disease activity is evaluated using the 28-joint count Disease Activity Score (DAS28) (26), C-reactive protein (CRP) level (normal range ≤10 mg/liter), and patient’s global, pain, and fatigue scores on a visual analog scale (VAS) and physician’s global score on a VAS. In cases of clinical signs and/or symptoms of axial involvement, the treating rheumatologist monitors axial disease activity with the Bath Ankylosing Spondylitis Disease Activity Index (27), Bath AS Functional Index (28), and Bath AS Metrology Index (29) (introduced in 2003). Bath AS data were not included in this study since only a limited number of patients had baseline data recorded (20).

It is recommended that data on disease activity and functional status be collected at least biannually or if the medical treatment is altered (19).

Data quality. Queries were sent to the hospitals regarding treatment series with incomplete followup (20). All observations were censored as of April 20, 2012. All calculations were based on observed data, and no imputation of missing data was performed. Due to the observational clinical study design, no specific monitoring or cross checking of data was performed as part of this study. However, all Danish departments of rheumatology that report to the DANBIO registry regularly participate in audits in order to optimize data quality (19).

Drug survival. Drug survival was calculated as the number of days that individual patients continued treatment with the drug. The start date was the date the first dose was given, and the stop date was the date of the first missed dose. Temporary treatment interruptions, e.g., due to infections or surgery, of ≤3 months’ duration were allowed. If a patient restarted treatment with the same biologic drug after >3 months’ treatment interruption, the second treatment course with the drug was deleted from the data set (n = 67 cases).

The reasons for drug discontinuation are recorded in DANBIO in prespecified categories: lack of treatment effect, AEs, disease remission, pregnancy, surgery, cancer, death,
infections, loss to followup, and other reasons. The registration in DANBIO does not distinguish between primary and secondary lack of response. Thus, it was not possible to distinguish between these reasons for switching therapy. Below, “switching-AE” denotes switching due to side effects, infection, death, or cancer. “Switching–lack of effect” denotes switching due to a lack or loss of effect. “Switching–other” denotes switching due to any other cause (pregnancy, surgery, loss to followup, remission), or multiple reasons for drug discontinuation.

**Treatment response.** At baseline, 3 months, and 6 months, disease activity was evaluated using the CRP level, DAS28, patient’s pain, fatigue, and global scores on a VAS, and physician’s global score on a VAS, and physical function was evaluated using HAQ scores.

Clinical response was evaluated as achievement of an ACR20, ACR50, ACR70 response (30), or a European League Against Rheumatism (EULAR) good response (31). Arbitrarily, we classified patients as “responders” if they achieved a clinical response (yes or no) at both the 3- and 6-month visits compared to the baseline registration data. Similarly, patients were considered to be in DAS28 remission if they had a DAS28 of <2.6 at both the 3- and 6-month visits. In the case of missing data at either the 3- or 6-month visit, one record indicating clinical response was sufficient in order to classify the patient as a responder. Complete baseline and outcome data for the calculations of ACR and EULAR responses during the first treatment course were available for 530 (37%) and 624 (44%) of the 1,422 patients, respectively.

The overall long-term treatment response was evaluated at the 2-year visit (the first visit >104 weeks after initiating the first TNFi). A 2-year time period was chosen arbitrarily to allow for an acceptable number of switch episodes without excluding too many patients with insufficient followup time. Patients who switched treatment from the first TNFi after the 2-year visit were excluded from this analysis (n = 67).

**Statistical analysis.** Statistical analyses were performed using SPSS version 16.0 and SAS version 9.0 software. Demographic and descriptive data are presented as the median and interquartile range (IQR). Groups were compared by nonparametric testing (using the chi-square and Mann-Whitney tests for unpaired data and Wilcoxon’s signed rank test for paired data). The proportion of patients in whom treatment responses were achieved was expressed as the number needed to treat (NNT), calculated as the reciprocal value of response rates. In all statistical tests, P values less than 0.05 were considered significant.

Kaplan-Meier plots and log rank tests were used to assess drug survival. Unadjusted/univariate and multivariate Cox regression analyses with hazard ratios (HRs) were used for the identification of factors associated with drug survival in the second treatment course. Logistic regression analyses and odds ratios (ORs) were used to identify factors associated with clinical response. In the regression analyses, age, disease duration, baseline CRP, DAS28, HAQ, and VAS scores were included as continuous variables, and sex, type of TNFi (current and previous treatment), concomitant MTX (yes/no), calendar year of starting TNFi, and reason for discontinuation of the first TNFi (AE/lack of effect/other) were included as categorical variables. Only a few patients had a history of leflunomide use (20), and this variable was not included in the analysis. The variables with the highest P values were excluded stepwise (backward selection), leaving only statistically significant variables in the final model.

**RESULTS**

**DANBIO data and exclusion criteria.** By January 1, 2012, 3,178 patients diagnosed as having PsA had been registered in DANBIO. We excluded 1,646 patients who were treated with DMARDs only, 53 patients treated with biologic agents as part of clinical trials, 42 patients not followed up in the registry since the start of their first TNFi, and 15 patients who did not receive a biologic drug marketed to treat PsA as the first biologic agent. Thus, 1,422 patients who were naive for biologic drugs and had been registered in DANBIO from the time of initiation of the first TNFi were included. Of these, a subgroup of 548 patients (switchers) had received treatment with ≥2 different biologic drugs (TNFi or other) during followup. The total number of treatment courses was 2,241.

**Baseline characteristics of the patients and patient disposition.** Among the 1,422 patients included, 699 (49%) were women, and their median age was 48 years (IQR 39–56 years). Median followup time was 2.3 years (IQR 1.0–4.3 years). The patient flow is shown in Table 1. When data were censored, 548 patients (39%) had switched treatment, 632 patients (44%) were still treated with the original TNFi, and 242 (17%) had stopped treatment without starting a new TNFi. The main reasons for switching were lack of effect (57% of switchers; n = 311) or AE (28% of switchers; n = 152).

Among the 548 patients who started treatment with a second biologic agent, 245 patients continued treatment, 189 (34%) switched to a third treatment, and 114 patients stopped without starting a new TNFi. The main reason for switching to a third biologic was lack of effect (62% of switchers; n = 118) (Table 1). Similarly, 57 of the 189 patients (30%) switched to a fourth biologic drug, and 20 of those 57 patients (35%) switched to a fifth biologic drug. The median time interval between the first missed dose of the first TNFi and starting the second biologic drug was 15 days (IQR 1–62 days).

The most frequently used first-line drugs were infliximab from 2001 to 2006 and adalimumab from 2007 to 2011. Etanercept was most frequently used as second-line (49%) and third-line (30%) treatment. Frequent drug sequences were as follows: adalimumab then etanercept (n = 155 patients), infliximab then etanercept...
(n = 107), infliximab then adalimumab (n = 101), etanercept then adalimumab (n = 84), adalimumab then infliximab (n = 35), and etanercept then infliximab (n = 24). Other combinations were used in <20 patients (Table 1). Biologic agents other than TNFi were initiated in only 50 of 2,241 treatment series and will not be further addressed herein.

The average infliximab doses at the start of the first, second, and third treatment courses were 3.5 mg/kg, 4.5 mg/kg, and 4.3 mg/kg, respectively. The average doses at the last registered visit were 3.8 mg/kg, 5.0 mg/kg, and 5.3 mg/kg, respectively. At baseline, 765 of 1,422 patients (54%) were receiving concomitant MTX. MTX was more frequently combined with infliximab than with the other TNFi agents (P < 0.001).

Switchers were more frequently women, had a shorter disease duration, had higher HAQ, DAS28, and fatigue and pain scores (on a VAS), and had more

<table>
<thead>
<tr>
<th>Table 2. Baseline demographics and disease activity at initiation of treatment with the first TNFi*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonswitchers</strong></td>
</tr>
<tr>
<td>Continuous treatment (n = 632)</td>
</tr>
<tr>
<td>Age, years (range)</td>
</tr>
<tr>
<td>48 (39–56)</td>
</tr>
<tr>
<td>Women, no. (%)</td>
</tr>
<tr>
<td>259 (41)</td>
</tr>
<tr>
<td>Disease duration, years</td>
</tr>
<tr>
<td>5 (1–10)</td>
</tr>
<tr>
<td>Symptom duration, years</td>
</tr>
<tr>
<td>7 (4–14)</td>
</tr>
<tr>
<td>Methotrexate use, no. (%)</td>
</tr>
<tr>
<td>347 (55)</td>
</tr>
<tr>
<td>DAS28</td>
</tr>
<tr>
<td>4.3 (3.6–5.1)</td>
</tr>
<tr>
<td>HAQ, mg/liter</td>
</tr>
<tr>
<td>0.9 (0.5–1.4)</td>
</tr>
<tr>
<td>CRP, mg/liter‡</td>
</tr>
<tr>
<td>10 (3–20)</td>
</tr>
<tr>
<td>Fatigue score‡</td>
</tr>
<tr>
<td>63 (39–78)</td>
</tr>
<tr>
<td>Global score‡</td>
</tr>
<tr>
<td>66 (46–80)</td>
</tr>
<tr>
<td>Pain score‡</td>
</tr>
<tr>
<td>61 (38–74)</td>
</tr>
<tr>
<td>Physician’s score‡</td>
</tr>
<tr>
<td>32 (21–48)</td>
</tr>
<tr>
<td>Tender joints (28-joint count)</td>
</tr>
<tr>
<td>4 (2–9)</td>
</tr>
<tr>
<td>2 (0–5)</td>
</tr>
</tbody>
</table>

* Except where indicated otherwise, values are the median (interquartile range). TNFi = tumor necrosis factor α inhibitor; DAS28 = Disease Activity Score 28 joints; HAQ = Health Assessment Questionnaire; CRP = C-reactive protein.
† By Mann-Whitney and chi-square tests.
‡ Assessed on a 100-mm visual analog scale.
swollen and tender joints compared to nonswitchers when they started the first TNFi (Table 2). Compared to patients who continued the same treatment, nonswitchers who stopped treatment without starting a new treatment were more frequently women, had higher baseline HAQ, DAS28, and global and fatigue scores (on a VAS), and had more tender joints (Table 2).

Among the 548 switchers, baseline disease activity when they started the first treatment course was similar irrespective of the reason for switching (data not shown).

**Drug survival.** The median overall drug survival of the first TNFi was 2.2 years (95% confidence interval [95% CI] 1.9–2.5 years). Drug survival decreased after switching (Figure 1). Median drug survival of the first TNFi among switchers was 0.7 years (95% CI 0.6–0.8 years).

**Treatment response.** Disease activity was significantly reduced after 3 and 6 months’ treatment compared to baseline during the first, second, and third treatment courses (Table 3).

During the first treatment course, the proportion of patients in whom an ACR20 response was achieved within 3–6 months was 47% (NNT 2.2). Corresponding rates during the second and third treatment course were 22% (NNT 4.5) and 18% (NNT 5.3), respectively. Similarly, ACR50 response rates during the first, second, and third treatment courses were 33% (NNT 3.1), 13% (NNT 7.9), and 6% (NNT 16), respectively. ACR70 response rates were 17% (NNT 5.9), 5% (NNT 20), and 2% (NNT 48). The proportions of patients in whom a good response according to the EULAR criteria was achieved were 45% (NNT 2.3), 19% (NNT 5.3), and 17% (NNT 5.8), respectively, and the proportions of patients in DAS28 remission were 43% (NNT 2.3), 34% (NNT 2.9), and 22% (NNT 4.4), respectively (Figure 2). Response rates were significantly lower during the second and third treatment courses compared to the first (all $P < 0.05$).

Patient demographics (sex, age, and disease duration) at baseline of the second and third treatment courses were similar among patients with missing and nonmissing data on ACR response rates (all $P > 0.05$; data not shown), whereas men ($P = 0.03$) and patients with a longer disease duration ($P = 0.02$) more often had missing response data during the first treatment course.

At the 2-year visit, the proportions of nonswitchers versus switchers who had an ACR20 response were 57% versus 47% ($P = 0.1$), the proportions who had an

<table>
<thead>
<tr>
<th>Treatment course</th>
<th>Withdrawn n</th>
<th>Patients still treated, n</th>
<th>Maintaining treatment after 2 years, %</th>
<th>Drug survival, years Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>790</td>
<td>1422</td>
<td>514</td>
<td>231</td>
</tr>
<tr>
<td>2</td>
<td>303</td>
<td>548</td>
<td>143</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>103</td>
<td>189</td>
<td>57</td>
<td>37</td>
</tr>
</tbody>
</table>
ACR50 response were 45% versus 32% ($P = 0.02$), the proportions who had an ACR70 response were 35% versus 17% ($P = 0.001$), and the proportions with a EULAR good response were 60% versus 41% ($P < 0.001$).
Predictors of drug survival and response during the second treatment course. In univariate Cox regression analysis, drug survival of the second biologic agent was longer in men ($P = 0.02$), in patients with fewer tender joints ($P = 0.004$), and in patients with lower fatigue score on a VAS ($P = 0.007$). Patients who started the second TNFi in earlier years had longer drug survival ($P = 0.03$). Differences in disease duration, baseline CRP, HAQ, DAS28, swollen joint count, VAS global score, VAS pain score, use of MTX, type of TNFi (current or previous), reason for withdrawal of the first TNFi, and age were not statistically significant. In multivariate Cox regression analysis, the only predictor of longer drug survival was lower fatigue score on a VAS (HR 1.1 cm [95% CI 1.04–1.3], $P = 0.007$).

The predictors of EULAR and ACR20/50/70 responses after 3–6 months of treatment according to multiple logistic regression analysis are shown in Table 4. Fewer tender joints at baseline when the second TNFi was started predicted ACR20 response, ACR50 response, and a good response according to the EULAR criteria. Lower HAQ score predicted ACR50 response and a EULAR good response. Higher DAS28 predicted ACR20, ACR50, and ACR70 responses and a EULAR good response, and no MTX use predicted ACR20 and ACR50 responses. Patients who stopped treatment with the previous TNFi due to an AE had a lower chance of ACR20 and ACR50 responses than patients who stopped due to lack of effect, and patients who stopped for other reasons had a higher chance of response (Table 4).

**DISCUSSION**

This study based on the national DANBIO registry including 1,422 patients with PsA showed that switching of TNFi occurs frequently in clinical practice and that nearly 40% of patients switched treatment during a median of 2.3 years of followup. Response rates and drug survival times decreased after switching from the first to the second TNFi. However, significant decreases in disease activity were observed during the first, second, and third treatment courses, and at the 2-year visit 47% of switchers had an ACR20 response and 41% had a good response according to the EULAR criteria.

Only a few and mainly minor studies have previously addressed treatment switching in PsA patients (13–17). We found that lack of treatment effect was the main reason for switching and explained the switch in the majority of cases, followed by AEs in 1 of 4 patients. An observational study from the British Society for Rheumatology Biologics Register found switching in 178 (31%) of 566 patients with PsA followed up for up to 3.5 years (18). Gomez-Reino and Carmona reported switching in only 15 (5%) of 289 PsA patients followed up in the Spanish Base de Datos de Productos Biológicos registry for up to 4 years, and 21 (33%) of 63 patients with PsA followed up for up to 4 years, and switching was mainly due to loss of effect (32). Other observational studies on switching in PsA have included <15 switch episodes (13,14). Varying followup times, prescription guidelines, and access to treatment may, at least in part, explain the different switch rates.

In this study, switchers had higher baseline disease activity and were more frequently women, which is consistent with previous reports (17). Higher baseline disease activity among switchers has also been found in...
patients with rheumatoid arthritis (RA) (33,34) and those with ankylosing spondylitis (AS) (35), probably reflecting more severe or refractory disease in these patient groups. In RA, AS, and PsA, women have shorter drug survival (20,36–38) and experience poorer effects of TNFi treatment than men (20,39,40), and women have higher switch rates in AS (20), but why and how sex affects the response to TNFi is poorly understood (40).

The response rates were significantly lower in the patients receiving the second or third treatment compared to those who remained with the first TNFi, and the NNT to achieve ACR20 during the second treatment course was 4.5, compared to 2.2 during the first. Chakravarty et al found a similar 6-month response rate among 30 switchers in the Consortium of Rheumatology Researchers of North America registry (23%; NNT 4.3) (17). Coates et al reported a reduction in DAS28 of 1.2 among 7 of 12 switchers at 12 weeks (NNT 1.7) compared to 58 of 60 patients during the first treatment course (NNT 1) (14), whereas the other observational studies of patients with PsA who switched treatment lack response data (16,18). Similarly, drug survival decreased after switching, a tendency previously observed in other observational studies (16–18,41). Compared to other populations with arthritis, switchers with PsA seem to have poorer drug survival rates than patients with AS (16,35) but better rates than patients with RA (16,32,42).

Recent EULAR guidelines recommend switching to a second TNFi in case of failure of the first (1). This strategy is supported by our data showing that the ACR20 response rates were similar among switchers and nonswitchers at the 2-year visit, and an ACR20 response and/or a good response according to the EULAR criteria was achieved in approximately half of the switchers. Furthermore, there were significant decreases in disease activity 3 months after starting the second TNFi compared to the baseline visit. A similar tendency was even observed during the third treatment course. Thus, disease activity decreased when a new TNFi was introduced, which supports the notion that switching has some value in patients in whom initial TNFi treatment has failed. Furthermore, since ACR20/50/70 and EULAR responses are based on relative improvements compared to baseline disease activity, a carryover effect from previous treatments may have caused underestimates of the effects of switching. This might explain why switching was more effective when evaluated by DAS28 remission criteria.

To our knowledge, no previous reports on TNFi-treated PsA patients have described the predictors of clinical response after switching. We found that low numbers of tender joints and low HAQ score at the initiation of treatment with the second TNFi were associated with clinical response. Lower fatigue score predicted both response and longer drug survival. This is consistent with previous studies of TNFi-naive patients with PsA, AS, or RA, in which lower fatigue and HAQ scores were associated with response (20,39,43) and longer drug survival (36) of the first TNFi. This might reflect a lower degree of chronic disability and impairment in these patient groups.

The combination of TNFi therapy with synthetic DMARDs in PsA is still debated, and several studies have shown no convincing additional effect of combining MTX and TNFi versus TNFi monotherapy (4,6,10,18). Due to the nonrandomized study design, the apparently negative or absent effect of concomitant MTX in the present study may be a proxy for comorbidities or other patient-related factors.

The infrequent use of etanercept in our cohort may reflect the perception that this drug is less effective in psoriasis (4). A Danish registry study based on 742 patients with psoriasis treated with TNFi showed adalimumab to be the preferred first-line treatment in a dermatology setting (44). Thus, the activity and extent of psoriasis in skin and nails might affect treatment choice.

This study has some limitations. In DANBIO, the 28-joint count and DAS28 score are used to monitor disease activity. Only recently has it become possible to register a 68/66-joint count (45). Although the DAS28 has been validated in PsA patients (46), the lack of information regarding arthritis in, e.g., the distal joints of hands and feet might have affected our results.

We evaluated the clinical effect using the ACR and EULAR responses. Although these response parameters were developed to monitor relative changes in disease activity among RA patients, they have been validated in patients with PsA (2,46,47) and are widely used in clinical trials (5–12). However, a relative change in disease activity of, e.g., 20% and achievement of an ACR20 response is not necessarily sufficient to consider a patient well treated in a clinical setting (48). The impact of treatment on other disease manifestations, such as skin psoriasis, enthesitis, and dactylitis, which are not routinely registered in DANBIO, might affect whether the treatment was considered to be effective (2,49,50). Furthermore, it is not explicitly registered in DANBIO whether the PsA patient has axial spondyloarthritis. Only a small percentage of patients had Bath AS scores recorded (20), and these data were therefore not included in the statistical analyses. The effect of
TNFi on axial disease manifestations might also have affected the decision to continue or to switch therapy (20,51).

The nature of an observational registry study confers some limitations regarding the reliability of the results. Incompleteness of data is an inherent problem within registry studies (52,53). In the present study, we found no demographic differences among patients with missing/nonmissing response rate data during the second and third treatment courses, whereas there was a tendency toward biased registration during the first TNFi treatment course, with less missing data among women and patients with shorter disease duration. This may have affected our results.

In conclusion, nearly 40% of patients with PsA switched TNFi agents in routine care during up to 10 years of followup, mainly due to lack of effect. The response and remission rates and drug survival decreased after switching. After 2 years, however, a clinical response had been achieved in half of the switchers. Therefore, switching to another TNFi should be considered in patients with PsA, irrespective of the reason for discontinuation of the first TNFi.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Glintborg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design. Glintborg, Østergaard, Krogh, Loft, Lindegaard, Hetland. Acquisition of data. Glintborg, Krogh, Andersen, Tarp, Holland-Fischer, Nordin, Jensen, Olsen, Hetland. Analysis and interpretation of data. Glintborg, Østergaard, Krogh, Tarp, Loft, Nordin, Jensen, Hetland.

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Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: results from the nationwide registries DANBIO and ICEBIO

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Abstract

Objective. The aim of this study was to describe dose regimens, dose escalation and clinical outcomes in TNF-α inhibitor (TNFi) naïve patients with PsA treated with infliximab in routine rheumatology care.

Methods. We conducted an observational cohort study based on the nationwide Danish Rheumatologic Database (DANBIO) and Center for Rheumatology Research (ICEBIO) registries. Stratified by country, characteristics of patients treated with ≤3 mg infliximab/kg body weight, 3–5 mg/kg or ≥5 mg/kg every 8 weeks were described. Outcomes were evaluated by ACR 20%, 50% and 70% (ACR20/50/70) responses and European League Against Rheumatism good response after 6 months, disease activity after 12 months, Kaplan–Meier plots and regression analyses.

Results. Four hundred and sixty-two patients (376 Danish, 86 Icelandic) received treatment with infliximab. In Danish patients, the starting dose was ≤3 mg/kg in 110 patients (29%), 3–5 mg/kg in 157 (42%), ≥5 mg/kg in 38 (10%) and unregistered in 71 (19%). In Icelandic patients, corresponding numbers were 64 (74%), 17 (27%), 0 (0%) and 5 (6%). Patients with a higher body weight received lower doses per kilogram. Danish patients received higher doses than Icelandic patients at baseline [median 3.1 (interquartile range 3.0–3.8) vs 2.3 (2.1–2.9) mg/kg, P < 0.05] and after 12 months [3.3 (3.0–4.5) vs 2.9 (2.2–3.5) mg/kg, P < 0.0001]. After 12 months, 58% of Danish and 66% of Icelandic patients maintained treatment. Danish patients had shorter drug survival than Icelandic patients (1183 vs 483 days). In univariate analyses stratified by country, time until dose escalation, response rates, drug survival and 1-year’s disease activity were independent of starting dose. Drug survival was shorter among patients not receiving concomitant MTX.

Conclusion. In clinical practice, >70% of Icelandic and Danish PsA patients treated with infliximab received sustained doses below the 5 mg/kg every 8 weeks recommended in international guidelines. Lower starting doses did not affect drug survival or response.

Key words: PsA, outcome, drug survival, biological treatment, infliximab, routine care, clinical registry.
Introduction

Therapy with TNF-α inhibitors (TNFis) has improved treatment outcome in patients with PsA who have failed treatment with conventional synthetic DMARDs (csDMARDs) [1–8]. By March 2013, four TNFis were marketed in Denmark and Iceland to treat PsA: adalimumab, etanercept, golimumab and infliximab [7, 9–12]. The recommended dose regimens for adalimumab, etanercept and golimumab in PsA are equal to the regimens in RA, i.e. fixed dosage independent of the patient's body weight. For infliximab, patients with PsA are recommended higher doses than patients with RA, i.e. 5 vs 3 mg/kg body weight every 8 weeks [13–16]. This recommendation is based on data from randomized placebo-controlled clinical trials [4, 6, 17, 18]. Data on the effectiveness of lower infliximab doses in PsA are, however, scarce [19–23].

The Danish nationwide DANBIO registry now includes >10 years of prospective follow-up of patients with inflammatory arthritis treated with biologics in routine care [24, 25]. Similarly, Icelandic patients have been registered and followed in the ICEBIO registry since 2007 [26].

Based on data from DANBIO and ICEBIO we aimed to describe the following: (i) the infliximab dose regimens used in clinical practice, (ii) dose escalation and (iii) whether the starting dose regimen affected (a) treatment response and (b) drug survival in TNFi-naive patients with PsA receiving their first infliximab treatment course.

Patients and methods

The nationwide Danish DANBIO registry commenced in 2000 and covers >90% of Danish adults treated with biologics due to rheumatic disease in routine care [27–29]. Prospective data registration in the Icelandic ICEBIO registry started in 2007. Biologic treatment courses, which were started in Iceland before 2007, have been registered retrospectively. Currently ICEBIO covers >95% of all biologic treatment given in Iceland in patients with rheumatic disorders (B. Gudbjorsson, 2013, personal communication). According to Danish legislation, the registration and publication of data from clinical registries does not require patient consent or approval by an ethics committee. In Iceland, this study was approved by the National Bioethics Committee (VSNb201310035/03.15) and the Data Protection Authority (2012080907HGK).

In Iceland, local hospital guidelines in PsA recommend infliximab doses of 200 mg every 8 weeks, irrespective of the patient's body weight. In cases of insufficient response, doses are increased stepwise to 300, 400 or 500 mg [26, 30]. In Denmark, no national treatment guidelines existed during the study period.

By March 2013, 4966 patients with a diagnosis of PsA according to the treating physician had been registered (4742 patients in DANBIO, 224 in ICEBIO). Among these, 3237 patients were treated only with csDMARDs. The remaining 1729 patients were treated with biologic DMARDs (bDMARDs): 462 patients received infliximab as the first bDMARD, 705 adalimumab, 371 etanercept, 51 golimumab and 19 received other biologic drugs. We excluded 82 patients treated with bDMARDs as part of clinical trials and 39 patients with insufficient data on their first TNFi treatment course. Only the 462 patients who received infliximab as the first bDMARD were included in the present study.

DANBIO and ICEBIO use a common web-based system (www.danbio-online.dk) [31]. Baseline demographics include age, gender, body weight, height, disease duration, previous or current treatment with MTX or other csDMARDs. Functional status and peripheral disease activity are monitored prospectively by the Health HAQ [32], the 28-joint DAS (DAS28) [33], CRP level (normal range ≤ 10 mg/l) and visual analogue scales (VASs) for pain, patient’s global assessment and fatigue. It is not explicitly registered whether a patient has spinal disease. Data registration is recommended to occur at least biannually, or when the medical treatment is changed [24].

Infliximab dose regimens

The infliximab dose per infusion was reported as (i) the total dose per infusion (in mg) and (ii) the dose measured in milligrams per kilogram of body weight. The patients were treated at weeks 0 (baseline), 2 and 6 and thereafter at regular intervals (typically every 8 weeks). Arbitrarily patients were divided into three categories according to dose per kilogram of body weight at the baseline visit: ≤ 3, 3–5, > 5 mg/kg. Dose escalation was defined as increased dose and/or reduced time intervals between infusions compared with baseline.

Data quality

Queries were sent to the departments regarding treatment series with incomplete data (infliximab dose regimens and/or body weight) and the registries were corrected accordingly.

Treatment duration

Treatment duration was the number of days individual patients maintained infliximab treatment. The start date was the date the first dose was given and the stop date was the date of the first missed dose. Temporary treatment interruptions of < 3 months were allowed. All observations were censored by 15 March 2013. Among patients with no follow-up since 15 November 2012, data were censored according to the last visit registered.

The reasons for drug discontinuation are registered in DANBIO/ICEBIO in pre-specified categories: lack of treatment effect (LOE), adverse events (AEs), disease remission, pregnancy, surgery, cancer, death, infections, loss to follow-up and other reasons. In the following, reasons for discontinuation are divided into three categories: AEs (including infection, death or cancer), LOE and other (including pregnancy, surgery, loss to follow-up, remission or multiple reasons for discontinuation).

Treatment response

Disease activity and physical function were evaluated at baseline and after 3, 6 and 12 months of therapy. The
baseline visit was defined as the time window from 30 days before until 6 days after the initiation of therapy. For the 3-month visit the time window was 10–17 weeks, for the 6-month visit it was 18–32 weeks and for the 12-month visit it was 46–64 weeks after initiation of treatment. If more than one registration occurred within a given time window, the one closest to the given time point was selected for analysis. If a patient had no registrations within a given time window, data were registered as missing for the given visit.

In the analyses of the 12-month outcome, the last observation carried forward (LOCF) method was used among patients with missing data at the 12-month visit and among patients who had stopped treatment within the first year. All other calculations were based on observed data with no imputation of missing data.

Clinical response was evaluated as achievement of ACR 20%, 50% or 70% response (ACR20/50/70) [34] or the European League Against Rheumatism (EULAR) good response [35]. We classified patients as responders if they achieved clinical response (yes/no) at both the 3- and 6-month visits compared with baseline. In case of missing data at either the 3- or 6-month visit, one registration of clinical response was sufficient to characterize the patient as a responder. Patients who had stopped treatment within the first 10 weeks of therapy were considered non-responders (non-responder imputation, n = 44).

Statistics

Statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA) and SAS version 9.0 (SAS Institute, Cary, NC, USA) software. Demographic and descriptive data are presented as median [interquartile range (IQR)]. Groups were compared by non-parametric tests (chi-squared, Mann–Whitney, Wilcoxon signed rank test). A P-value of < 0.05 was considered statistically significant.

Kaplan–Meier plots and log-rank tests were performed for infliximab drug survival analyses and to analyse time until dose escalation. Univariate and multivariate Cox regression analyses with hazard ratios (HRs) were used to identify the impact of baseline infliximab dose on drug survival. In the subanalysis of time to discontinuation due to AEs, discontinuations due to ineffectiveness were censored. Similarly, discontinuations due to AEs were censored in the analysis of discontinuation due to ineffectiveness. Logistic regression analyses and odds ratios were calculated to identify the impact of baseline infliximab dose on clinical response. Baseline infliximab dose was included in all analyses as a categorical variable (≤3, 3–5, >5 mg/kg). Additional sensitivity analyses were performed with the baseline dose (in mg/kg) as a continuous variable.

All multivariate analyses were performed stratified by country to avoid statistical interaction. The following baseline variables were considered a priori confounders and included in all multivariate analyses: gender, MTX use (yes/no), patient age, time interval between infusions (weeks), disease duration (years), HAQ and DAS28.

Calendar year of starting treatment and body weight were considered intermediate variables potentially influenced by the starting dose of infliximab and were not included.

Results

A total of 462 infliximab-treated patients (376 Danish, 86 Icelandic) were included. Baseline demographics for Danish and Icelandic patients are shown in Table 1 and Table 2, respectively. The median starting infliximab dose was 3.1 mg/kg (IQR 3.0–3.8) for Danish patients and 2.3 mg/kg (2.1–2.9) for Icelandic patients (P = 0.0001). After up-titration, 94% of patients received infliximab at 8-week intervals. Danish patients had lower body weight [80 kg (IQR 68–94) vs 87 (77–97), P = 0.001], lower BMI [27 kg/m² (IQR 24–30) vs 29 (26–32), P = 0.001], higher DAS28 [4.7 (IQR 3.8–5.5) vs 4.2 (3.3–4.9), P = 0.009] and higher tender joint count (TJC) [6 (IQR 2–11) vs 4 (2–6), P = 0.006] compared with Icelandic patients upon initiation of therapy, whereas other baseline characteristics [age, gender distribution, height, disease duration, MTX use, VAS score, swollen joint count (SJC) and CRP] were similar (all P > 0.05).

At baseline, Danish patients treated with >5 mg/kg infliximab had lower SJC and lower VAS physician score compared with Danish patients on lower doses, whereas other measures of disease activity were similar (Table 1). Doses >5 mg/kg were more often started in the later years and in women (Table 1). Among Icelandic patients there was a tendency towards higher VAS physician score and TJC among patients starting treatment with >5 mg/kg, and no patients started on doses >5 mg/kg (Table 2). In both Denmark and Iceland, patients with higher body weight and BMI received lower doses per kilogram (Table 1 and Table 2).

At 12 months median infliximab doses for Danish and Icelandic patients were 3.3 mg/kg (IQR 3.0–4.5) and 2.9 (2.2–3.5) (P < 0.0001) every 8 (8–8) weeks, respectively. The median dose per infusion was 300 mg (IQR 200–300) and 200 (200–300) (P < 0.01), respectively. Danish patients had similar disease activity irrespective of the baseline infliximab dose (LOCF, Kruskal–Wallis test; Table 3). Similar results were found in Icelandic patients (data not shown, all P > 0.05). There were no differences in DAS28, VAS score, SJC, TJC or HAQ after 12 months between Danish and Icelandic patients (Mann–Whitney, all P > 0.05, data not shown).

At the latest registered visit, 247 patients (53%) received infliximab in unaltered or reduced regimens, whereas 145 patients (31%) (53% of Icelandic and 26% of Danish patients) had an increased dose due to either increased dose per infusion (65 patients, median dose increase/kg 1.2 mg/kg (IQR 0.8–1.8)), shortening of the time interval between infusions (32 patients) or both (48 patients). In 2% of patients the infliximab dose was increased but the time intervals were prolonged or vice versa. Data were missing in 13% of patients. Danish patients on increased infliximab dose regimens had longer treatment duration [median 819 days (IQR 321–1723)].
TABLE 1 Baseline demographics and disease activity for Danish patients registered in DANBIO according to infliximab dose at the baseline visit

<table>
<thead>
<tr>
<th></th>
<th>Infliximab dose/kg (n = 305)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>≤ 3 mg</td>
</tr>
<tr>
<td>Patients, n</td>
<td>376</td>
<td>110</td>
</tr>
<tr>
<td>Infliximab dose, mg</td>
<td>290 (200–300)</td>
<td>200 (200–293)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>204 (54)</td>
<td>50 (45)</td>
</tr>
<tr>
<td>Dosing interval, weeks</td>
<td>8 (8–8)</td>
<td>8 (8–8)</td>
</tr>
<tr>
<td>Year starting TNFi, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2</td>
<td>20 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>2003–5</td>
<td>104 (28)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>2006–8</td>
<td>145 (39)</td>
<td>54 (49)</td>
</tr>
<tr>
<td>2009–12</td>
<td>107 (28)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Concomitant MTX, n (%)</td>
<td>260 (69)</td>
<td>82 (75)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7 (3–13)</td>
<td>9 (3–17)</td>
</tr>
<tr>
<td>Age, years</td>
<td>48 (40–56)</td>
<td>46 (40–55)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>80 (68–94)</td>
<td>82 (71–100)</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>172 (165–178)</td>
<td>172 (166–180)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (24–30)</td>
<td>28 (25–32)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.1 (0.8–1.6)</td>
<td>1.1 (0.6–1.6)</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.7 (3.8–5.5)</td>
<td>4.9 (3.7–5.6)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>10 (4–25)</td>
<td>10 (5–24)</td>
</tr>
<tr>
<td>SJC, n (range)</td>
<td>2 (1–6)</td>
<td>3 (0–7)</td>
</tr>
<tr>
<td>TJC, n (range)</td>
<td>6 (2–11)</td>
<td>6 (2–14)</td>
</tr>
<tr>
<td>VAS physician, score (range)</td>
<td>37 (23–55)</td>
<td>38 (26–57)</td>
</tr>
<tr>
<td>VAS global, mm</td>
<td>69 (51–84)</td>
<td>67 (50–84)</td>
</tr>
<tr>
<td>VAS fatigue, mm</td>
<td>68 (47–83)</td>
<td>69 (45–77)</td>
</tr>
<tr>
<td>VAS pain, mm</td>
<td>62 (43–76)</td>
<td>65 (45–78)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) unless stated otherwise. *Missing data on baseline infliximab dose in 71 patients. P-value in Kruskal-Wallis test. TNFi: TNF-α inhibitor; DAS28: 28-joint DAS; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

compared with the patients receiving unaltered/reduced doses [371 days (159–1249)] (P < 0.001). Similar results were found in Icelandic patients [1207 days (432–2139) vs 307 (120–757)], P < 0.001.

The numbers of Danish and Icelandic patients receiving starting doses of ≤3, 3-5 or >5 mg/kg are shown in Fig. 1. Among patients with available data and who were treated for >100 days, 77% (205/265) of Danish and 96% (69/72) of Icelandic patients received sustained infliximab doses ≤5 mg/kg (Fig. 1).

Data on baseline infliximab dose per kilogram were missing in 71 Danish and 5 Icelandic patients. Danish patients with missing data had similar gender, BMI and age distribution to the 305 patients with available data (all P > 0.05), whereas patients with missing data more often started treatment during earlier years (P < 0.0001). In Icelandic patients, baseline demographics were similar between patients with available and those with missing data on baseline dose (all P > 0.05).

Cumulated follow-up time for Danish and Icelandic patients was 1185 patient-years and the median follow-up time was 550 days (95% CI 383, 317). Overall, 116 patients (25%) stopped treatment due to LOE and 134 (29%) stopped due to AEs. The reasons for stopping treatment were similar for Danish and Icelandic patients (P = 0.4).

The starting infliximab dose per kilogram was similar between patients who continued treatment [median 3.0 mg/kg (IQR 2.6–3.8)] and patients who stopped due to LOE [3.1 mg/kg (2.7–3.6)] or AEs [3.1 mg/kg (2.9–3.5)] (P = 0.2).

At the latest visit, patients who stopped treatment due to LOE received higher infliximab doses compared with patients who stopped due to AEs [median 3.5 mg/kg (IQR 3.0–4.7) vs 3.1 (2.9–3.7), P = 0.002].

After 12 months, 58% of Danish and 66% of Icelandic patients were still on the drug. Drug survival was significantly shorter among Danish compared with Icelandic patients [median 483 days (95% CI 372, 594) vs 1183 (470–1896), log rank 7.7, P = 0.005] (Fig. 2A).

The starting infliximab dose did not affect survival (Danish patients: Fig. 2B; Icelandic patients: Fig. 2C). For Danish patients, drug survival was shorter in patients not receiving concomitant MTX (Fig. 2D) and when treatment was started in later years (Fig. 2E). Similar results were found when Kaplan–Meier analyses were performed among Icelandic patients (MTX use, P = 0.1; treatment start year, P = 0.003). The start dose did not affect the time until dose escalation (P = 0.9). The median number of days until dose escalation was similar for Danish and Icelandic patients [266 days (IQR 131–560) vs 290 (182–559), P = 0.2].
In multivariate Cox regression analysis among Danish patients, infliximab starting dose as a categorical value did not affect drug survival ($P = 0.5$). In a similar analysis with starting dose as a continuous variable, patients on a lower dose had shorter drug survival [HR 0.7/mg/kg (95% CI 0.55, 0.95), $P = 0.02$]. The same pattern was observed when looking only at patients who withdrew due to AEs [HR 0.7/mg/kg (95% CI 0.55, 0.95), $P = 0.02$].

### Table 2: Baseline demographics and disease activity for Icelandic patients registered in ICEBIO according to infliximab dose at the baseline visit

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Infliximab dose/kg ($n = 81^a$)</th>
<th>$P$-value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\leq 3$ mg</td>
<td>$3-5$ mg</td>
</tr>
<tr>
<td>Patients, n</td>
<td>86</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>Infliximab dose, mg</td>
<td>200 (200-200)</td>
<td>200 (200-200)</td>
<td>200 (200-350)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>48 (56)</td>
<td>35 (54)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Dosing interval, weeks</td>
<td>8 (8-8)</td>
<td>8 (8-8)</td>
<td>8 (8-8)</td>
</tr>
<tr>
<td>Year starting TNFi, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2</td>
<td>5 (6)</td>
<td>5 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2003-5</td>
<td>15 (17)</td>
<td>10 (16)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>2006-8</td>
<td>25 (29)</td>
<td>16 (25)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>2009-12</td>
<td>41 (48)</td>
<td>33 (52)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Concomitant MTX, n (%)</td>
<td>53 (61)</td>
<td>40 (63)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8 (3-17)</td>
<td>7 (3-17)</td>
<td>7 (2-35)</td>
</tr>
<tr>
<td>Age, years</td>
<td>48 (36-54)</td>
<td>49 (37-55)</td>
<td>43 (35-62)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>87 (77-97)</td>
<td>92 (80-99)</td>
<td>65 (61-86)</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>172 (166-182)</td>
<td>174 (167-182)</td>
<td>167 (162-169)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (26-32)</td>
<td>30 (27-33)</td>
<td>24 (21-30)</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.8 (0.3-1.1)</td>
<td>0.8 (0.3-1.0)</td>
<td>1.4 (0.2-2.1)</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.2 (3.3-4.9)</td>
<td>4.2 (3.3-4.9)</td>
<td>4.8 (4.4-6.0)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>8 (5-19)</td>
<td>9 (4-19)</td>
<td>9 (6-39)</td>
</tr>
<tr>
<td>SJC, n (range)</td>
<td>3 (1-5)</td>
<td>3 (1-5)</td>
<td>5 (1-8)</td>
</tr>
<tr>
<td>TJC, n (range)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
<td>6 (5-17)</td>
</tr>
<tr>
<td>VAS physician, score (range)</td>
<td>55 (42-67)</td>
<td>51 (40-64)</td>
<td>72 (56-89)</td>
</tr>
<tr>
<td>VAS global, mm</td>
<td>35 (37-81)</td>
<td>64 (38-80)</td>
<td>89 (47-97)</td>
</tr>
<tr>
<td>VAS fatigue, mm</td>
<td>74 (45-80)</td>
<td>72 (49-80)</td>
<td>91 (47-100)</td>
</tr>
<tr>
<td>VAS pain, mm</td>
<td>65 (42-81)</td>
<td>63 (45-80)</td>
<td>88 (47-97)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) unless stated otherwise. $^a$Missing data on baseline infliximab dose in five patients. $^b$ $P$-value in Kruskal-Wallis test. TNFi: TNF-α inhibitor; DAS28: 28-joint DAS; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

### Table 3: Disease activity at the 1-year visit for Danish patients according to the baseline infliximab dose

<table>
<thead>
<tr>
<th></th>
<th>Baseline infliximab dose/kg$^a$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\leq 3$ mg</td>
<td>$3-5$ mg</td>
</tr>
<tr>
<td>Number still treated after 12 months, n (%)</td>
<td>70 (64)</td>
<td>89 (57)</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.8 (0.2-1.3)</td>
<td>0.6 (0.1-1.1)</td>
</tr>
<tr>
<td>DAS28</td>
<td>3.0 (2.3-3.9)</td>
<td>3.1 (2.1-4.2)</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>5 (2-10)</td>
<td>5 (2-11)</td>
</tr>
<tr>
<td>SJC, n (range)</td>
<td>0 (0-3)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>TJC, n (range)</td>
<td>1 (0-4)</td>
<td>2 (0-6)</td>
</tr>
<tr>
<td>VAS physician, mm</td>
<td>33 (13-62)</td>
<td>33 (15-63)</td>
</tr>
<tr>
<td>VAS global, mm</td>
<td>47 (16-68)</td>
<td>50 (25-76)</td>
</tr>
<tr>
<td>VAS pain, mm</td>
<td>27 (13-59)</td>
<td>32 (10-56)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range), unless stated otherwise. $^a$Missing data on baseline dose, $n = 39$ (16%). Last observation carried forward (LOCF) method. DAS28: 28-joint DAS; VAS: visual analogue scale; SJC: swollen joint count; TJC: tender joint count.
Fig. 1 Study flow chart of infliximab dose according to treatment duration, stratified by country

A Danish patients

<table>
<thead>
<tr>
<th>Start dose</th>
<th>Stopped treatment after ≤100 days</th>
<th>Treatment duration &gt;100 days. Dose regimen at latest registered visit. N=718</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 mg/kg, n=576</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5 mg/kg, n=17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 mg/kg, n=58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown, n=71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In multivariate Cox regression analysis of Icelandic patients, those who started treatment with doses ≤3 mg/kg had longer drug survival than patients starting on higher doses [≤3 vs 3-5 mg/kg, HR 0.2 (95% CI 0.001, 0.55), P = 0.02]. In a similar analysis with infliximab starting dose as a continuous variable, the starting dose was not statistically significant (P = 0.6). Stratified analyses according to the cause of treatment termination were not performed in Icelandic patients due to few events.

In Danish patients, EULAR good response and ACR20/50/70 response rates after 6 months were 33%, 38%, 23% and 10%, respectively. EULAR and ACR response data were available in 54% and 63% of patients, respectively, with no systematic differences between patients with complete and incomplete data, except for more patients with missing ACR response data during earlier years. The response rates were not associated with baseline disease activity and demographics as the Danish and Icelandic populations [23]. The Swedish studies provide no data on infliximab response rates and survival [23, 43], so we do not know whether the different regimens affected outcome.

Drug survival may be perceived as a measure of treatment effectiveness [45]. In Danish patients, drug survival was longer among patients who received higher baseline infliximab doses, thus indicating a positive effect of higher doses. However, the infliximab dose only affected drug survival in multivariate and not univariate analyses. In Icelandic patients, the picture was less clear, perhaps due to limited statistical power. The different treatment strategies in Denmark vs Iceland might have an impact on the results. In Iceland, patients had lower disease
activity at treatment start and the majority of patients received a fixed starting dose of 200 mg. In Denmark, the starting dose was chosen according to the preference of the treating physician. Thus confounding by indication or channelling bias cannot be ruled out and differences in disease severity, co-morbidities or other psoriatic disease manifestations might have affected drug effectiveness as judged by drug survival.

Observational and registry studies provide a valuable supplement to RCTs regarding prescription practice and treatment outcome when drugs are used in routine care [29, 46]. In real life, with more liberal treatment criteria than in RCTs, drug retention rates, and thus effectiveness, are often lower. In addition, patients who stopped treatment within 3 months were classified as non-responders in the present study. As expected, we found the effectiveness of infliximab in routine care to be lower than drug efficacy in RCTs. Thus RCTs of infliximab in PsA have reported drug efficacy (ACR20/50/70 response rates) to be approximately 50%, 35% and 20%, respectively [6, 47]. We did not find effectiveness to be associated with the baseline dose of infliximab. The current study demonstrated that the clinical use of infliximab and adherence to national and international guidelines varied between Denmark and Iceland. This illustrates that extrapolation of outcome data across countries must be done with caution and that publication of clinical data from various countries is of importance.

We found that concomitant MTX improved infliximab drug survival. This is in accordance with previous studies regarding TNFi treatment in PsA [25, 43, 48–51]. The possible beneficial effect of MTX combination therapy in PsA might be reduced formation of anti-chimeric antibodies [23, 51, 52].

Drug survival was shorter among patients who started treatment during the later years. This might illustrate a change in prescription practice with initiation of TNFi treatment among less ill patients with poorer treatment outcomes [53]. Also, the availability of more TNFis might lead to early switching [12]. This could also explain why many patients stopped infliximab treatment due to LOE although they only received a lower infliximab dose;
alternatively, economic considerations or fear of AEs might have affected this decision. This study has limitations to consider. Few patients started treatment with infliximab ≥5 mg/kg and a lack of power to detect potential beneficial effects of higher doses cannot be excluded. Similarly, the patients who stopped treatment due to LOE while receiving doses <5 mg/kg might have experienced an effect on higher doses. Response data were only available in approximately half of the patients, and this might have affected our results. Although ACR and EULAR responses were originally developed to monitor treatment effect in RA, they have been widely used in PsA [54, 55]. However, these measures do not include data on all joints potentially affected in PsA, e.g., hips, DIP joints of the hand or ankles and joints of the feet. This may be of importance when these response measures are used in a clinical setting and may cause an underestimation of disease activity [56]. This might perhaps explain the relatively low median SJC upon initiation of infliximab therapy seen in the present study. Spinal disease might affect the starting dose: perhaps patients with symptoms of spinal disease more frequently received higher doses in accordance with the guidelines for AS. Furthermore, enthesitis, dactylitis or other psoriatic disease manifestations are potential confounders, but we did not have data to investigate this. To address these issues further, a future randomized clinical trial comparing low vs traditional infliximab doses in PsA would be of relevance. Preferably such a trial should include data on not only 68-joint disease activity, but also skin and other psoriatic disease domains.

In conclusion, this observational study from two countries demonstrated that infliximab doses below the recommended 5 mg/kg were widely used in PsA in routine care. A low starting dose with subsequent step-up therapy seemed an effective strategy. Concomitant use of MTX was associated with improved drug survival.

Rheumatology key messages

- In Denmark and Iceland, infliximab doses <5 mg/kg are widely used in routine treatment of PsA.
- A low infliximab starting dose with subsequent step-up therapy seems effective in PsA.

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EXTENDED REPORT

Association between tobacco smoking and response to tumour necrosis factor \(\alpha\) inhibitor treatment in psoriatic arthritis: results from the DANBIO registry

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ABSTRACT

Objectives To investigate the association between tobacco smoking and disease activity, treatment adherence and treatment responses among patients with psoriatic arthritis (PsA) initiating the first tumour necrosis factor \(\alpha\) inhibitor therapy (TNFi) in routine care.

Methods Observational cohort study based on the Danish nationwide DANBIO registry. Kaplan–Meier plots, logistic and Cox regression analyses by smoking status (current/previous/never smoker) were calculated for treatment adherence, ACR20/50/70-responses and EULAR-good-response. Additional stratified analyses were performed according to gender and TNFi-subtype (adalimumab/etanercept/infliximab).

Results Among 1388 PsA patients included in the study, 1148 (83%) had known smoking status (33% current, 41% never and 26% previous smokers). Median follow-up time was 1.22 years (IQR 0.44–2.96). At baseline, current smokers had lower Body Mass Index (27 kg/m\(^2\)) (23–30 kg/m\(^2\)) (24–31)) (median (IQR)), shorter disease duration (3 years (1–8)5 years (2–10)), lower swollen joint count (2 (0–5)/3 (1–6)), higher visual-analogue-scale (VAS) patient global (72 mm (54–87)/68 mm (50–80)), VAS fatigue (72 mm (51–86)/63 mm (40–77)) and Health Assessment Questionnaire (HAQ) score (1.1 (0.7 to 1.5)/1.0 (0.5 to 1.5)) than never smokers (all p<0.05). Current smokers had shorter treatment adherence than never smokers (1.56 years (0.97 to 2.15)/2.43 years (1.88 to 2.97), (median (95% CI)), log rank p=0.02) and poorer 6 months’ EULAR-good-response rates (23%/34%), ACR20 (24%/33%) and ACR50 response rates (17%/24%) (all p<0.05, most pronounced in men. In current smokers, the treatment adherence was poorer for infliximab (HR) 1.62, 95% CI 1.06 to 2.48) and etanercept (HR 1.74, 1.14 to 2.66) compared to never smokers, but not for adalimumab (HR 0.80, 0.52 to 1.23).

Conclusion In PsA, smokers had worse baseline patient-reported outcomes, shorter treatment adherence and poorer response to TNFi’s compared to non-smokers. This was most pronounced in men and in patients treated with infliximab or etanercept.

INTRODUCTION

Tumour necrosis factor \(\alpha\) inhibitors (TNFi) are effective therapies in patients with psoriatic arthritis (PsA) who have insufficient response to synthetic disease-modifying antirheumatic drugs (sDMARD). However, only ~60% of patients achieve ACR20 response. Thus, it is important to identify potential response modifiers to facilitate a rational and effective individualised treatment strategy. The impact of tobacco smoking is of particular interest since smoking is a potentially modifiable lifestyle factor.

Smoking is a possible risk factor for developing PsA, but results are conflicting. However, little is known about the impact of smoking on disease activity and TNFi treatment response in PsA. In axial spondyloarthritis, smoking increases disease activity and radiographic progression and reduces quality of life. In rheumatoid arthritis (RA) smokers have higher disease activity, and TNFi treatment is less efficacious.

The nationwide DANBIO registry includes data on patients with rheumatologic diseases treated with TNFi in Denmark. We have previously described demographics and outcomes in patients with PsA treated with TNFi. The aim of the present study was to investigate differences between smokers and non-smokers regarding disease activity, treatment responses and adherence rates in patients with PsA initiating their first TNFi therapy in routine care. Furthermore, to study if the impact of smoking was influenced by gender and TNFi drug type.

PATIENTS AND METHODS

The DANBIO registry covers >90% of Danish adults treated in routine care with biologics due to rheumatic disease. According to Danish legislation, the registration and publication of data from clinical registries do not require patient consent or approval by ethics committees. Physicians are recommended to report data prospectively by an online system at least biannually and when medication is changed.

Baseline demographics include smoking habits, age, gender, Body Mass Index (BMI), disease duration, previous or current treatment with methotrexate (MTX) or other sDMARD. Functional status and peripheral disease activity are monitored by Health Assessment Questionnaire (HAQ).
28-joint Disease Activity Score (DAS28), C-reactive protein (CRP) level (normal range ≤10 mg/L), and visual analogue scales (VAS) for scores of pain, patient’s global and fatigue. It is not explicitly registered in DANBIO whether PsA patients have axial disease. Due to a limited number of registrations of axial disease activity at baseline and follow-up, these data were not included in the present study.

By 1 January 2012, 1536 patients with a diagnosis of PsA according to the treating rheumatologist had been registered and treated with a biological drug (bDMARD). We excluded patients treated with golimumab (n=19), bDMARDs other than TNFi (n=42), patients participating in clinical trials (n=34) or not followed in DANBIO since start of their first TNFi (n=33), leaving 1388 patients in the study.

**Tobacco smoking status**

In this study, patients were divided into three groups according to smoking status: current (≥1 cigarette/day), previous and never smokers. In previous smokers, the number of years since smoking cessation was recorded. Smokers, who had stopped smoking the same year as they started TNFi, were defined as previous smokers (n=24).

Queries were sent to the departments regarding patients with incomplete data on smoking status. Information was then obtained from hospital files or by asking the patients.

**Treatment adherence**

Treatment adherence was calculated as the number of years individual patients maintained treatment. Start date was the date of the first given dose, and stop date was the date of the first missed dose. Temporary treatment interruptions (eg, due to infections or surgery) of ≤3 months’ duration were allowed. All observations were censored at April 20th 2012. Among patients with no follow-up since December 2011, data were censored according to the last visit registered.

Reasons for drug discontinuation are registered in DANBIO in pre-specified categories: lack of effect, adverse events, disease remission, pregnancy, surgery, cancer, death, infections, loss to follow-up and other reasons. In the following, reasons for discontinuation are divided into three categories: ‘adverse events’ (including infection, death or cancer), ‘lack of effect’ and ‘other’ (including pregnancy, surgery, loss to follow-up, remission and other reasons for discontinuation).

**Disease activity**

Disease activity was evaluated at baseline and after 3 and 6 months’ therapy. The baseline visit was defined as a visit within the time window that ranged from 5 days before until 6 days after initiation of therapy. For the 3 months’ visit, the time window was 10–17 weeks, and for the 6 months’ visit 18–32 weeks after treatment start. If more than one registration occurred within a given time window for an individual patient, the registration closest to the given time-point was selected for analysis. If a patient had no registrations within a given time window, data were registered as missing for the given visit.

Clinical response was evaluated as achievement of ACR20/50/70 or EULAR-good-response. Arbitrarily, we classified patients as ‘responders’ if they achieved clinical response (yes/no) at the 3-months’ and 6 months’ visits compared to baseline. In case of missing data at either the 3-months’ or 6 months’ visit, one registration of clinical response was sufficient to characterise the patient as responder. Patients who stopped treatment within the first 3 months of therapy were considered non-responders (n=272).

**Statistics**

Statistical analyses were performed by SPSS (V20.0, SPSS, Chicago, Illinois, USA). Demographic and descriptive data are presented by medians/IQR. Groups were compared by non-parametric tests (χ², Kruskal–Wallis and Mann–Whitney tests). In all tests, p values <0.05 were considered statistically significant. Calculations were based on observed data and no imputation of missing data was performed.

Kaplan–Meier plots and log rank tests were performed for analyses of treatment adherence for current, never and previous smokers. By univariate and multivariate Cox regression analyses we studied the impact of smoking on treatment adherence and associated HRs. The assumption of proportional hazards in the Cox regressions models was not fulfilled for previous smokers compared with current and never smokers and, therefore, only the latter two smoking categories were included (figure 1A). Univariate and multivariate logistic regression analyses and ORs were calculated to identify the impact of smoking (current/never) on clinical responses. Previous smokers were included in subanalyses. The following baseline factors were considered a priori confounders and included in all multivariate analyses: age (in quartiles), gender, disease duration (in tertiles), calendar year of starting TNFi (in tertiles). Age, disease duration and year of treatment start were transformed into categorical variables to allow for possible non-linear effects. Baseline smoking status were current smokers.

In the subanalysis of time to discontinuation due to adverse events, discontinuations due to ineffectiveness were treated as censored observations and vice versa.

**RESULTS**

A total of 1388 bDMARD-naive patients initiating treatment with adalimumab, etanercept or infliximab as the first TNFi were included (table 1). Among 1148 patients (83%) with known smoking status, 33% were current, 41% never and 26% previous smokers. Patients with missing smoking information had lower BMI, younger age, longer disease duration, higher CRP, higher SJC, lower VAS global and fatigue scores, compared to patients with available smoking information (table 1). Thirty-four percent of women and 31% of men with known smoking status were current smokers.

At baseline, current smokers had shorter disease duration, lower BMI, higher HAQ, higher VAS fatigue and VAS global compared to previous and never smokers (table 1). Previous smokers were older than current and never smokers. The reasons for stopping TNFi treatment were independent of smoking status (table 1). Male current smokers had higher HAQ (1 (0.6–1.4) vs 0.8 (0.4–1.3), (median (IQR)), p=0.03) and shorter disease duration (3 years (1–10) vs 6 years (2–13), p=0.03) than male never smokers, whereas VAS scores, DAS28 and BMI were similar (all p>0.05). Female current smokers had lower BMI (25 kg/m² (23–29) vs 28 kg/m² (24–32), p=0.001),
higher VAS fatigue (77 mm (60–89) vs 61 mm (40–79), p =0.003) and shorter disease duration (2 years (1–6) vs 4 years (1–8), p =0.02) compared to female never smokers, whereas VAS global, DAS28 score and HAQ scores were similar (all p >0.05).

The median follow-up time for all included patients was 2.15 years (1.05 years – 2.97) in never smokers (median (95% CI)) versus 2.97 years (2.94) in current smokers vs 2.96 (current smokers 1.05 years – 2.97) in never smokers (median (95% CI)) in Kaplan–Meier analyses stratified for gender, age, disease duration and start year of TNFi, we found no significant difference in treatment adherence between current smokers and never smokers, neither overall (HR 1.18 (0.97 to 1.44)) nor in males (HR 1.22 (0.97 to 1.67)) or females (HR 1.14 (0.87 to 1.5)).

In Kaplan–Meier analyses stratified according to TNFi drug type, estimated median survival time was poorer among current versus never smokers in patients treated with etanercept (1.0 year (0.66 to 1.39) vs 3.5 years (2.6 to 4.4), median (95% CI), log rank p =0.01), while smoking had no impact on adherence in patients treated with infliximab (1.2 years (0.69 to 1.61) vs 1.5 years (1.1 to 1.9), p =0.3) or adalimumab (2.8 years (1.9 to 3.7) vs 2.4 years (1.5 to 3.4), p =0.3). Similar results were found in univariate Cox regression analyses (data not shown). In multivariate Cox regression analyses adjusted for gender, age, disease duration and start year of TNFi, we found no significant difference in treatment adherence between current smokers and never smokers, neither overall (HR 1.18 (0.97 to 1.44)) nor in males (HR 1.22 (0.97 to 1.67)) or females (HR 1.14 (0.87 to 1.5)).

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Univariate Cox regression analyses stratified according to stop reason showed a comparable effect of current smoking on drug termination due to ‘adverse events’ and ‘lack of effect’ (HR 1.32 (0.98 to 1.78) and (HR 1.28 (0.98 to 1.67), respectively, both p=0.07 compared to never smokers).

Changes between baseline and 3 months’ and 6 months’ disease activity were calculated for VAS patient’s global, VAS pain, CRP, tender and SJC according to smoking status. There was a non-significant tendency towards a greater decline in CRP after 6 months among never compared to current smokers (4.5 mg/L (0.3–17) vs 3 mg/L (0–11), p=0.08), whereas, data were insignificant at 3 months (p=0.6). No significant differences were found for delta VAS scores or delta joint counts among current versus never smokers at 3 months and 6 months (all p>0.05, data not shown).

Current smokers had lower EULAR-good-response and ACR20/50 response rates than had never smokers, whereas, ACR70 response rates were similar (figure 2). Twenty-three percent of current smokers achieved a EULAR-good-response after 6 months compared to 34% of never smokers (p=0.01). The rates for ACR20 and ACR50 response were 24%/33% (p=0.04) and 17%/24% (p=0.04), respectively. These differences were mainly present among men with EULAR-good-response: 24%/42% (p=0.002); ACR20: 25%/41% (p=0.01) and ACR50 response rates: 21%/32% (p=0.05) (figure 2). In univariate logistic regression analysis, current smokers had lower odds of achieving EULAR-good-response (OR=0.6 (95% CI 0.4 to 0.9) vs never smokers, p=0.01) and ACR20 (OR=0.7 (0.4 to 0.9), p=0.04), ACR50 (OR=0.6 (0.4 to 0.9) p=0.05) and ACR70 (OR=0.6 (0.4 to 1.16), p=0.14) responses. In multivariate analyses, the negative impact of smoking on treatment responses (ACR20/50/70 and EULAR-good-response) only reached statistical significance in gender-stratified analyses, where smoking was associated with a lower EULAR-good-response rate in men (OR=0.5 (0.3 to 0.9), p=0.03 current vs never smokers). In logistic regression subanalyses stratified by type of TNFi, smoking status did not affect response rates (overall and by gender, all p>0.05).

In subanalyses, previous smokers were included as an additional group. In Kaplan–Meier analysis, previous smokers initially had drug adherence similar to current smokers. Beyond ~6 months, the drug adherence for previous smokers was intermediate to those for never smokers and current smokers (figure 1A). When previous smokers were stratified according to number of years since smoking cessation, the drug adherence improved with more years since smoking cessation (figure 1D).

Figure 1  Kaplan–Meier drug adherence curves according to: (A) smoking status, all patients (log rank 7.7, p=0.02). (B) smoking status (current vs never), men (log rank 6.3, p=0.01). (C) smoking status (current vs never), women (log rank 1.1, p=0.3). (D) smoking stop year among previous smokers (log rank 1.0, p=0.053).
In men, previous smokers tended to have higher EULAR-good-response and ACR20 response rates than current smokers, and lower rates compared to never smokers (univariate logistic regression analyses, data not shown) (figure 2).

**DISCUSSION**

In this observational study of 1388 PsA patients initiating their first treatment with a TNFi, one-third of patients were current smokers. Current smokers had higher HAQ and patient VAS scores, but lower rates compared to never smokers upon start of TNFi, which may indicate a more aggressive disease course among smokers. However, objective markers of disease activity (CRP and SJC) were independent of smoking status. One may hypothesise that a worse disease perception or a poorer general health condition among current smokers contributed to earlier TNFi treatment. Alternatively, sDMARD therapy may be less effective in smokers.

The differences in baseline disease activity and demographics according to smoking status might explain, at least in part, why current smokers had poorer treatment response and treatment adherence in univariate but not multivariate analyses. However, in multivariate subanalyses, smoking was associated with poorer treatment response in men and poorer treatment adherence among patients treated with etanercept or infliximab. The non-randomised study design implies that these findings must be interpreted with caution due to the risk of residual confounding or uneven distribution of baseline demographics. Two previous studies have described the impact of smoking on TNFi treatment response in PsA. An observational study of 440 patients found current smoking to be associated with shorter 3-year TNFi drug survival. A single-centre study of 78 TNFi-treated PsA patients reported smokers to have poorer treatment response and lower drug retention rates after 6 months’ treatment in univariate analyses. Further studies are needed to confirm the relationship between smoking and treatment outcome in PsA. In RA, several studies have reported poorer TNFi adherence and treatment response among smokers. It has been suggested that smoking causes higher levels of inflammatory activity.22 35 36 altered bioavailability of antirheumatic drugs, cutaneous vasoconstriction and slower absorption from subcutaneous injection, or increased basal metabolic rate.20 37 38 Few studies analysed the impact of smoking according to type of TNFi, and found that smoking mainly affected infliximab treatment.6 22 This might be explained by differences in drug metabolism or formation of antichimeric antibodies.22 39

### Table 2 Impact of smoking on treatment adherence stratified by TNFi drug type

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Infliximab</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td>0.22</td>
<td>1</td>
</tr>
<tr>
<td>Current</td>
<td>0.76 (0.49 to 1.18)</td>
<td>1.56 (1.01 to 2.41)</td>
<td>1.74 (1.13 to 2.68)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>0.02</td>
<td>1</td>
</tr>
<tr>
<td>Women</td>
<td>1.66 (1.10 to 2.56)</td>
<td>1.05 (0.69 to 1.6)</td>
<td>1.10 (0.71 to 1.69)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>3–7</td>
<td>0.91 (0.55 to 1.50)</td>
<td>1.02 (0.59 to 1.76)</td>
<td>0.93 (0.53 to 1.61)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>0.73 (0.43 to 1.22)</td>
<td>0.71 (0.44 to 1.13)</td>
<td>1.04 (0.71 to 1.69)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤38</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>39–47</td>
<td>0.61 (0.32 to 1.2)</td>
<td>1.16 (0.67 to 2.01)</td>
<td>1.16 (0.63 to 2.11)</td>
</tr>
<tr>
<td>48–56</td>
<td>1.18 (0.71 to 2.0)</td>
<td>1.08 (0.58 to 2.03)</td>
<td>1.14 (0.61 to 2.11)</td>
</tr>
<tr>
<td>≥57</td>
<td>1.02 (0.57 to 1.82)</td>
<td>1.05 (0.58 to 1.91)</td>
<td>1.16 (0.59 to 2.24)</td>
</tr>
<tr>
<td>TNFi start year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2006</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2007–2009</td>
<td>1.32 (0.76 to 2.28)</td>
<td>1.61 (0.98 to 2.64)</td>
<td>1.39 (0.83 to 2.32)</td>
</tr>
<tr>
<td>2010–2011</td>
<td>0.76 (0.37 to 1.55)</td>
<td>3.74 (1.83 to 7.61)</td>
<td>1.48 (0.77 to 2.8)</td>
</tr>
<tr>
<td>Baseline swollen joint count, number per joint increase</td>
<td>1.02 (0.97 to 1.07)</td>
<td>1.04 (0.98 to 1.09)</td>
<td>Not included*</td>
</tr>
</tbody>
</table>

Multivariate Cox regression analyses including a priori confounders. *Swollen joint count did not alter the OR of smoking by >10% and was not included in the multivariate analysis.
Figure 2  Treatment response rates after 6 months treatment according to current vs never smokers (Mann–Whitney). (A) EULAR-good-response rates. (B) ACR20 response rates. (C) ACR50 response rates. (D) ACR70 response rates. Y-axis: percentage of patients achieving response.

We found that previous smokers who had stopped smoking more than ~4 years ago had nearly same drug adherence rates as never smokers. This may illustrate a gradual normalisation of pathological processes and smoking-related behaviour, and is noticeable, as tobacco smoking is a potentially modifiable lifestyle factor. Studies in RA have found previous smoking to have no or an intermediate impact on the effect of TNFi treatment and the evaluation of treatment outcome. However, these data are not included in DANBIO, and this might have affected our results, as smoking is suspected to increase the severity of skin psoriasis and to decrease the potential for clinical evaluation of this patient group.

The strengths of this study are the high external validity for routine care due to inclusion of an unselected nationwide population of patients with PsA and the long follow-up time. Our study also has limitations. Smoking status was retrieved cross-sectionally although smoking status might alter later on. An obvious misclassification occurs when previous smokers resume smoking during follow-up. However, the exclusion of previous smokers from all main analyses made this bias less important. Furthermore, we had no valid data on the number of package years and thus the potential dose-response relationship between smoking and outcome could not be investigated. In Denmark, heavy smokers are more often men. One might assume that the stronger impact of smoking among male patients is associated with greater exposure to tobacco. Smoking may be linked to comorbid disease, depression, socioeconomic and lifestyle factors, which all potentially affect baseline disease activity and treatment outcome. Psoriatic manifestations in, for example, skin and nails may influence the decision on when to start TNFi treatment and the evaluation of treatment effect. However, these data are not included in DANBIO, and this might have affected our results, as smoking is suspected to increase the severity of skin psoriasis and to decrease the effect of TNFi on psoriatic skin lesions.

In conclusion, we found current smoking to have a negative impact on treatment duration and clinical response in TNFi treatment of PsA, most pronounced in men and among patients treated with infliximab and etanercept. The effects seemed partially reversible, which stresses the importance of smoking cessation programmes for these patients. Clinicians should beware that current smokers potentially have higher HAQ and VAS scores compared with non-smokers, and this might affect the clinical evaluation of this patient group.

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Competing interests MH-F: UCB, MSD, Roche: Consulting fees, speaking fees, honoraria. AGL: Abbvie: Advisory board, Wyeth: Investigator.

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Clinical and epidemiological research
REFERENCES


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Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years’ surveillance in the Danish nationwide DANBIO registry

Bente Glintborg,¹ Mikkel Østergaard,² Niels Steen Krogh,³ Lene Dreyer,⁴ Hanne Lene Kristensen,⁵ Merete Lund Hetland²,⁶

ABSTRACT

Objectives To use prospectively registered data from the Danish nationwide rheumatological database (DANBIO) to describe disease activity, clinical response, treatment duration and predictors of drug survival (ie, number of days individual patients maintained treatment) and clinical response among patients with ankylosing spondylitis (AS) receiving their first treatment series with a tumour necrosis factor α (TNFα) inhibitor.

Methods 842 TNFα inhibitor naive patients with AS were identified in DANBIO. Clinical response, drug survival and predictors thereof were investigated. ‘Clinical response’ was defined as a 50% or 20 mm reduction in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) within 6 months compared with baseline. Achievement of a BASDAI <40 mm within 6 months was used as a second response parameter.

Results 603 patients (72%) were men, disease duration 5 (1–13) years (median (IQR), age 41 (32–50) years. 445 (53%) received infliximab, 247 (29%) adalimumab and 150 (18%) etanercept. Parameters at baseline/1-year follow-up were: C-reactive protein (CRP): 14 (7–27)/5 (2–10) mg/l, BASDAI 59 (44–72)/21 (8–39) mm, Bath Ankylosing Spondylitis Functional Index (BASFI) 50 (34–67)/24 (9–45) mm, Bath Ankylosing Spondylitis Metrology Index 40 (20–50)/20 (10–40) mm. Within 6 months, 407/644 patients (63%) achieved a clinical response. Median drug survival was 4.3 years. One- and 2-year survival rates were 74% and 63%, respectively. Baseline characteristics associated with longer drug survival were male gender, CRP >14 mg/l and low visual analogue scale fatigue (Cox regression analysis). Age, TNFα inhibitor and methotrexate use were insignificant. CRP >14 mg/l, lower BASFI and younger age at baseline was associated with clinical response and achievement of a BASDAI <40 mm (logistic regression analysis).

Conclusion TNFα inhibitors provide a rapid and sustained decrease of disease activity among patients with AS in clinical practice. Factors associated with continued treatment, clinical response and achievement of a BASDAI <40 mm were identified.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease affecting 0.1–1.4% of the population.¹ Several placebo-controlled randomised trials have shown excellent efficacy of tumour necrosis factor α (TNFα) inhibitors in AS,²–⁸ and the drugs are recommended for the treatment of patients with continuously active disease.⁹ ¹⁰

Randomised clinical trials generally include relatively homogeneous patient-populations who fulfil a strict set of inclusion criteria and are followed up for a limited time period. Many patients treated with biological agents in ‘real life’ would have been excluded from clinical trials owing to advanced age, comorbidity or polypharmacy.¹¹ Thus, data from observational registries on post-marketing use provide a valuable supplement to the knowledge from clinical trials about drug tolerability, drug survival, drug effects and adverse effects.¹²–¹⁶

Currently, the reported real-life data for TNFα inhibitor use among patients with AS are mainly retrospective analyses of patient files or small observational studies.¹³ ¹⁴ ¹⁷–²⁰ Although prospective rheumatological registries have been established in several countries and may serve as research tools,¹¹ ²¹–²⁴ only two clinical registry reports on patients with AS have been published²⁵ ²⁶ and neither of them assessed predictors of treatment response and drug survival.

The Danish nationwide rheumatological database (DANBIO) prospectively registers treatment and disease activity in patients with rheumatological disease treated with biological drugs. The mandatory reporting of biological treatment to the database makes coverage and completeness of data high.²⁷ ²⁸ The registry currently includes up to 8 years of follow-up. Several papers have previously described DANBIO data in patients with rheumatoid arthritis,¹⁶ ²⁷–³¹ whereas data for patients with AS have not been published until now.

Our aims were based on DANBIO data to report drug efficacy and drug survival as well as to identify baseline predictors of drug survival in Danish patients with AS receiving their first treatment course with a TNFα inhibitor in routine care.

PATIENTS AND METHODS

Patients

DANBIO is a Danish nationwide rheumatological database that collects data on patients treated with biological and other disease-modifying...
antirheumatic drugs (DMARDs). More than 90% of the patients who are prescribed biological treatment are included in the database.27 28 By 15 November 2008, 5366 patients receiving biological treatment had been registered in DANBIO. Among these, 842 patients were diagnosed with AS and included in this study (table 1).

The DANBIO data available in patients with AS were baseline demographics including patient age, gender, disease duration, previous or current treatment with methotrexate (MTX) or other DMARD. Disease activity parameters are prospectively reported to DANBIO by an online system and include visual analogue scales (VAS) for pain, patient’s global score and fatigue score. Registrations of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) were introduced in year 2003.31 A doctor or a trained nurse measures the BASMI score and registers the C-reactive protein (CRP) level.32 Data collection occurs two to four times annually. HLA-B27 status is not registered in the database.

Methods

Disease activity and clinical response

Disease activity was evaluated by the CRP, VAS scores, BASDAI, BASFI and BASMI at 0, 2 and 6 weeks, 6 months, 1, 2, 3, 4 and 5 years after initiation of anti-TNF treatment (table 2). Drug efficacy was primarily evaluated by ‘clinical response’ ( reduction in BASDAI of at least 50% or >20 mm compared with baseline according to the ASAS guidelines (BASDAI 50%/20 mm response)).33 34 Arbitrarily, we classified patients as ‘responders’ if they achieved a clinical response (yes or no) at least at one registration during the first 6 months’ treatment. As a second measure of drug efficacy, we identified the number of patients having a BASDAI score <40 mm at least once during the first 6-month treatment.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Demographic variables at baseline</th>
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</thead>
<tbody>
<tr>
<td>Women (n (%))</td>
<td>239 (28)</td>
</tr>
<tr>
<td>Age (years (median (quartiles)))</td>
<td>41 (22–50)</td>
</tr>
<tr>
<td>Disease duration (years (median (quartiles)))</td>
<td>5 (1–13)</td>
</tr>
<tr>
<td>Methotrexate use (n (%))</td>
<td>343 (41)</td>
</tr>
<tr>
<td>TNFα inhibitor used (n (%))</td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>247 (29)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>150 (18)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>445 (53)</td>
</tr>
<tr>
<td>Year of treatment initiation (n (%))</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>3 (0)</td>
</tr>
<tr>
<td>2001</td>
<td>15 (2)</td>
</tr>
<tr>
<td>2002</td>
<td>18 (2)</td>
</tr>
<tr>
<td>2003</td>
<td>48 (6)</td>
</tr>
<tr>
<td>2004</td>
<td>117 (14)</td>
</tr>
<tr>
<td>2005</td>
<td>155 (19)</td>
</tr>
<tr>
<td>2006</td>
<td>150 (18)</td>
</tr>
<tr>
<td>2007</td>
<td>188 (22)</td>
</tr>
<tr>
<td>January to November 2008</td>
<td>148 (18)</td>
</tr>
<tr>
<td>Reasons for drug discontinuation (n (%))</td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>115 (14)</td>
</tr>
<tr>
<td>Adverse events or side effects</td>
<td>69 (8)</td>
</tr>
<tr>
<td>Planning pregnancy</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Disease remission</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Not stated</td>
<td>72 (8)</td>
</tr>
<tr>
<td>Total</td>
<td>310 (37)</td>
</tr>
</tbody>
</table>

Numbers in brackets show quartiles or percentages of total population (n = 842).

RESULTS

Treatment duration

Drug survival was calculated as the number of days individual patients maintained treatment. The start date was the date of the first given dose and the stop date was the date of the first missed dose. All observations were censored at 15 November 2008. Reasons for drug discontinuation were registered.

Queries were sent to treating hospitals about 139 patients who had had no follow-up since 30 June 2008 and no registrations of stopping date. Subsequently, data on treatment duration was complete in 803 of 842 patients (95%). In the 39 patients with incomplete follow-up, data were censored according to the last visit registered in DANBIO.

Ethics

The DANBIO database has been approved by the Danish Board of Health and the Danish Data Registry. The registration of data among patients treated with biological agents does not require patient consent. Publication of data does not require approval by the ethics committee.

Statistics

All statistical analyses were done by SPSS software (version 16.0, SPSS, Chicago, Illinois, USA). Demographic and descriptive data are presented as median and range. Groups were compared by non-parametric testing (unpaired data: χ2 and Mann–Whitney tests, paired: Wilcoxon signed ranks test). Kaplan–Meier plots, log rank tests and Cox regression analyses were used for drug survival analysis. We converted each of the continuous baseline variables BASDAI, BASFI, BASMI and VAS scores into quartiles in order to visualise Kaplan–Meier drug survival curves. CRP was converted into a binary variable (below/above the median value 14 mg/l). Logistic regression analysis was used for the identification of factors associated with (a) clinical response and (b) BASDAI score <40 mm within 6 months of treatment. The factors with least significance were excluded stepwise (backward selection), leaving only statistically significant factors in the model. In the Cox and logistic regression analysis, gender, type of TNFα inhibitor, baseline CRP and baseline MTX use were included as categorical variables, whereas patient age and baseline BASDAI were continuous variables. All interactions involving sex, patient age, disease duration, MTX use and drug type were tested. Each interaction pair was included in the overall statistical model and thereafter excluded in the backward selection process if the interaction was statistically insignificant. A p value <0.05 was considered statistically significant.

Patient characteristics

The number of patients with AS initiating their first treatment series with TNFα inhibitors increased over the years. The majority of patients received infliximab (table 1). A total of 810 patients (37%) withdrew from TNFα inhibitor treatment. Table 1 shows reasons for drug discontinuation. Of the 238 cases with a known reason for withdrawal, lack of efficacy (115/238 patients, 48%) was the most prevalent reason, whereas 69 patients (69/238, 29%) stopped owing to adverse effects. Details of the adverse events were provided in several cases and included infections (13 patients), cardiovascular events—for example, hypertension, palpitations, angina (six patients), rashes (nine patients) or anaphylaxia (three patients) and other allergic reactions (five patients).

At baseline, 343 patients (41%) received concomitant MTX. Among infliximab users, 254/445 (57%) received MTX.
Table 2 Disease activity at baseline and during follow-up

<table>
<thead>
<tr>
<th>Follow-up time</th>
<th>Baseline</th>
<th>2 Weeks</th>
<th>6 Weeks</th>
<th>6 Months</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>14 (27)</td>
<td>4 (28)*</td>
<td>4 (27)*</td>
<td>5 (27)*</td>
<td>5 (27)*</td>
<td>5 (27)*</td>
<td>5 (27)*</td>
<td>6 (30)*</td>
<td>9 (30)*</td>
</tr>
<tr>
<td>BASDAI (mm)</td>
<td>59 (47–72)</td>
<td>39 (19–56)*</td>
<td>26 (12–49)*</td>
<td>26 (11–45)*</td>
<td>21 (8–39)*</td>
<td>21 (8–41)*</td>
<td>20 (8–36)*</td>
<td>20 (7–32)*</td>
<td>20 (6–32)*</td>
</tr>
<tr>
<td>BASFI (mm)</td>
<td>50 (34–67)</td>
<td>37 (19–55)*</td>
<td>31 (13–50)*</td>
<td>31 (13–50)*</td>
<td>30 (10–40)*</td>
<td>24 (9–45)*</td>
<td>24 (9–44)*</td>
<td>22 (9–43)*</td>
<td>22 (9–41)*</td>
</tr>
<tr>
<td>BASMI (mm)</td>
<td>40 (20–50)</td>
<td>30 (10–50)*</td>
<td>30 (10–50)*</td>
<td>30 (10–50)*</td>
<td>20 (10–40)*</td>
<td>20 (10–40)*</td>
<td>20 (10–40)*</td>
<td>40 (10–50)**</td>
<td>40 (20–70)</td>
</tr>
<tr>
<td>Thorax excursion (cm)</td>
<td>3 (2–5)</td>
<td>2 (3–5)*</td>
<td>4 (3–5)*</td>
<td>4 (3–5)*</td>
<td>4 (3–5)*</td>
<td>4 (3–5)*</td>
<td>4 (3–5)*</td>
<td>4 (3–5)*</td>
<td>4 (3–5)*</td>
</tr>
<tr>
<td>VAS pain (mm)</td>
<td>65 (45–78)</td>
<td>30 (14–56)*</td>
<td>22 (10–46)*</td>
<td>20 (9–48)*</td>
<td>19 (7–40)*</td>
<td>18 (5–39)*</td>
<td>17 (6–26)*</td>
<td>15 (6–28)*</td>
<td>23 (7–35)*</td>
</tr>
<tr>
<td>VAS fatigue (mm)</td>
<td>68 (48–81)</td>
<td>49 (20–70)*</td>
<td>34 (14–62)*</td>
<td>33 (14–59)*</td>
<td>29 (9–52)*</td>
<td>25 (6–45)*</td>
<td>18 (7–41)*</td>
<td>41 (4–42)*</td>
<td>23 (10–53)*</td>
</tr>
<tr>
<td>VAS global (mm)</td>
<td>67 (48–81)</td>
<td>36 (15–60)*</td>
<td>26 (11–51)*</td>
<td>24 (10–51)*</td>
<td>20 (8–44)*</td>
<td>18 (6–40)*</td>
<td>18 (6–37)*</td>
<td>18 (7–33)*</td>
<td>21 (11–49)*</td>
</tr>
<tr>
<td>Patients treated with an (n)</td>
<td>842</td>
<td>818</td>
<td>794</td>
<td>769</td>
<td>696</td>
<td>504</td>
<td>345</td>
<td>213</td>
<td>139</td>
</tr>
<tr>
<td>Patients with a visit (n)</td>
<td>745</td>
<td>395</td>
<td>458</td>
<td>515</td>
<td>515</td>
<td>390</td>
<td>264</td>
<td>168</td>
<td>128</td>
</tr>
</tbody>
</table>

*p<0.001 compared with baseline, **p<0.001 <p<0.01, ***p<0.01 <p<0.05.
†Among patients with incomplete follow-up data (n=39), follow-up time is estimated according to the latest visit registered in DANBIO.
The baseline visit was the time point at which patient received the first dose of TNFα inhibitor. Outcome data were reported according to the registrations in DANBIO at the following time points: 2 weeks of treatment (time interval 1–4 weeks), 6 weeks (5–9 weeks), 6 months (18–32 weeks), 1 year (46–64 weeks), 2 years (91–117 weeks), 3 years (143–182 weeks), 4 years (183–233 weeks), 5 years (234–285 weeks) and 6 years (286–338 weeks). If more DANBIO registrations occurred within a given time interval, the one closest to the given time point was selected. If a patient had no registrations within a given time interval, data were registered as missing for the given time point.

Baseline BASMI and CRP were significantly higher in men than women, whereas women had higher thorax excursion and C-reactive protein than among those receiving adalimumab or etanercept, both at baseline (χ² test, p<0.001) and during the whole period of observation (p<0.0001).

Baseline BASMI and CRP were significantly higher in men than women, whereas women had higher thorax excursion range, BASDAI, BASFI and VAS scores (Mann–Whitney test, all p<0.05, figure 1). Age (41 vs 41 years) and disease duration (6 vs 4 years) were similar among men and women (Mann–Whitney test, p<0.05).

Therapeutic effect
All outcome parameters decreased during follow-up (follow-up vs baseline, Wilcoxon test, all p<0.05) and thorax excursion increased (follow-up vs baseline, p<0.05) (table 2). At 6 months, CRP levels in men had decreased more than in women (10 vs 3 mg/l respectively, Mann–Whitney, p<0.001), whereas the decrease in BASDAI levels was similar among men and women (27 vs 22 mm respectively, p=0.09).

At baseline, 644 of the 842 included patients (76%) had a BASDAI score registered. Among these, 407 patients (65%) achieved a clinical response (BASDAI 50%/20 mm response) at least once during the first 6 months and 456 (71%) achieved a clinical response at least once during the whole treatment course. In 338 patients (52%), the majority (>50%) of registered BASDAI scores during the observation period were compatible with clinical response.

Overall, 794 patients (94%) had at least one BASDAI registration at baseline or during follow-up. Among these, 528 patients (66%) had at least one BASDAI score <40 mm during the first 6 months’ treatment and 554 patients (70%) had at least one BASDAI score <40 mm during the whole treatment course. In 445 patients (56%), the majority of registered BASDAI scores during the observation period were <40 mm.

Drug survival
The patients were treated for a total of 1513 patient-years. Median drug survival was 4.3 years. Unadjusted 1- and 2-year retention rates were 74% and 63%, respectively.

The crude retention rates were similar among patients receiving infliximab, adalimumab and etanercept (p=0.2). As shown in figure 2, male gender (panel A, log rank test p<0.0001), low baseline BASDAI (panel B, p<0.007), low VAS fatigue (panel C, p<0.0001) and CRP >14 mg/l (panel D, p<0.0001) were all associated with improved drug survival. Similar results were found for low BASFI (p=0.003), whereas baseline VAS pain (p<0.09), VAS global (p=0.08) and BASMI (p=0.9) did not affect drug survival.

Baseline disease parameters and patient characteristics were included in a Cox regression analysis in order to identify baseline factors associated with drug survival. Baseline VAS pain and VAS fatigue were strongly intercorrelated (Spearman’s r>0.84, p<0.0001) and so was baseline BASDAI and VAS pain/VAS global (both r>0.72, p<0.0001). Thus, VAS pain and VAS global were excluded from the regression analysis. In the final model, male gender, low baseline VAS fatigue and high CRP were associated with better drug survival, whereas patient age, type of biological drug, baseline MTX use, BASDAI, BASFI and VAS fatigue were not associated (table 3).

In a stratified multiple Cox regression analysis including only side effects as the event causing drug termination, sex was the
only significant statistical predictor (female gender p<0.001, HR=3.37, 95% CI 2.10 to 5.41). Similarly, including only lack of treatment effect as the event causing drug termination, CRP ≤14 mg/l (p=0.006, HR=1.98 (1.22 to 3.2) and higher baseline VAS fatigue (p<0.001, HR=1.25/cm (1.11 to 1.39)) were statistically significant factors.

Prediction of clinical response and achievement of BASDAI <40 mm

In a logistic regression analysis (backward stepwise selection) with clinical response (BASDAI 50%/20 mm response) as the dependent variable, CRP >14 mg/l (OR=0.45 (low vs high) (95% CI 0.31 to 0.64) p<0.001), lower baseline BASFI (OR=0.87/cm increase (0.78 to 0.97) p=0.008) and younger age (OR=0.98/year increase (0.97 to 0.99/year) p=0.03) were associated with clinical response, whereas biological drug, gender, disease duration, BASFI, BASMI, VAS scores and baseline MTX use were without statistical significance (all p>0.05). The analysis was adjusted for the baseline BASDAI level.

In a similar logistic regression analysis (backward selection) with achievement of BASDAI <40 mm at least once during 6 months’ treatment as the dependent variable, CRP >14 mg/l (OR=0.39, 95% CI 0.26 to 0.60, p<0.001), lower baseline BASFI (OR=0.86, 0.77 to 0.99, p=0.02) and younger age (OR=0.98/year, 0.97 to 1.00/year, p=0.048) were predictive of the patient achieving BASDAI <40 mm. Biological drug, gender, disease duration, BASFI, BASMI, VAS scores and MTX use were without significance (all p>0.05).

We tested for interactions between baseline BASDAI, age, disease duration, biological drug, MTX use and gender, and no statistically significant interactions were found.

**DISCUSSION**

This report from a nationwide prospective registry of 842 patients with AS receiving their first treatment series with a TNFα inhibitor documents the efficacy of anti-TNFα treatment in clinical practice. The measures of disease activity showed a rapid and sustained decrease and almost two-thirds of patients achieved a clinical response within 6 months. Male gender, low baseline VAS fatigue and baseline CRP >14 mg/l were associated with longer treatment continuation, whereas younger age, lower BASFI and higher baseline CRP levels predicted good treatment response.

Figure 2  Crude survival curves of tumour necrosis factor α inhibitor drug use according to (A) sex; (B) baseline BASDAI; (C) baseline VAS fatigue; (D) baseline CRP. x-Axis, treatment duration (years); y-axis, cumulated survival rate. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; VAS, visual analogue scale.
Our cohort of patients followed for up to 8 years represents the largest cohort of TNFα inhibitor treated patients with AS with the longest observation time reported till now. Only few have previously published prospective real-life data in patients with AS. Carmona and Gómez-Reino found a 1-year TNFα inhibitor survival rate of 88% among 657 Spanish patients with AS, whereas a Norwegian study among 249 patients with AS reported a survival rate of 77.5%—a number very similar to the 74% found in our study. A Finnish group did not report survival rates but stated that 49/229 patients (21%) discontinued treatment within up to a 2-year follow-up. Thus, real-life retention rates of TNFα inhibitors among patients with AS seem uniformly high despite the fact that treatment strategy, attitudes and actions must be expected to vary considerably between countries. Observational data are difficult to compare with the tightly controlled setting of a randomised trial. However, in a randomised clinical trial, Braun et al reported that 54/69 (78%) patients with AS completed their first year of infliximab treatment and similarly, Davis et al found that 95/128 (74%) patients with AS completed 96 weeks of etanercept treatment. Thus survival rates seem similar across observational and randomised studies.

The treatment response with TNFα inhibitors was rapid and sustained. Among the patients with a BASDAI measurement at baseline, we found that 65% achieved good clinical response within 6 months’ treatment. Until recently, only the total BASDAI score was registered in DANBIO and therefore a calculation of Assessment of SpondyloArthritis International Society response criteria ASAS20 or ASAS40,36 which includes relative or absolute changes in BASDAI question five and six, was not possible. This makes comparison to studies using ASAS response criteria difficult. Two other studies reporting real-life data found a similar response rate when using the BASDAI 50%/20 mm response parameter—namely, 71% among patients with AS treated with TNFα inhibitors or 60% within 3-month treatment with etanercept. In a recent open-label study among 1250 patients with AS treated with adalimumab, 57% achieved >50% reduction in BASDAI score within 3 months. In randomised controlled studies, 45–58% of patients achieve a 50% reduction in BASDAI. Individually tailored treatment, dose adjustments or concomitant use of DMARDs may, at least in part, explain why TNFα inhibitor treatment might perform better in clinical practice than in randomised trials.

A high disease activity at baseline illustrated by a higher VAS fatigue was associated with shorter treatment duration. Others have previously reported a similar effect for a high baseline BASDAI. It is well known from previous studies that disease activity at baseline influences treatment outcome and drug survival, although results are not uniform. It has been speculated that high subjective disease activity scores might relate to late disease dominated by irreversible changes and thus a poorer treatment outcome. However, in this study we did not find any effect of disease duration on treatment outcome. Furthermore, patients with high baseline activity might have substantial relative improvements without necessarily achieving clinical remission.

On the other hand, increased CRP levels at baseline were associated with longer treatment duration, good clinical response and achievement of a BASDAI <40 mm within 6 months. Similar results have previously been reported. CRP is a biomarker of inflammation and increased levels might identify patients with more active disease who are more likely to benefit from TNFα inhibitor treatment than patients with chronic, less inflammatory active disease.

Concomitant MTX is not recommended during biological treatment of AS. However, 41% of our patients received MTX at baseline, and it was most prevalent among patients treated with infliximab. This is in agreement with previous studies reporting frequent use of MTX, especially among patients with peripheral joint disease or treated with infliximab. The influence of MTX on drug survival varies between studies. In our study, concomitant MTX use did not affect drug survival or treatment effects. A Norwegian study found similar results, whereas a French study reported poorer drug survival among MTX users. The non-randomised design makes interpretation difficult. Confounding by indication cannot be ruled out and MTX use may be a marker of more serious disease or in other ways reflect the patient’s status—for example, peripheral joint involvement.

Overall, the treatment with TNFα inhibitors was well tolerated and only a few patients stopped owing to adverse events. Our finding that drug termination occurred more frequently owing to lack of efficacy rather than adverse effects has also been reported by others, although results are conflicting.

We found a significant difference in baseline disease activity between women and men. Furthermore, men responded better.

### Table 3: Baseline predictors of discontinuing treatment with tumour necrosis factor α inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted analysis</th>
<th></th>
<th>Adjusted analysis</th>
<th></th>
<th>Final model after backwards selection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p Value</td>
<td>HR</td>
<td>p Value</td>
<td>HR</td>
<td>p Value</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Man</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Woman</td>
<td>1.96 (1.55 to 2.45)</td>
<td>&lt;0.0001</td>
<td>1.46 (1.06 to 2.01)</td>
<td>0.02</td>
<td>1.46 (1.07 to 2.00)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>BASDAI (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤14 mg/l</td>
<td>1.70 (1.33 to 2.12)</td>
<td>&lt;0.0001</td>
<td>1.53 (1.13 to 2.07)</td>
<td>0.006</td>
<td>1.53 (1.14 to 2.05)</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;14 mg/l</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Methotrexate use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used</td>
<td>1.17 (0.93 to 1.47)</td>
<td>0.18</td>
<td>1.35 (0.98 to 1.86)</td>
<td>0.07</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Not used</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Biological treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>0.86 (0.66 to 1.13)</td>
<td>0.29</td>
<td>0.73 (0.49 to 1.10)</td>
<td>0.13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.77 (0.57 to 1.05)</td>
<td>0.09</td>
<td>0.71 (0.46 to 1.06)</td>
<td>0.09</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0.05</td>
<td>1.01 (0.99 to 1.02)</td>
<td>0.41</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Numbers in brackets are 95% CI.

Results from multiple Cox regression analysis (n = 842).

BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, function index; CRP, C-reactive protein.
to treatment evaluated by the achievement of clinical response and reductions in CRP and BASDAI levels. One may hypothesise that women scored higher in the subjective parameters BASDAI, BASFI and VAS because of weaker musculoskeletal performance or a general tendency towards reporting poorer scores in questionnaires. 10, 40–42 Shorter treatment survival and poorer treatment outcome has been reported among female patients with AS, 10 26 or rheumatoid arthritis. 12, 24, 40 Why women apparently respond differently to TNFα inhibitors is unclear, and any interactions between rheumatic disease, gender, sex hormones and TNFα inhibitors remain to be further investigated. 40, 43

We render the quality of data high. According to previous reports, >90% of Danish patients treated with biological agents are registered in the database, 28 probably owing to the mandatory registration irrespective of a patient’s consent. Thus, the coverage is much lower in databases using voluntary registration and requiring patient consent. 26

In conclusion, this analysis of 842 patients with AS in a nationwide prospective database registry documents that TNFα inhibitors provide a rapid and sustained decrease in disease activity. The majority of patients achieved a good clinical response. Baseline CRP >14 mg/l and low VAS fatigue was associated with longer treatment continuation, whereas high CRP, low BASFI and younger age predicted good treatment response and achievement of BASDAI <40 mm. Men maintained treatment longer than women. Other parameters, including drug type and MTX use, did not significantly affect drug survival or treatment efficacy. The treatment was well tolerated and only a few patients stopped treatment owing to adverse effects.

Competing interests MUH has received consulting fees, speaking fees and/or research grants from Abbott, Centocor, Roche, Schering-Plough, UCB-Nordic and Wyeth (less than US$10 000 each), and on behalf of DANBIO, she has received grants from Abbott, Bristol-Meyers Squibb, Roche, Schering-Plough, UCB-Nordic and Wyeth (more than US$10 000 each). MO has received consulting fees, speaking fees and/or research grants from Abbott, Amgen, Bristol-Meyers Squibb, Centocor, Gemaab, GlaxoSmithKline, Novo, Pfizer, Roche, Schering-Plough, UCB-Nordic and Wyeth (less than US$10 000 each).

Provenance and peer review Not commissioned; externally peer reviewed.

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35. Pincus T, Yazici Y, van Vollenhoven R. Why are only 50% of courses of anti-tumor necrosis factor agents continued for only 2 years in some settings? Need for long-term observations in standard care to complement clinical trials. J Rheumatol 2006;33:2372–3.
EXTENDED REPORT

Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry

Bente Glintborg,1,2 Mikkel Østergaard,3 Niels Steen Krogh,4 Ulrik Tarp,5 Natalia Manilo,6 Anne Gitte Rasmussen Loft,7 Annette Hansen,1 Annette Schlemmer,8 Victoria Fana,9 Hanne M Lindegaard,10 Henrik Nordin,11 Claus Rasmussen,12 Leif Ejstrup,13 Dorte Vendelbo Jensen,14 Peter Mosborg Petersen,15 Merete Lund Hetland2,3

ABSTRACT

Objective To investigate frequencies and reasons for switching, treatment responses and drug survival in patients with ankylosing spondylitis (AS) switching tumour-necrosis-factor-α inhibitor (TNFi) treatment in routine clinical care.

Methods AS patients were identified in the Danish nationwide DANBIO registry. Disease activity, treatment responses (50% or 20 mm reduction in Bath AS Disease Activity Index (BASDAI)), duration and rates of drug survival and predictors thereof were studied in patients receiving ≥2 different biological drugs.

Results Of 1436 AS patients starting TNFi treatment, 432 patients (30%) switched to a second and 137 (10%) to a third biological drug. Compared with non-switchers, switchers were more frequently women (33%/22%), had shorter disease duration (3 years/5 years) and higher BASDAI (62.5/26 mm/56/43–69 mm (median (interquartile-range))), Bath AS Functional Index (BASFI) (69/39–71 mm/47/31–65 mm) and visual-analogue scale (VAS) global, pain and fatigue scores when they started the first TNFi (all p<0.01). Main reason for switching was lack of response (56%). During the first, second and third treatment BAS- and VAS scores had decreased after 6 months’ treatment (all p<0.05). Median drug survivals were 3.1, 1.6 and 1.8 years respectively (p<0.001). After 2 years of treatment 52% of switchers and 63% of non-switchers had achieved response (number needed to treat 1.9 and 1.6, respectively, p=0.01). Drug survivals were similar regardless of the reason for switching. Male gender and low BASFI predicted drug survival of the second TNFi.

Conclusions Nearly one-third of AS patients in clinical practice switched biological treatment. Response rates and drug survivals were lower among switchers, however, half of switchers achieved treatment response.

INTRODUCTION

The beneficial effect of tumour-necrosis-factor-α inhibitor (TNFi) treatment in ankylosing spondylitis (AS) has been documented in several randomised trials.1–3 However, some patients experience lack of treatment effect (LOE) and some patients terminate treatment due to side effects.

In Denmark, four TNFi are currently marketed for the treatment of AS (infliximab, etanercept, adalimumab and golimumab). The drugs have different chemical structures, routes of administration and pharmacokinetics.4 Thus, if a patient fails to achieve adequate response during the first treatment or experiences adverse events (AE), a switch to a second TNFi seems appealing.

Among patients with rheumatoid arthritis (RA), switching has become daily practice5–10 and approximately 55% of RA switchers achieve ACR20 response.11 However, the rate and success of switching may be different in patients with AS.12–15

Currently, experiences from switching in patients with AS mainly originate from one large open label trial15 and several smaller observational studies including few treatment centres or less than 50 switch episodes.16–18

The Danish nationwide DANBIO registry now includes up to 10 years of prospective follow-up of patients with inflammatory arthritis treated with biologics in routine care.19 We have previously described treatment response and predictors thereof in AS patients receiving the first TNFi treatment.20 The aims of the present study were to investigate frequencies and reasons for switching, treatment responses, drug survivals and predictors thereof among patients switching TNFi treatment.

PATIENTS AND METHODS

The Danish DANBIO-registry is a nationwide registry that was commenced in year 2000 and approved as a clinical quality registry in 2006. DANBIO covers >90% of adults treated with biologics due to rheumatic disease in routine care.21–23 According to Danish legislation, any registration and publication of data from clinical registries does not require patient consent or approval by Ethics Committees.

Biological treatment courses initiated before 1 January 2011 were included in the present study and follow-up was until 20 April 2011. By 1 January 2011, 2039 patients with a diagnosis of AS according to specialists in rheumatology had been registered. It is not explicitly stated in DANBIO how individual patients fulfill the diagnostic criteria for AS.
Table 1  Baseline demographics and disease activity when patients started the first tumour necrosis factor inhibitor

<table>
<thead>
<tr>
<th></th>
<th>Non-switchers N=1004</th>
<th>Switchers N=432</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>41 (33–51)</td>
<td>41 (32–49)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Women, n (%)</strong></td>
<td>218 (22)</td>
<td>142 (33)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>5 (1–14)</td>
<td>3 (1–11)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Symptom duration</strong></td>
<td>14 (6–22)</td>
<td>11 (4–19)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Use of methotrexate, n (%)</strong></td>
<td>262 (26)</td>
<td>157 (36)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>CRP (mg/l)</strong></td>
<td>13 (5–27)</td>
<td>13 (5–26)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>VAS fatigue (mm)</strong></td>
<td>65 (46–78)</td>
<td>74 (56–87)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>VAS global (mm)</strong></td>
<td>66 (46–79)</td>
<td>72 (57–85)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>VAS pain (mm)</strong></td>
<td>62 (44–77)</td>
<td>70 (51–81)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>BASDAI (mm)</strong></td>
<td>56 (43–69)</td>
<td>62 (52–76)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>BASFI (mm)</strong></td>
<td>47 (31–65)</td>
<td>54 (39–71)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>BASMI</strong></td>
<td>40 (20–60)</td>
<td>40 (20–60)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Mann-Whitney and χ² tests. Numbers are median (quartiles) unless otherwise stated.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; VAS, visual analogue scale.

criteria for AS. Patients with psoriatic arthritis were excluded from this analysis. We excluded 518 AS patients only treated with disease-modifying anti-rheumatic drugs (DMARDs), 84 patients treated with biologicals as part of clinical trials, and one patient who did not receive TNFi as the first biological. Thus, 1436 biologically naïve patients, who had been registered in DANBIO from the time of initiation of the first TNFi were included. Of these, a subgroup of 452 patients (switchers) had received treatment with ≥two different biological drugs (TNFi or other) during follow-up (table 1). The total number of treatment courses was 2061.

Axial disease activity was assessed by Bath AS Disease Activity Index (BASDAI), Bath AS Function Index (BASFI), Bath AS Metrology Index (BASMI) and thorax excursion range (introduced in year 2003). C reactive protein (CRP) level (normal range ≤10 mg/l), visual analogue scales (VAS) for pain, global and fatigue scores were also registered. Since year 2010 the AS Disease Activity Score (ASDAS) was registered. Data collection occurred at minimum biannually.

Queries were sent to the hospitals regarding treatment series with incomplete follow-up. All calculations were based on observed data and no imputation of missing data was performed. All observations were censored at 20 April 2011.

Drug adherence

Drug survival was calculated as the number of days individual patients maintained treatment with the drug. Start date was the date of the first given dose and stop date was the date of the first missed dose. Temporary treatment interruptions (eg, due to infections or surgery) of <3 months’ duration were allowed. If a patient restarted treatment with the same biological drug after >3 months treatment interruption, the second treatment course with the drug was deleted from the dataset (62 cases).

The reasons for drug discontinuation are registered in pre-specified categories: LOE, AE, pregnancy, surgery, infections, loss to follow up and other. In the following, *switching-AE* denotes switching due to side effects, infection, death or cancer. *Switching-LOE* denotes switching due to lack of effect. *Switching-other* denotes switching due to any other cause (pregnancy, surgery, lost to follow up, disease remission) or several reasons for drug discontinuation.

**Treatment response**

Disease activity was evaluated by the CRP, VAS pain, fatigue and global, BASDAI, BASFI and BASMI-scores 0, 3 and 6 months after initiation of therapy.

Treatment response during each treatment course was evaluated as a reduction in BASDAI of at least 50% or >20 mm (BASDAI 50%/20 mm response). We classified patients as ‘responders’ if they achieved a sustained BASDAI 50%/20 mm response (yes/no) at both the 3 and 6-months’ visits compared with the BASDAI registration at 0 months. Thus only patients treated >3 months were included in this analysis. The individual components of the BASDAI score were not registered in DANBIO until year 2008, and therefore Assessment of SpondyloArthritis international Society (ASAS) response is not reported.

The overall long-term treatment response was evaluated at the 2-year visit (defined as the first visit >104 weeks after initiating the first TNFi). This time point was chosen arbitrarily to allow for an acceptable number of switch episodes without excluding too many patients with insufficient follow-up time. The BASDAI 50%/20 mm response at the 2-year visit was compared with the baseline BASDAI at the first treatment course, irrespective of switch episodes in the meantime. Thus, only patients with a registration of BASDAI at baseline and follow-up for ≥2 years were included in this analysis (609 patients). Also, the proportion of patients with BASDAI <40 mm at the 2-year visit was evaluated.

In the subgroup of patients with available ASDAS, disease activity was reported as the median ASDAS and the proportion of patients attaining ASDAS <2.1 (inactive/moderate disease activity) at the latest visit registered after ≥2 years follow-up.

**Statistics**

Statistical analyses were performed by SPSS (V16.0, SPSS Inc., Chicago, Illinois, USA) and SAS software (V9.0, SAS Institute Inc, Cary, North Carolina, USA). Demographic and descriptive data are presented by medians/IQR. Groups were compared by non-parametric testing (unpaired data: χ² and Mann-Whitney tests, paired: Wilcoxon signed ranks test). The proportion of patients achieving treatment responses were expressed as Number-Needed-to-Treat (NNT) calculated as the reciprocal value of response rates. In all statistical tests, a p value <0.05 was considered statistically significant.

Kaplan Meyer plot and log rank test were used to visualise drug survival. Unadjusted/univariate and multivariate Cox regression analysis with HR were used for the identification of factors associated with drug survival of the second treatment course. Logistic regression analyses and OR were used to identify factors associated with BASDAI 50%/20 mm response. In the regression analyses, patient age, baseline CRP, BASDAI, BASFI, BASMI and VAS scores were included as continuous variables whereas gender, type of TNFi (current and previous treatment), use of methotrexate (yes/no) and reason for discontinuation of the first TNFi (AE/LOE/other) were included as categorical variables. The variables with the highest p value were excluded stepwise (backward selection) leaving only statistically significant variables in the final model.

In the following, unless otherwise stated, the term *baseline* is used to describe disease activity upon starting the individual treatment course.

**RESULTS**

**Baseline characteristics and patient disposition**

Among the included 1436 patients, 560 (25%) were women and median age was 41 years (IQR 33–50 years). Median
follow-up time was 2.4 years (IQR 1.0–4.8 years). The patient flow is outlined in figure 1. When data were censored, 432 patients (32%) had switched treatment and 773 patients were still treated with the original TNFi. Switchers were more frequently women, had shorter disease duration, were more frequently treated with methotrexate and had higher VAS scores, BASFI and BASDAI compared with non-switchers when they started the first TNFi (table 1). More non-switchers who continued treatment vs non-switchers who stopped treatment without starting a new TNFi, were men (80 vs 71%, p=0.002), but baseline disease activities were similar in the groups (all \( p>0.05 \), data not shown).

The most prevalently used first line drug was infliximab in year 2001–2008 and adalimumab in year 2009–2010. Adalimumab was the most frequently used second (46%) and third line (31%) treatment (table 2). Biologicals other than TNFi were only initiated in 19 of 2061 treatment series and will not be discussed further. The most frequent combinations of first and second TNFi were: infliximab-adalimumab (161 patients), infliximab-etanercept (88 patients), adalimumab-etanercept (84 patients), etanercept-adalimumab (36 patients).

Baseline infliximab doses among patients starting infliximab as the first, second and third treatment were 296 mg (3.9 mg/kg), 364 mg (4.6 mg/kg) and 560 mg (5.0 mg/kg), respectively. Similarly, the average doses at the latest registered visit were 524 mg (4.2 mg/kg), 532 mg (4.9 mg/kg) and 590 mg (5.4 mg/kg), respectively. At the latest visit, 21% of patients received infliximab every 6 weeks, 11% every 7 weeks and 56% every 8 weeks. Baseline use of methotrexate was more frequent among infliximab users and patients with peripheral joint disease (both \( p<0.01 \), data not shown).

A total of 251 patients stopped the first TNFi without starting a new. The main reason for switching was LOE (240 patients, 56% of switchers) or AE (118 patients, 27%). Among the 432 patients who started treatment with a second biological, 137 switched to a third (32%), 217 patients continued treatment, and 78 patients stopped without starting a new. The main reason for switching to a third biological was LOE (86 patients, 63% of switchers) (figure 1). Similarly, 39/137 patients (28%) switched to a fourth biological, and 12/39 patients (31%) switched to a fifth. Among the 432 switchers, baseline disease activity was similar irrespective of the reason for switching (see supplementary table S1).

Drug survival
Drug survival decreased after switching \( (p<0.001) \) (figure 2). Median drug survival of the first TNFi among switchers was 0.7 years (95% CI 0.6 to 0.8 years).

Treatment response
Most scores decreased after 3 and 6 months’ treatment during the first, second and third treatment course (table 3). For switchers, baseline CRP was significantly lower at the second and third treatment course compared with the first \( (p<0.05) \) (figure 5). Baseline BASDAI and VAS global were significantly lower at the second treatment course compared with the first \( (p<0.001) \). For switchers, the delta values for the decrease in CRP, BASDAI and VAS global between baseline and 6 months were similar at the second and third treatment course compared with the first \( (all \ p>0.05) \) (figure 3).

![Figure 1](http://ard.bmj.com/)

Figure 1  Flow -chart of treatment course 1, 2 and 3 and reasons for drug discontinuation \( (n= 1,436) \). Numbers show the number of patients. LOE: Lack of effects, AE: adverse events.

### Table 2 Number of treatment courses according to biological drug

<table>
<thead>
<tr>
<th>Biological drug</th>
<th>Total (%)</th>
<th>1*</th>
<th>2*</th>
<th>3</th>
<th>4, 5, 6, 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>781 (38)</td>
<td>532 (37)</td>
<td>197 (46)</td>
<td>42 (31)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>452 (22)</td>
<td>231 (16)</td>
<td>172 (40)</td>
<td>40 (29)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>741 (36)</td>
<td>653 (45)</td>
<td>42 (10)</td>
<td>37 (27)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>59 (3)</td>
<td>20 (1)</td>
<td>15 (3)</td>
<td>9 (7)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>9 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>3 (2)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>8 (0)</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>5 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>1 (1)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not stated</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>2061 (100)</td>
<td>1436 (100)</td>
<td>432 (100)</td>
<td>137 (100)</td>
<td>56 (100)</td>
</tr>
</tbody>
</table>


Number of patients, number in brackets show percentages of total.
During the first treatment course, the proportion of patients achieving BASDAI 50%/20 mm response within 6 months was 54% (NNT=1.9). Corresponding rates during the second and third treatment course were 37% (NNT=2.7) and 30% (NNT=3.4).

At the 2-year visit, 52% of switchers (NNT=1.9) and 63% of non-switchers (NNT=1.6) (p=0.01) had a BASDAI <40 mm. Switchers had received a median of two biological drugs (IQR 2–2).

Among patients treated ≥2 years, 316 patients had an available ASDAS-score at their latest visit. The proportion of patients with ASDAS<2.1 was 37% among switchers and 71% of non-switchers (p<0.001). Median ASDAS among switchers and non-switchers were 2.5 (IQR 1.8–3.5) and 1.6 (1.0–2.3), respectively.

Predictors of drug survival and response during the second treatment course

In univariate Cox regression, drug survival of the second biological was longer in men (p=0.03), patients treated with adalimumab (p=0.03), patients previously treated with infliximab (p=0.004) and patients with lower BASFI (p=0.03). Baseline CRP, BASDAI, BASMI and VAS-scores, age, use of methotrexate and reason for withdrawal of the first TNFi were not statistically significant. In multivariate Cox regression, predictors of longer drug survival were male gender (HR 1.76 (95% CI 1.2 to 2.5), p=0.002) and low baseline BASFI (HR1.07/cm (1.0–1.15), p=0.046), whereas type of TNFi (current or previous), reason for withdrawal of first TNFi, use of methotrexate, age, CRE, BASMI, BASDAI and VAS scores at the start of the second treatment were not predictive.

Predictors of BASDAI 50%/20 mm response during the second treatment course were higher CRP at baseline (OR 1.05/mg/l (95% CI 1.0 to 1.05), p=0.02), lower VAS fatigue (0.6/cm (0.5–0.9), p=0.008), and lower BASFI (0.6/cm(0.2–0.8), p=0.001) (multiple logistic regression analysis corrected for baseline BASDAI). Type of TNFi (current or previous), reason for withdrawal of first TNFi, gender, age, BASMI, VAS global, VAS pain and age were not significant.

DISCUSSION

In this study of 1432 patients with AS we found that almost one third switched TNFi during up to 10 years of follow-up. Switchers were more frequently women and patients with high baseline subjective disease activity. The main reason for switching was LOE. The disease activity decreased significantly during the second and third treatment course. Although switchers had poorer treatment response and shorter drug survival than non-switchers, approximately half of switchers achieved clinical response. Two years after switching, half of switchers maintained treatment with the second biological.

Lack of efficacy explained half of the switch episodes, followed by AE in one out of four. Switches were almost exclusively between TNFi. Previous observational studies have included a limited number of switch-episodes. Lie et al found switching in 77/514 (15%) AS patients during 9 years of follow-up mainly due to AE. A French study described switching in 99/377 (26%) patients with spondyloarthropaties during 8 years of follow-up, the main reason was LOE. These differences are unexplained but possibly reflect regional differences in prescription practice.

We found that switchers were more often women and had higher subjective disease activity compared with non-switchers when starting the first TNFi, CRP and BASMI were similar. The Norwegian study found no such differences, however, the study may have been underpowered as baseline data only was available in 39% of switchers. Studies performed in RA patients report a similar tendency towards higher baseline disease activity among switchers. This might reflect that
switchers are patients refractory to treatment for example, due to chronic disability or comorbidities.31

In the present study, response rates were markedly reduced among switchers. Similar results were found by Lie et al22 Rudwaleit et al reported response among 41% of 326 adalimumab treated patients with AS who previously failed treatment with infliximab and/or etanercept compared with 63% among TNFi-naïve patients (p<0.001).14 Furthermore, we found decreased drug survival after switching. Similar tendencies have previously been demonstrated.9 13 14 22

Although the response rates and drug survivals decreased after switching, the 6 months’ response rate was 57% during the second treatment course. After 2 years’ of treatment, 52% of switchers had achieved BASDAI50/20 mm response and 54% a BASDAI <40 mm. Rudwaleit et al and Lie et al reported BASDAI50 response among 41%14 and 28% of switchers.22 Observational studies including <25 patients report 45–83% response rates.8 15–18 A retrospective study among 56 switchers found a 80% response rate after 5 months’ treatment.20 It should be noted that several clinical studies measure response rates as 50% reductions in BASDAI,14 17 22 which is a more conservative measure than the BASDAI50%/20 mm response used in the current study. However, in spite of great variation in study design and methodology, previous studies overall describe high response rates among AS patients switching therapy.

Increased CRP and low BASFI were associated with treatment response during the second treatment course. A similar pattern has previously been described among AS patients receiving their first TNFi.24 31–36 However, one previous study among 99 patients with spondyloarthopathies switching TNFi found no predictors,20 perhaps due to lack of power. Perhaps increased levels of CRP identify patients with higher cytokine mediated inflammation and therefore better response to TNFi. On the contrary, higher BASFI might be associated with chronic disability or psychological factors irresponsible to treatment.31

Currently, inflammatory markers and functional status are not included in the guidelines for prescribing TNFi in AS. However, possible predictors must be interpreted with caution in clinical settings; we found increased CRP to predict clinical response after switching and 50% of patients with CRP>10 mg/l achieved a BASDAI 50%/20 mm within 6 months. However, 50% of patients with normal CRP also achieved response. More complicated models are needed in order to predict clinical outcome of therapy in individual patients.32

We found longer treatment duration of the second biological drug in men compared with women. This is in accordance with previous studies, not only in AS but also RA and psoriatic arthritis.24 36–41 Why clinical response differs according to gender is still unclear.

The main switch patterns were from infliximab to adalimumab or etanercept. This reflects that infliximab was the first TNFi marketed to treat AS. Among patients starting treatment in year 2008 and thereafter, the most prevalent switch was from adalimumab to etanercept (48/157 switches). Drug survival during the second treatment course was longer among adalimumab treated patients and among patients previously treated with infliximab. However, we found no difference in efficacy among the different TNFi. Due to the non-randomised study design, these results must be interpreted with caution. Comorbidity, route of drug administration (subcutaneous/intravenous) and altered clinical practice due to marketing of new drugs might have affected the results.13 38

The treatment response of the second biological drug was similar among switchers due to LOE and AE. Some have reported similar results17 20 22—others describe better treatment effects among AE-switchers.8 12 14 Our study was limited by the fact that it was not possible to distinguish between treatment termination due to lack of or loss of treatment effect. According to some studies, patients who stop treatment due to secondary loss of treatment effect especially benefit from switching.14 Smoking status, comorbid disease, concomitant use of NSAIDs, enthesitis and HLAB27 status are factors that might influence treatment outcome.32 However these data are not routinely registered in DANBIO.

In conclusion, nearly one-third of AS patients switched TNFi in routine care during up to 10 years of follow-up, mainly due to inefficacy. The response rates and drug adherences decreased after switching.33 However, half of the switchers achieved clinical response. Thus, irrespective of the reason for discontinuation of the first TNFi, switching to another TNFi should be considered.

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**Table 3** CRP level, VAS and BAS scores during the first (n=1436), second (n=432) and third treatment course (n=137)

<table>
<thead>
<tr>
<th>Treatment course</th>
<th>Treatment duration</th>
<th>P 0 vs 3 months</th>
<th>P 0 vs 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 months</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (5.0–26)</td>
<td>4.0 (1.0–9.0)</td>
<td>4.0 (1.0–9.0)</td>
</tr>
<tr>
<td>2</td>
<td>8.0 (2.0–20)</td>
<td>5.0 (2.0–11)</td>
<td>3.0 (1.0–7.0)</td>
</tr>
<tr>
<td>3</td>
<td>9.0 (3.0–21)</td>
<td>4.0 (1.0–12)</td>
<td>6.0 (2.0–11)</td>
</tr>
<tr>
<td>BASFI (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50 (50–60)</td>
<td>33 (16–60)</td>
<td>32 (12–61)</td>
</tr>
<tr>
<td>2</td>
<td>50 (50–60)</td>
<td>38 (12–67)</td>
<td>36 (15–65)</td>
</tr>
<tr>
<td>3</td>
<td>50 (50–60)</td>
<td>60 (46–76)</td>
<td>57 (30–76)</td>
</tr>
</tbody>
</table>

---

Outcome data were reported according to the registrations in DANBIO at the following time-points: 0 months (upon initiation of therapy), 3 months (10–17 weeks), 6 months (18–32 weeks). If more registrations occurred within a given time interval, the one closest to the given time-point was selected. If a patient had no registrations within a given time interval, data were registered as missing for the given time-point.

BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Function Index; BASMI, Bath AS Metrology Index; CRF C reactive protein; VAS, visual analogue scale.

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Results from Wilcoxon signed rank test. Values are medians and IQR. The main switch patterns were from infliximab to adalimumab or etanercept. This reflects that infliximab was the first TNFi marketed to treat AS. Among patients starting treatment in year 2008 and thereafter, the most prevalent switch was from adalimumab to etanercept (48/157 switches). Drug survival during the second treatment course was longer among adalimumab treated patients and among patients previously treated with infliximab. However, we found no difference in efficacy among the different TNFi. Due to the non-randomised study design, these results must be interpreted with caution. Comorbidity, route of drug administration (subcutaneous/intravenous) and altered clinical practice due to marketing of new drugs might have affected the results.13 38

The treatment response of the second biological drug was similar among switchers due to LOE and AE. Some have reported similar results17 20 22—others describe better treatment effects among AE-switchers.8 12 14 Our study was limited by the fact that it was not possible to distinguish between treatment termination due to lack of or loss of treatment effect. According to some studies, patients who stop treatment due to secondary loss of treatment effect especially benefit from switching.14 Smoking status, comorbid disease, concomitant use of NSAIDs, enthesitis and HLAB27 status are factors that might influence treatment outcome.32 However these data are not routinely registered in DANBIO.

In conclusion, nearly one-third of AS patients switched TNFi in routine care during up to 10 years of follow-up, mainly due to inefficacy. The response rates and drug adherences decreased after switching.33 However, half of the switchers achieved clinical response. Thus, irrespective of the reason for discontinuation of the first TNFi, switching to another TNFi should be considered.
Figure 3  Disease activity for switchers at baseline, 3 months and 6 months during biological treatment course 1 (red), course 2 (grey) and course 3 (green) (n=432). Columns show medians. Panel A: C reactive protein (CRP), panel B: Bath AS Activity Index (BASDAI), panel C: Visual analogue scale (VAS) global. This figure is only reproduced in colour in the online version.
Clinical and epidemiological research

Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry

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Abstract

Objectives. To investigate the association between tobacco smoking and disease activity, treatment adherence and treatment responses in patients with AS treated with their first tumour necrosis factor-alpha inhibitor (TNFi) therapy in routine care.

Methods. Observational cohort study based on the Danish nationwide DANBIO registry. Kaplan–Meier plots, Cox and logistic regression analyses by smoking status (current/never/previous) were calculated for treatment adherence and BASDAI 50%/20 mm-response. Additional stratified analyses were performed for gender and TNFi-type.

Results. Of 1576 AS patients included in the study, 1425 (90%) had known smoking status (current/never/previous: 43%/41%/16%). The median follow-up time was 2.02 years (IQR 0.69–5.01). At baseline, current smokers compared with never smokers had longer disease duration (4 years (1–12)/2 years (0–10)), higher BASDAI (61 mm (47–73)/58 mm (44–70)), BASFI (53 mm (35–69)/46 mm (31–66)) and BASMI (40 mm (20–60)/30 mm (10–50)) scores (all P < 0.01). Current and previous smokers had shorter treatment adherence than never smokers (current: 2.30 years (1.81–2.79) (median (95% CI)); previous: 2.48 years (1.56–3.40), never: 4.12 years (3.29–4.95), P < 0.0001). Similar results were found in multivariate analyses (current versus never smokers, HR 1.41 (95% CI 1.21–1.65), P < 0.001), most pronounced among men. Current smokers had poorer 6 months’ BASDAI50%/20 mm-response rate than never smokers (42%/58%, P < 0.001). In multivariate analyses, current smokers had lower odds of achieving...
The nationwide DANBIO registry includes clinical data on patients with rheumatic diseases treated with TNFi in routine care in Denmark [24, 25]. We have previously described demographics and clinical outcomes in patients with AS treated with TNFi [1]. The primary aim of the present study was to compare effectiveness in current smokers, previous smokers and never smokers regarding disease activity, treatment responses and adherence rates in patients with AS initiating their first TNFi therapy in routine care. The secondary aim was to study whether the impact of smoking was influenced by gender and TNFi type.

Methods

The DANBIO registry was initiated in the year 2000 and covers >90% of Danish adults suffering from rheumatic disease treated in routine care with biologics [24, 26]. According to Danish legislation, the registration and publication of data from clinical registries do not require patient consent or approval by ethics committees. Physicians are recommended to report data prospectively by an online system at least biannually and when medication is changed (www.danbio-online.dk).

Baseline demographics include smoking habits, age, gender, BMI, disease duration, current treatment with MTX or other conventional synthetic DMARDs (csDMARD). In addition to CRP level (normal range ≤10 mg/l) and visual analogue scales (VASs) for scores of pain, patient’s global, fatigue and physician’s global assessments, the patient’s functional status and disease activity are monitored by BASDAI, BASFI and BASMI, which are validated disease outcome measures in AS [27, 28]. By 1 January 2014, 1775 patients with a diagnosis of AS had been registered and treated with a biologic drug (bDMARD), according to the treating rheumatologist. We excluded patients treated with certolizumab pegol (n = 5) and bDMARDs other than TNFi (n = 12), patients participating in clinical trials (n = 140), patients not followed in DANBIO since the commencement of their first TNFi (n = 19) or with erroneous baseline registrations (n = 23), leaving 1576 patients in the study.

Tobacco smoking

Patients were divided into three groups according to smoking status: current (≥1 cigarette/day), previous and never smokers. In previous smokers, the number of years since smoking cessation was recorded. Smokers who had stopped smoking the year they started TNFi were classified as previous smokers (n = 25). Queries were sent to the departments regarding patients with incomplete data on smoking status. A rheumatologist then obtained the information from the medical records or by asking the patients.

Treatment adherence

Treatment adherence was calculated as the number of years each patient maintained treatment. Start date was the date of the first given dose and stop date was the date...
of the first missed dose. Temporary treatment interruptions (e.g. due to infections or surgery) of ≤ 3 months’ duration were allowed. All observations were censored by 1 September 2014. Among patients with no follow-up since June 2014, data were censored according to the last visit registered.

The reasons for drug discontinuation are registered in DANBIO in pre-specified categories: lack of effect, adverse events, disease remission, pregnancy, surgery, cancer, death, infections, loss to follow-up and other reasons. In the following, reasons for discontinuation are divided into three categories: adverse events (including infection, death or cancer), lack of effect and other (including pregnancy, surgery, loss to follow-up, remission and other reasons for discontinuation).

**Treatment response**

Disease activity was evaluated at baseline and after 3 and 6 months’ therapy. The baseline visit was defined as a visit within the time frame that ranged from 60 days before until six days after initiation of therapy. For the 3 months’ visit, the time frame was 10–17 weeks, and for the 6 months’ visit the time frame was 18–32 weeks after treatment start. If more than one registration occurred within a given time frame for an individual patient, the registration closest to the given time-point was selected for analysis. If a patient had no registrations within a given time window, data were registered as missing for the given visit.

In accordance with international recommendations, clinical response was defined as achievement of either a 50% or a 20-mm reduction in BASDAI (BASDAI50%/20 mm response) [27, 28]. Arbitrarily and in agreement with previous studies, we classified patients as responders if they achieved clinical response (yes/no) at both the 3 and 6 months’ visits compared with baseline. In the case of missing data at either the 3 or 6 months’ visit, one registration of clinical response was sufficient to classify the patient as a responder. Patients who stopped treatment within the first 3 months of therapy were considered non-responders (n = 112). Response rates were calculated as the proportion of patients who achieved a BASDAI50%/20 mm response.

**Statistics**

Statistical analyses were performed by SPSS (version 20.0, SPSS Inc., Chicago, Illinois, USA). Demographic and descriptive data are presented by medians/interquartile ranges (IQRs). Groups were compared by non-parametric tests ($\chi^2$, Kruskal–Wallis and Mann–Whitney tests). In all tests, P-values < 0.05 were considered statistically significant. Calculations were based on observed data and no imputation of missing data was performed. Kaplan–Meier plots and log rank tests were performed for analyses of treatment adherence for current, previous and never smokers. Additional testing was done in order to ensure that proportionality was present during the observation period (data not shown). We performed univariate and multivariate Cox regression analyses to study the impact of smoking on treatment adherence and calculated hazard ratios (HRs) for treatment discontinuation with time in study as the underlying time scale. Univariate and multivariate logistic regression analyses and odds ratios (ORs) were calculated to identify the impact of smoking (current/previous/never) on the achievement of clinical response. The following baseline factors were considered a priori as confounders and included in all multivariate analyses: age (in quartiles), gender, disease remission (in tertiles), calendar year of starting TNFi (in tertiles). Age, disease duration and year of treatment start were included as categorical variables to allow for possible non-linear effects. Baseline MTX use (yes/no) and TNFi type (adalimumab/etanercept/golimumab/infliximab) were considered potential confounders and were added one by one to the multivariate model, but were only included if they altered the OR/HR of smoking by >10%. Baseline VAS scores, CRP, BMI, BASDAI, BASFI and BASMI were considered intermediate variables between tobacco smoking and outcomes and not included in the main multivariate analyses. For sensitivity we performed multivariate logistic regression analyses (current vs never smokers) that besides the a priori confounders additionally included all the variables in which the baseline values differed significantly among current vs never smokers. The latter analysis was also performed where the confounding effect of all variables was adjusted for by use of propensity score. Stratified analyses were performed according to gender and TNFi type (adalimumab/etanercept/infliximab, but not for golimumab, owing to limited data).

**Results**

**Characteristics at baseline**

A total of 1576 bDMARD-naive patients initiating treatment with adalimumab, etanercept, golimumab or infliximab as the first TNFi were included (Table 1). Among the 1425 patients (90%) with known smoking status, 43% were current, 41% never and 16% previous smokers, and 39% of women and 44% of men were current smokers. Patients with missing smoking status were more often men and were more often treated with golimumab, in contrast to patients with available smoking information (Table 1).

At baseline, current smokers had higher BASDAI, BASMI and BASFI scores compared with never smokers and had higher BASDAI, patient global and pain scores compared with previous smokers (Table 1). Previous smokers were older and had longer disease duration than current and never smokers. The reasons for stopping TNFi treatment were independent of smoking status (Table 1). Male current smokers had significantly higher BASDAI, BASFI, BASMI and physician global scores and a longer disease duration than male never smokers, whereas age, CRP, BMI, patient’s pain, fatigue and global scores were similar (data not shown). Female current smokers had significantly higher BASFI and physician global scores than female never smokers, whereas age, BMI, disease
TABLE 1 Demographics and patient characteristics

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Current</th>
<th>Never</th>
<th>Previous</th>
<th>Current versus never P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Current versus previous P value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Smoking status unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number, n (%)</td>
<td>614 (39)</td>
<td>578 (37)</td>
<td>233 (15)</td>
<td>–</td>
<td>–</td>
<td>151 (10)</td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>41 (32–50)</td>
<td>39 (32–50)</td>
<td>48 (40–57)</td>
<td>0.3</td>
<td>&lt;0.0001</td>
<td>41 (32–51)</td>
</tr>
<tr>
<td>Disease duration, median (IQR), years</td>
<td>4 (1–12)</td>
<td>2 (0–10)</td>
<td>9 (1–19)</td>
<td>0.01</td>
<td>0.003</td>
<td>3 (0–15)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>161 (26)</td>
<td>192 (33)</td>
<td>57 (24)</td>
<td>0.008</td>
<td>0.6</td>
<td>32 (21)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Body mass index, median (IQR), kg/m²</td>
<td>25 (23–29)</td>
<td>26 (22–28)</td>
<td>26 (24–29)</td>
<td>0.4</td>
<td>0.1</td>
<td>25 (22–28)</td>
</tr>
<tr>
<td>TNFi drug type, n (%)</td>
<td>Adalimumab 231 (38)</td>
<td>230 (40)</td>
<td>110 (47)</td>
<td>0.4</td>
<td>0.03</td>
<td>54 (36)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Etanercept 104 (17)</td>
<td>107 (19)</td>
<td>42 (18)</td>
<td>21 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab 231 (38)</td>
<td>193 (33)</td>
<td>74 (32)</td>
<td>49 (32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Golimumab 48 (8)</td>
<td>48 (8)</td>
<td>7 (3)</td>
<td>27 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFi start year, n (%)</td>
<td>2000–04</td>
<td>81 (13)</td>
<td>68 (12)</td>
<td>25 (11)</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>2005–09</td>
<td>335 (55)</td>
<td>302 (52)</td>
<td>122 (52)</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>2010–13</td>
<td>198 (32)</td>
<td>208 (36)</td>
<td>86 (37)</td>
<td>0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>MTX use, n (%)</td>
<td>171 (28)</td>
<td>149 (26)</td>
<td>50 (31)</td>
<td>0.4</td>
<td>0.06</td>
<td>37 (25)</td>
</tr>
<tr>
<td>CRP, median (IQR), mg/l</td>
<td>13 (5–26)</td>
<td>10 (4–23)</td>
<td>10 (4–21)</td>
<td>0.07</td>
<td>0.8</td>
<td>13 (6–23)</td>
</tr>
<tr>
<td>BASDAI, median (IQR)</td>
<td>61 (47–73)</td>
<td>58 (44–70)</td>
<td>54 (41–69)</td>
<td>0.005</td>
<td>0.002</td>
<td>62 (44–71)</td>
</tr>
<tr>
<td>BASFI, median (IQR)</td>
<td>53 (35–69)</td>
<td>46 (31–66)</td>
<td>51 (33–69)</td>
<td>0.002</td>
<td>0.3</td>
<td>50 (36–70)</td>
</tr>
<tr>
<td>BASMI, median (IQR)</td>
<td>40 (20–60)</td>
<td>30 (10–50)</td>
<td>40 (20–60)</td>
<td>0.0001</td>
<td>0.7</td>
<td>40 (15–50)</td>
</tr>
<tr>
<td>Patient global (0–100), median (IQR), mm</td>
<td>69 (52–82)</td>
<td>69 (49–83)</td>
<td>67 (46–79)</td>
<td>0.3</td>
<td>0.04</td>
<td>71 (52–84)</td>
</tr>
<tr>
<td>Patient pain (0–100), median (IQR), mm</td>
<td>67 (49–78)</td>
<td>65 (45–79)</td>
<td>62 (44–76)</td>
<td>0.3</td>
<td>0.02</td>
<td>65 (45–78)</td>
</tr>
<tr>
<td>Patient fatigue (0–100), median (IQR), mm</td>
<td>69 (51–82)</td>
<td>70 (46–91)</td>
<td>68 (46–77)</td>
<td>0.3</td>
<td>0.07</td>
<td>71 (56–84)</td>
</tr>
<tr>
<td>Physician global (0–100), median (IQR), mm</td>
<td>40 (25–58)</td>
<td>33 (22–49)</td>
<td>38 (21–59)</td>
<td>0.001</td>
<td>0.7</td>
<td>33 (21–47)</td>
</tr>
<tr>
<td>Stop reason, n (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Lack of efficacy</td>
<td>162 (40)</td>
<td>140 (44)</td>
<td>67 (46)</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Adverse events</td>
<td>117 (29)</td>
<td>77 (24)</td>
<td>38 (26)</td>
<td>0.4</td>
<td>0.5</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Other</td>
<td>117 (29)</td>
<td>88 (28)</td>
<td>40 (27)</td>
<td>0.4</td>
<td>0.5</td>
<td>24 (29)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (2)</td>
<td>10 (3)</td>
<td>2 (1)</td>
<td>0.4</td>
<td>0.5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Changes at 3 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Change in Patient global, median (IQR), mm</td>
<td>26 (6–48)</td>
<td>33 (16–59)</td>
<td>22 (7–43)</td>
<td>0.003</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Change in Patient pain, median (IQR), mm</td>
<td>28 (8–49)</td>
<td>37 (13–55)</td>
<td>22 (7–46)</td>
<td>0.03</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Change in Patient fatigue, median (IQR), mm</td>
<td>19 (2–38)</td>
<td>24 (6–51)</td>
<td>20 (2–33)</td>
<td>0.009</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Change in BASDAI, median (IQR)</td>
<td>23 (7–41)</td>
<td>29 (14–45)</td>
<td>18 (9–35)</td>
<td>0.004</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Change in BASFI, median (IQR)</td>
<td>14 (1–29)</td>
<td>18 (6–35)</td>
<td>12 (1–26)</td>
<td>0.005</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Change in BASMI, median (IQR)</td>
<td>10 (0–20)</td>
<td>10 (0–20)</td>
<td>10 (0–20)</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Baseline demographics, disease activity and reasons for terminating TNFi treatment, according to smoking status at the baseline visit (n = 1576) and changes in disease activity measures between baseline and 3 months’ follow-up.<sup>a</sup>Mann–Whitney or χ². <sup>b</sup>Mann–Whitney or χ². <sup>c</sup>Significantly different (P < 0.05) compared with all patients with known smoking status. <sup>†</sup>Percentages of patients who have terminated treatment according to smoking status. <sup>‡</sup>Change at three months compared with baseline, shown as decreases. Patients with available data at baseline (percentage/%): smoking (90), age (100), disease duration (89), gender (100), BMI (61), drug type (100), start year (100), MTX use y/n (100), CRP (75), BASDAI (76), BASFI (76), BASMI (65), patient global (69), pain (69), fatigue (58), physicians global (56). IQR: interquartile range; TNFi: TNF-α inhibitor; VAS: Visual Analogue Scale; n: number.

duration, patient’s pain, fatigue and global scores, BASDAI and BASMI were similar (data not shown).

Treatment adherence

The total follow-up time was 5983 patient years, with a median follow-up time of 2.02 years (IQR 0.69–5.01). Current and previous smokers had poorer treatment adherence than never smokers (Fig. 1 and Table 2). The tendency was the same in stratified analyses according to gender, but the results reached statistical significance mainly in men (Table 2).

Among previous smokers, patients who had stopped smoking during the previous 5 years (n = 106) had similar drug survival to the patients who had stopped ≥ 6 years previously (n = 111) (Kaplan–Meier, log rank P = 0.8). Patients with missing smoking data had similar treatment adherence to patients with known smoking status (log rank, P = 0.6).
Treatments adherence was poorer among current vs never smokers in patients, regardless of type of TNFi-inhibitor (Cox regression analyses, Table 3). Previous smokers had poorer treatment adherence than never smokers for adalimumab and etanercept (Table 3).

Disease activity and treatment response

Measures of disease activity had improved less in current smokers than in never smokers at 3 months’ follow-up (Table 1). Similar tendencies were observed at 6 months for patient global, BASDAI and BASFI scores (data not shown). Both current and previous smokers had lower response rates than never smokers (Fig. 2).

Current and previous smokers had significantly lower odds of achieving response than never smokers, both overall and stratified according to gender (Table 4). For stratified analyses according to TNFi drug type, similar results were found among current versus never smokers for all three TNFi and a tendency of lower odds of response in previous smokers (Table 4).

A sensitivity analysis using multivariate regression including all the variables that differed among current vs never smokers at baseline (BASDAI, BASFI, BASMI, disease duration, VAS physician global) showed similar results (current vs never smokers, OR = 0.49 (95% CI 0.32–0.75, P < 0.001)). When the same covariates were adjusted for in the regression analysis as a propensity score, the results were unaltered (data not shown).

There was no statistically significant interaction between smoking and gender or between smoking and TNFi drug type (both P > 0.05 in Cox and logistic regression analyses).

Discussion

In this study of patients with AS who initiated treatment with the first TNFi in a real-life setting, more than half were current or previous smokers. At the start of treatment, current smokers had higher disease activity compared with never and previous smokers. Both current and previous smoking had a negative impact on treatment effectiveness and increased the risk of withdrawing from treatment. These findings are important, since smoking is potentially modifiable.

We found that current smokers had significantly higher BASMI, BASDAI and BASFI scores and a trend towards a higher CRP level at the start of TNFi treatment compared with never smokers. The negative impact of smoking on disease activity has previously been described in cross-sectional studies among patients with AS [9, 11–13, 29, 30]. In an English survey of 612 patients with established AS, smoking was associated with aggravation in patient-reported outcomes, including function, pain and quality of life [9]. Similar results have been reported in patients with early axSpA [10]. However, these studies included none or only low numbers of TNFi-treated patients [9–11, 29, 30]. The negative impact of smoking may be caused by increased systemic inflammation [29, 31], accelerated radiographic progression [8, 14, 32, 33], decreased functional activity, reduced lung capacity, as well as comorbidities or socioeconomic challenges [9, 10, 29, 34]. Finally, smoking might exacerbate the development of abnormal neuromuscular processing and chronic pain due to vasoconstriction and psychological sensitivity [9, 35].

The fact that only approximately half of AS patients benefit from treatment with their first TNFi [1, 4, 36, 37] has fuelled the search for baseline predictors of treatment response in individual patients [6]. However, many previous observational and randomized studies have not included data on smoking status [5, 6, 38, 39]. We found that current smokers had significantly poorer TNFi treatment adherence and treatment effect than never smokers. This is in accordance with a recent Swiss cohort study of 698 patients with axSpA, of whom ~20% had non-radiographic axSpA, and in which current smokers had an OR of 0.54 (0.31 to 0.95) for achieving BASDAI50% reduction after one year’s treatment compared with never smokers [16]. Other studies have found no such association. Among 422 Australian TNFi-treated AS patients, smoking had no effect on health-related quality of life [17]. The authors suggested that their inclusion of educational level in the multivariate analyses partly explained this because they found significant differences when educational level was omitted from the regression model [17]. In the current study, we had no data on educational level, and this may have influenced our results. An English cohort study based on data from the British Society for Rheumatology Biologics Register (BSRBR) did not find
that smoking status among the baseline factors predicted BASDAI response in AS patients. However, with only 261 patients (94 current smokers) that study may have been insufficiently powered to answer this question [36]. Furthermore, the multivariate analyses included possible intermediate variables (CRP, BASDAI and BASFI) between smoking and outcome. This might have caused overadjustment bias. Any negative effect of smoking on TNFi treatment effects may be due to elevated inflammatory biologic parameters or increased matrix metalloproteinase levels, which are also predictive factors [40].

According to our study and the Swiss results [16], smoking status seems to be an important risk factor, and future studies should consider including such data.

In the current study, previous smokers had similar treatment duration and treatment effects to those of current smokers. Previous smokers who had stopped smoking ≥6 years prior to TNFi start had similar treatment duration to the patients who had stopped smoking in recent years. This indicates a permanent negative impact of smoking. Contrasting results were found by Ciurea et al. [16] among PsA and RA patients, where previous smokers resemble never smokers—especially if smoking cessation happened many years ago [21, 22, 41]. The negative effects of previous smoking on outcome measures in the current study might partly be explained by the fact that previous smokers were older and had a longer disease duration than never smokers—although adjustment for these differences did not alter the association. Any potential differences in the effect of modification of smoking across rheumatic diseases remain unexplained. However, these diseases have different age and gender profiles, inflammatory and immune responses, and a uniform smoking effect is not necessarily to be expected [17]. Furthermore, previous studies in the general population have shown that smoking increases the prevalence of lower back pain and degenerative diseases of the back [42-44], which may contribute to the negative impact of ever smoking in AS.

The strengths of this study are the high external validity for routine care, owing to the inclusion of an unselected, nationwide, large population of patients with AS with long follow-up time and known smoking status in 90% of cases. Base-line characteristics and drug adherence were largely the same in patients with missing and known smoking status, which contradicts substantial selection bias. Our study also has limitations. Smoking status was retrieved cross-sectionally at commencement of the first TNFi, although smoking status might later change [21]. An obvious misclassification occurs when previous smokers resume smoking during follow-up. We had no data on duration of smoking or pack-years to

| TABLE 2 Impact of smoking on treatment adherence stratified by gender |
|-------------------------|-----------------|-----------------|-----------------|
|                        | Overall         | Men             | Women           |
|                        | HR (95% CI)     | P               | HR (95% CI)     | P               | HR (95% CI)     | P               |
| Smoking status         |                 |                 |                 |
| Current                | 1.32 (1.14, 1.53) | <0.0001         | 1.41 (1.17, 1.69) | <0.0001         | 1.32 (1.04, 1.70) | 0.03            |
| Previous               | 1.24 (1.02, 1.50) | 0.03            | 1.35 (1.06, 1.71) | 0.01            | 1.18 (0.83, 1.68) | 0.4             |
| Never                  | 1               |                 | 1               |                 | 1               |                 |
| Gender                 |                 |                 |                 |
| Women                  | 1.64 (1.41, 1.91) | <0.0001         | —               | —               | —               | —               |
| Men                    |                 |                 |                 |
| Disease duration, years|                 |                 |                 |
| 0-1                    | 1.45 (1.22, 1.73) | <0.0001         | 1.28 (1.04, 1.59) | 0.02            | 1.97 (1.41, 2.74) | <0.0001         |
| 2-7                    | 1.34 (1.11, 1.63) | 0.003           | 1.21 (0.96, 1.52) | 0.11            | 1.77 (1.22, 2.57) | 0.004           |
| ≥8                     | 1               |                 | 1               |                 | 1               |                 |
| Age, years             |                 |                 |                 |
| ≤31                    | 1.02 (0.82, 1.25) | 0.9             | 0.91 (0.71, 1.19) | 0.5             | 1.23 (0.86, 1.78) | 0.3             |
| 32-39                  | 0.86 (0.70, 1.06) | 0.17            | 0.77 (0.59, 1.00) | 0.05            | 1.03 (0.72, 1.46) | 0.9             |
| 40-49                  | 1.08 (0.89, 1.31) | 0.4             | 1.05 (0.84, 1.32) | 0.7             | 1.09 (0.77, 1.55) | 0.6             |
| ≥50                    | 1               |                 | 1               |                 | 1               |                 |
| TNFi start year        |                 |                 |                 |
| 2000-06                | 0.70 (0.58, 0.86) | <0.0001         | 0.69 (0.54, 0.88) | 0.003           | 0.79 (0.57, 1.11) | 0.18            |
| 2007-09                | 0.89 (0.74, 1.06) | 0.2             | 0.93 (0.74, 1.17) | 0.5             | 0.86 (0.64, 1.15) | 0.3             |
| 2010-13                | 1               |                 | 1               |                 | 1               |                 |

Univariate and multivariate Cox regression analyses (including a priori confounders). MTX use and TNFi drug type did not alter the HR of smoking by >10% and was not included in the multivariate analyses. HR: hazard ratio for withdrawal; TNFi: TNF-α inhibitor.
Table 3. Impact of smoking on treatment adherence stratified by TNFi drug type

<table>
<thead>
<tr>
<th>Treatment adherence, Kaplan-Meier analyses</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (95% CI)</td>
<td>P</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2.80 (2.01, 3.59)</td>
<td>0.02</td>
<td>2.29 (0.39, 4.20)</td>
</tr>
<tr>
<td>Never</td>
<td>5.73 (4.08, 7.38)</td>
<td></td>
<td>7.56 (4.03, 11.08)</td>
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</table>

<table>
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<tr>
<th>Multivariate Cox regression analyses</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>HR (95% CI)</th>
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<tr>
<td>Smoking status</td>
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<tr>
<td>Current</td>
<td>1.33 (1.02, 1.74)</td>
<td>0.04</td>
<td>2.09 (1.38, 3.18)</td>
<td>&lt;0.001</td>
<td>1.33 (1.05, 1.69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous</td>
<td>1.41 (1.02, 1.94)</td>
<td>0.04</td>
<td>2.16 (1.24, 3.77)</td>
<td>0.006</td>
<td>1.21 (0.85, 1.73)</td>
<td>0.3</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Women</td>
<td>1.79 (1.41, 2.27)</td>
<td>&lt;0.000</td>
<td>1.92 (1.28, 2.89)</td>
<td>0.002</td>
<td>1.42 (1.12, 1.81)</td>
<td>0.004</td>
</tr>
<tr>
<td>Men</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Disease duration, years</td>
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<tr>
<td>0–1</td>
<td>1.51 (1.12, 2.02)</td>
<td>0.006</td>
<td>1.32 (0.85, 2.04)</td>
<td>0.2</td>
<td>1.42 (1.08, 1.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>2–7</td>
<td>1.43 (1.04, 1.96)</td>
<td>0.03</td>
<td>1.02 (0.60, 1.73)</td>
<td>0.9</td>
<td>1.43 (1.07, 1.91)</td>
<td>0.02</td>
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<td>≥8</td>
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<td>Age, years</td>
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<tr>
<td>≤31</td>
<td>1.03 (0.73, 1.45)</td>
<td>0.9</td>
<td>1.06 (0.60, 1.85)</td>
<td>0.9</td>
<td>1.07 (0.76, 1.50)</td>
<td>0.7</td>
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<tr>
<td>32–39</td>
<td>0.79 (0.56, 1.11)</td>
<td>0.2</td>
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<td>0.6</td>
<td>0.90 (0.65, 1.25)</td>
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<tr>
<td>40–49</td>
<td>1.07 (0.78, 1.47)</td>
<td>0.7</td>
<td>0.92 (0.57, 1.48)</td>
<td>0.9</td>
<td>1.14 (0.85, 1.54)</td>
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<tr>
<td>≥50</td>
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<tr>
<td>TNFi start year</td>
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<tr>
<td>2000–06</td>
<td>0.62 (0.42, 0.90)</td>
<td>0.01</td>
<td>0.38 (0.23, 0.64)</td>
<td>&lt;0.0001</td>
<td>0.67 (0.47, 0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>2007–09</td>
<td>0.87 (0.67, 1.13)</td>
<td>0.3</td>
<td>0.66 (0.41, 1.06)</td>
<td>0.09</td>
<td>0.86 (0.61, 1.23)</td>
<td>0.4</td>
</tr>
<tr>
<td>2010–13</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

Log rank tests\(^a\) and multivariate Cox regression analyses (including a priori confounders). MTX use did not alter the HR of smoking by >10% and was not included in the multivariate analyses. HR: hazard ratio for withdrawal; TNFi: TNF-\(\alpha\) inhibitor.

Fig. 2. BASDAI50%/20 mm-response rates after 6 months’ treatment according to smoking status for all patients and stratified according to gender.

P-values are response rates among current versus never smokers (Chi square).
illustrate any dose–response relationship [9, 15]. In Denmark, heavy smokers are more often men [45, 46]. One might assume that the stronger impact of smoking among male patients was associated with greater exposure to tobacco. Smoking may be linked to comorbid disease, depression, socioeconomic factors and lifestyle, which all potentially affect baseline disease activity and treatment outcomes. We had no data with which to explore these issues further. In DANBIO, the clinical diagnosis for individual patients was registered according to the expert opinion of the treating physician. Currently, data regarding HLAB27 status, radiographic data and peripheral joint disease are not uniformly available in DANBIO. In conclusion, this study of AS patients treated with TNFi in clinical practice showed that current and previous smokers had significantly poorer patient-reported outcomes at baseline, shorter treatment adherence and poorer treatment response compared with never smokers.

Acknowledgements

We should like to thank all the Departments of Rheumatology in Denmark for reporting to the DANBIO registry.

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References

9 Mattey DL, Dawson SR, Healey EL, Packham JC. Relationship between smoking and patient-reported

| TABLE 4 Impact of smoking on treatment response for all patients, stratified by gender and TNFi drug type |

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>0.48 (0.35, 0.65)</td>
<td>&lt;0.0001</td>
<td>0.55 (0.38, 0.80)</td>
<td>0.001</td>
<td>0.34 (0.19, 0.62)</td>
<td>-0.001</td>
</tr>
<tr>
<td>Previous</td>
<td>0.53 (0.35, 0.80)</td>
<td>0.002</td>
<td>0.60 (0.37, 0.97)</td>
<td>0.04</td>
<td>0.40 (0.18, 0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
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<tr>
<th>Smoking status</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Adalimumab</td>
<td>Etanercept</td>
<td>Infliximab</td>
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</tr>
<tr>
<td>Current</td>
<td>0.45 (0.27, 0.76)</td>
<td>0.002</td>
<td>0.24 (0.10, 0.61)</td>
<td>0.003</td>
<td>0.57 (0.34, 0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous</td>
<td>0.58 (0.31, 1.10)</td>
<td>0.1</td>
<td>0.29 (0.10, 0.91)</td>
<td>0.03</td>
<td>0.58 (0.29, 1.14)</td>
<td>0.11</td>
</tr>
<tr>
<td>Never</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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</tbody>
</table>

Multivariate logistic regression analyses including a priori confounders (odds ratios for confounders not shown in table). MTX use did not alter the HR of smoking by >10% and was not included in the analyses. OR: odds ratio; TNFi: TNF-α inhibitor.

10 Chung HY, Machado P, van der Heijde D, D’Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort. Ann Rheum Dis 2012;71:809-16.


Ankylosing Spondylitis versus Nonradiographic Axial Spondyloarthritis: Comparison of Tumor Necrosis Factor Inhibitor Effectiveness and Effect of HLA-B27 Status. An Observational Cohort Study from the Nationwide DANBIO Registry

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ABSTRACT. Objective. To compare baseline disease activity and treatment effectiveness in biologic-naive patients with nonradiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) who initiate tumor necrosis factor inhibitor (TNFi) treatment and to study the role of potential confounders (e.g., HLA-B27 status).

Methods. Observational cohort study based on prospectively registered data in the nationwide DANBIO registry. We used Kaplan-Meier plots, Cox, and logistic regression analyses to study the effect of diagnosis (nr-axSpA vs AS) and potential confounders (sex/age/start yr/HLA-B27/disease duration/TNFi-type/smoking/baseline disease activity) on TNFi adherence and response [e.g., Bath Ankylosing Spondylitis Activity Index (BASDAI) 50%/20 mm].

Results. The study included 1250 TNFi-naive patients with axSpA (29% nr-axSpA, 50% AS, 21% lacked radiographs of sacroiliac joints). Patients with nr-axSpA were more frequently women (50%/27%) and HLA-B27–negative (85/338 = 25%), compared to AS (81/476 = 17%; p < 0.01). At TNFi start patients with nr-axSpA had higher visual analog scale scores [median (quartiles)] for pain: 72 mm (55–84)/65 mm (48–77); global: 76 mm (62–88)/68 mm (50–80); fatigue: 74 mm (55–85)/67 mm (50–80); and BASDAI: 64 (54–77)/59 (46–71); all p < 0.01. However, patients with nr-axSpA had lower C-reactive protein: 7 mg/l (3–17)/11 mg/l (5–22); and BAS Metrology Index: 20 (10–40)/40 (20–50); all p < 0.01. Median (95% CI) treatment adherence was poorer in nr-axSpA than in AS: 1.59 years (1.15–2.02) versus 3.67 years (2.86–4.49), p < 0.0001; but only in univariate and not confounder-adjusted analyses (p > 0.05). Response rates were similar in AS and nr-axSpA (p > 0.05). HLA-B27 negativity was associated with poorer treatment adherence [HLA-B27 negative/positive, nr-axSpA: HR 1.74 (1.29–2.36), AS: HR 2.04 (1.53–2.71), both p < 0.0001]; and lower response rates (nr-axSpA: 18/61 = 30% vs 93/168 = 55%; AS: 17/59 = 29% vs 157/291 = 54%, both p < 0.05).

Conclusion. In this nationwide cohort, patients with nr-axSpA had higher subjective disease activity at start of first TNFi treatment, but similar outcomes to patients with AS after confounder adjustment. HLA-B27 positivity was associated with better outcomes irrespective of axSpA subdiagnosis.

Key Indexing Terms:
AXIAL SPONDYLOARTHRITIS
OUTCOME
TUMOR NECROSIS FACTOR-A
REGISTRY

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Glintborg, et al: TNFi treatment in axSpA

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The disease spectrum of axial spondyloarthritis (axSpA) includes patients with radiographic axSpA (ankylosing spondylitis, AS), who fulfill the modified New York criteria, and patients with nonradiographic axSpA (nr-axSpA)1,2.

Since the introduction of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria aiming to identify patients with axSpA at earlier disease stages, it has been discussed how patients with nr-axSpA differ from patients with AS4,5. Only a minority of patients with nr-axSpA develops radiographic changes and AS within 10 years of follow-up6,7. Further, patients with nr-axSpA are more frequently women with a lower grade of spinal inflammation on spinal and sacroiliac magnetic resonance imaging (MRI)8,9, and other studies have demonstrated similar levels of pain and disability among patients with nr-axSpA and AS9,10,11.

The beneficial effect of tumor necrosis factor inhibitors (TNFi) on treatment outcomes is well established in AS9,12,13. In nr-axSpA, the effect of TNFi seems to depend on objective signs of inflammation, e.g., increased C-reactive protein (CRP) level and/or active inflammation on MRI5,14,15,16,17.

Few previous observational studies have compared TNFi treatment outcomes among patients with nr-axSpA versus AS9,18,19. These studies included < 100 patients with nr-axSpA18,19, were not nationwide18,19, did not include data on longterm outcomes or treatment duration9, reported results only from univariate analyses19, or did not include in multivariate analyses data on relevant potential confounders, e.g., HLA-B27 status, smoking status, or year of starting TNFi9,18.

The primary aim of our present study was to compare baseline disease activity and treatment effectiveness by univariate and confounder-adjusted analyses in a large cohort of biologic-naïve patients with AS versus nr-axSpA, who initiated TNFi treatment in clinical practice. Secondly, our aim was to explore the effect of potential confounders, e.g., HLA-B27 status and CRP.

MATERIALS AND METHODS

The DANBio quality registry was initiated in 2000 and covers > 90% of Danish adults with rheumatic diseases treated in routine care with biologic disease-modifying antirheumatic drugs (DMARD)20. In accordance with national treatment guidelines and quality indicators, patients are monitored prospectively by online registrations (www.danbio-online.dk) of disease activity and outcomes at least biannually and when medication is changed20,21. According to Danish legislation, registration and publication of data from clinical registries do not require patient consent or approval by ethics committees.

Baseline demographics include smoking habits, age, sex, body mass index, disease duration, and current treatment with conventional synthetic DMARD. Disease activity and functional status are monitored by serum CRP level (normal range ≤ 10 mg/l); visual analog scales (VAS) for patient’s global assessment (PtGA), pain, fatigue, and physician’s global assessment (P GA); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Function Index (BASFI); and Bath Ankylosing Spondylitis Metrology Index (BASMI). Registration of classification criteria (ASAS classification criteria, modified New York criteria) is optional and only available in a subset of patients.

All TNFi-naïve patients were identified in DANBio if they had initiated treatment with a biological drug between January 1 2005, and July 1, 2014, and had one of the International Classification of Diseases–10 diagnoses of AS (M45.9), sacroiliitis (M46.1), or inflammatory spondylopathy (M46.8, M46.9). All Danish departments of rheumatology were invited to participate in the study and to enter data regarding which classification criteria individual patients fulfilled upon start of their first biological drug. The additional data were collected from patient files [laboratory results (CRP, HLA-B27), patient history, objective examinations] and radiographic data. No second reading of radiographs or MRI was performed and no additional prospective laboratory testing or examinations were made. Thus, patients were classified as having axSpA if they fulfilled the ASAS criteria upon TNFi start2. According to available radiology descriptions of radiographs of the sacroiliac (SI) joints (sacroiliitis grade, uni- or bilaterally)3, patients were classified as having AS (M45.9), sacroiliitis (M46.1), or inflammatory spondylopathy (M46.8, M46.9). All Danish departments of rheumatology were invited to participate in the study and to enter data regarding which classification criteria individual patients fulfilled upon start of their first biological drug. The additional data were collected from patient files [laboratory results (CRP, HLA-B27), patient history, objective examinations] and radiographic data. No second reading of radiographs or MRI was performed and no additional prospective laboratory testing or examinations were made. Thus, patients were classified as having axSpA if they fulfilled the ASAS criteria upon TNFi start2. According to available radiology descriptions of radiographs of the sacroiliac (SI) joints (sacroiliitis grade, uni- or bilaterally)3, patients were classified as having AS or nr-axSpA. Patients with no available SI joint radiographs at treatment start were classified as “unspecified axSpA” (Figure 1).

Treatm ent adherence. Treatment adherence was calculated as the number of days each patient maintained treatment. Start date was the date of the first given dose and stop date was the date of the first missed dose. Temporary treatment interruptions (e.g., infections, surgery) of ≤ 3 months were allowed. All observations were censored by August 15, 2015.

Reasons for drug discontinuation are registered in DANBio and in prespec-
Biologically treated patients with diagnosis M45.9, M46.1, M46.8, M46.9 in DANBIO
Treatment started Jan 1, 2005–Jan 7, 2014
N = 2462

Not eligible
-Treated with blinded study medication, N = 96
-Not followed in DANBIO since start first TNFi, N = 59
-First biological treatment was not a TNFi, N = 23
-Erroneous registrations, N = 27
-mNYC negative, ASAS unknown, N = 91
-Classification criteria not validated, N = 830
(non-participating dept. N = 467)
(participating dept. N = 363)
N = 1126

ASAS-negative EXCLUDED
N = 86

ASAS-positive INCLUDED
N = 1250

mNYC-positive
N = 622

mNYC unknown
(no radiograph SI joints)
Unspecified axSpA*
N = 266

mNYC-negative
N = 362

Clinical/unknown
N = 70

Imaging
N = 292

AS
N = 622

Nr-axSpA
N = 362

Figure 1. Patient disposition, inclusion and exclusion. * 238/266 patients (89%) with unspecified axSpA had inflammation on magnetic resonance images of the SI joints. DANBIO: DANBIO registry of rheumatic diseases; TNFi: tumor necrosis factor inhibitor; mNYC: modified New York criteria; ASAS: Assessment of Spondyloarthritis international Society; SI: sacroiliac; axSpA: axial spondyloarthritis; AS: ankylosing spondylitis; nr-axSpA: nonradiographic axSpA.
patients who achieved BASDAI 50%/20-mm response. As secondary outcomes, ASAS response criteria for 40% improvement in disease activity (ASAS 40) and ASAS criteria for partial remission were calculated.22,24

Since November 2010, the ASAS Disease Activity Score (ASDAS) has been registered in DANBIO. Among patients with available data, we calculated the proportion of patients who achieved inactive disease (ASDAS < 1.3) at the 3- or 6-month visit (similar to the algorithm described for BASDAI 50%/20 mm response). Similarly, the proportion of patients with clinically important improvement in ASDAS (change of ≥ 1.1 between baseline and 3- or 6-month visit) was calculated.25

Characteristics at baseline. Age, sex, and the interaction terms HLA-B27*sex and diagnosis*sex remained in the model irrespective of p value.

Response rates were reported by percentages. The numbers needed to treat (NNT) to achieve response were calculated as the reciprocal values of the response rates.

All primary analyses were based on observed data without imputation of missing data. For the multivariate analysis, the following sensitivity analyses were performed: (1) multiple imputation of missing data (SPSS, 5 imputation steps); (2) exclusion of patients with nr-axSpA diagnosed according to the clinical arm of the classification criteria (n = 70; Figure 1); and (3) classification of all patients with unspecified axSpA as either AS or nr-axSpA.

RESULTS

Study population. Among 2462 biologic-naive patients with axSpA registered in DANBIO with a relevant diagnosis who initiated TNFi treatment between January 1, 2005, and July 1, 2014 (Figure 1), the diagnosis was validated retrospectively in 1336. Most of the patients who did not have the diagnosis validated came from departments that did not participate in the study. A total of 1250 patients (93%) fulfilled the ASAS criteria for axSpA and were included (Figure 1). Of these, 622 patients fulfilled the classification criteria for AS, 362 for nr-axSpA, and 266 patients had unspecified axSpA. Withdrawal analysis showed that the included and excluded patients had similar sex and age distribution (p > 0.05, not shown).

Characteristics at baseline. Patients with AS had longer disease duration, were older, more frequently men, and HLA-B27–positive compared to patients with nr-axSpA, and they more frequently had a history of uveitis but less frequently of dactylitis (Table 1). Patients with AS more often started treatment before 2008 and were more frequently treated with IFX, had higher CRP and BASMI but lower global, fatigue, and pain scores and lower BASDAI compared to patients with nr-axSpA (Table 1). Patients with unspecified axSpA more frequently started treatment after 2008 compared to patients with AS or nr-axSpA, and fewer were HLA-B27–positive (both p < 0.05).

Treatment adherence, AS versus nr-axSpA. The cumulated followup time was 3359 patient-years (median followup time: 2.5 yrs; 95% CI 2.01–3.00). Patients with nr-axSpA had poorer treatment adherence than patients with AS [median treatment duration, AS: 3.67 (2.86–4.49), nr-axSpA: 1.59 (1.15–2.02); p < 0.0001]. However, this was found only in univariate (Figure 2A) but not in multivariate analysis (Table 2). Men had longer treatment adherence than women in both AS and nr-axSpA (not shown). The treatment adherence was similar among patients with nr-axSpA who fulfilled the imaging classification criteria versus the clinical criteria [1.59 yrs (1.16–2.01) vs 1.33 yrs (0.0–3.27), p = 0.5].

Patients with nr-axSpA more often stopped treatment because of lack of effect compared to AS (Supplementary Table 1, available with the online version of this article).

Response rates, AS versus nr-axSpA. Changes in disease activity at the 3-month followup were similar among patients with nr-axSpA and AS for most scores but not for BASMI (Supplementary Table 2, available with the online version of this article). Treatment responses were similar among patients with AS and nr-axSpA (Figure 3A).

Treatment adherence and response rates, effect of HLA-B27. HLA-B27–positive patients stayed on treatment longer than HLA-B27–negative patients (Table 2). The same was true when stratified according to axSpA subgroup (univariate comparisons; log rank, Mantel-Cox test, both p < 0.0001; Figure 2B). Similar results were found in the sensitivity analyses.

HLA-B27–positive patients, regardless of diagnosis, had significantly higher response rates compared to HLA-B27–negative patients (Figure 3B). NNT to achieve BASDAI 50%/20 mm response was 2 for patients with AS who were HLA-B27–positive versus NNT = 4 for patients with AS who were HLA-B27–negative; similar values were found in nr-axSpA.

Treatment adherence and response rates, effect of increased CRP at baseline. At baseline, 51% (238/469) of patients with AS and 39% (113/290) of patients with nr-axSpA had increased CRP (> 10 mg/l). Treatment adherence lasted longer among patients with increased CRP (Table 2), but mainly in AS (Supplementary Figure, available online at jrheum.org). In contrast, BASDAI 50%/20 mm response rates were higher among patients with CRP > 10 mg/l in both AS and nr-axSpA [AS: 58% (118/204) vs 39% (76/196); nr-axSpA: 60% (52/87) vs 41% (55/134), both p < 0.005].
DISCUSSION
In this nationwide study of patients with nr-axSpA and AS initiating TNFi treatment in routine care, we found differences in baseline demographics and disease activity at treatment start, but similar response rates after 6 months of treatment. Treatment adherence was independent of diagnosis in adjusted analyses, while poorer adherence for patients with nr-axSpA was observed in univariate analyses. HLA-B27 status was strongly associated with outcomes irrespective of axSpA subtype.

Since the implementation of the ASAS criteria and the expansion of the axSpA disease spectrum with the nr-axSpA patient group, it has been discussed whether nr-axSpA and AS represent a continuum or 2 different disease entities.

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**Table 1.** Baseline demographics according to classification criteria at baseline (start of the first TNFi treatment course) for nr-axSpA, AS, and unspecified axSpA. Data are medians (interquartile ranges) unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>No. Pts. with Available Data, n</th>
<th>All Pts.</th>
<th>Nr-axSpA</th>
<th>AS</th>
<th>Unspecified AxSpA</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>362</td>
<td>266</td>
<td>622</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>40 (31–49)</td>
<td>38 (30–46)</td>
<td>42 (33–52)</td>
<td>38 (29–46)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>792 (63)</td>
<td>183 (51)</td>
<td>455 (73)</td>
<td>154 (58)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>HLA-B27–positive, n (%)</td>
<td>811 (65)</td>
<td>253 (70)</td>
<td>395 (83)</td>
<td>163 (61)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>728</td>
<td>25 (23–29)</td>
<td>25 (22–30)</td>
<td>26 (23–29)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>MTX, yes, n (%)</td>
<td>722</td>
<td>59 (16)</td>
<td>129 (21)</td>
<td>34 (13)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Manifestations ever, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>1177</td>
<td>1131 (91)</td>
<td>326 (90)</td>
<td>562 (90)</td>
<td>243 (91)</td>
<td>0.07</td>
</tr>
<tr>
<td>Family disposition</td>
<td>885</td>
<td>199 (16)</td>
<td>67 (19)</td>
<td>98 (16)</td>
<td>34 (13)</td>
<td>0.9</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>1119</td>
<td>441 (35)</td>
<td>146 (40)</td>
<td>190 (31)</td>
<td>105 (39)</td>
<td>0.05</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>909</td>
<td>218 (17)</td>
<td>72 (20)</td>
<td>95 (15)</td>
<td>51 (19)</td>
<td>0.5</td>
</tr>
<tr>
<td>Uveitis</td>
<td>1042</td>
<td>249 (20)</td>
<td>67 (19)</td>
<td>145 (23)</td>
<td>37 (14)</td>
<td>0.02</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1018</td>
<td>75 (6)</td>
<td>31 (9)</td>
<td>35 (6)</td>
<td>9 (3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>871</td>
<td>40 (3)</td>
<td>21 (6)</td>
<td>9 (1)</td>
<td>10 (4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>IBD</td>
<td>1031</td>
<td>104 (8)</td>
<td>31 (9)</td>
<td>42 (7)</td>
<td>31 (12)</td>
<td>0.5</td>
</tr>
<tr>
<td>NSAID response</td>
<td>876</td>
<td>614 (49)</td>
<td>179 (49)</td>
<td>310 (49)</td>
<td>125 (47)</td>
<td>0.9</td>
</tr>
<tr>
<td>Elevated CRP</td>
<td>1093</td>
<td>575 (46)</td>
<td>164 (45)</td>
<td>307 (49)</td>
<td>104 (39)</td>
<td>0.003</td>
</tr>
<tr>
<td>Symptom duration, yrs</td>
<td>1040</td>
<td>9 (3–18)</td>
<td>6 (3–13)</td>
<td>13 (6–23)</td>
<td>5 (2–11)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>1155</td>
<td>1 (0–6)</td>
<td>1 (0–3)</td>
<td>3 (1–12)</td>
<td>1 (0–3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>976</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>377 (30)</td>
<td>97 (27)</td>
<td>216 (41)</td>
<td>64 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>177 (14)</td>
<td>42 (12)</td>
<td>103 (20)</td>
<td>32 (12)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>422 (33)</td>
<td>119 (33)</td>
<td>204 (39)</td>
<td>99 (37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First TNFi drug, n (%)</td>
<td>1525</td>
<td>519 (41)</td>
<td>151 (42)</td>
<td>258 (41)</td>
<td>110 (41)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>8 (1)</td>
<td>5 (1)</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>183 (15)</td>
<td>53 (14)</td>
<td>100 (16)</td>
<td>30 (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>246 (20)</td>
<td>85 (23)</td>
<td>88 (14)</td>
<td>73 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>294 (24)</td>
<td>68 (19)</td>
<td>174 (28)</td>
<td>52 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>376 (30)</td>
<td>79 (21)</td>
<td>259 (41)</td>
<td>38 (14)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>First TNFi start yr, n (%)</td>
<td>1250</td>
<td>442 (35)</td>
<td>132 (36)</td>
<td>194 (31)</td>
<td>116 (45)</td>
<td></td>
</tr>
<tr>
<td>2005–2008</td>
<td>432 (34)</td>
<td>151 (41)</td>
<td>169 (27)</td>
<td>112 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009–2011</td>
<td>376 (30)</td>
<td>79 (21)</td>
<td>259 (41)</td>
<td>38 (14)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>2012–2014</td>
<td>442 (35)</td>
<td>132 (36)</td>
<td>194 (31)</td>
<td>116 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>964</td>
<td>3 (9–20)</td>
<td>7 (3–17)</td>
<td>11 (5–22)</td>
<td>6 (2–16)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BASDAI, mm</td>
<td>1012</td>
<td>61 (49–73)</td>
<td>64 (54–77)</td>
<td>59 (46–71)</td>
<td>63 (51–74)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BASDAI, question 5, mm</td>
<td>783</td>
<td>73 (52–86)</td>
<td>75 (55–91)</td>
<td>71 (51–84)</td>
<td>74 (54–86)</td>
<td>0.02</td>
</tr>
<tr>
<td>BASDAI, question 6, mm</td>
<td>785</td>
<td>60 (36–86)</td>
<td>68 (39–90)</td>
<td>56 (32–83)</td>
<td>59 (39–86)</td>
<td>0.02</td>
</tr>
<tr>
<td>BASFI, mm</td>
<td>980</td>
<td>50 (34–68)</td>
<td>52 (33–69)</td>
<td>49 (34–67)</td>
<td>51 (31–67)</td>
<td>0.7</td>
</tr>
<tr>
<td>PGA, mm</td>
<td>676</td>
<td>37 (22–51)</td>
<td>38 (22–53)</td>
<td>38 (22–53)</td>
<td>35 (22–45)</td>
<td>0.6</td>
</tr>
<tr>
<td>BASMI</td>
<td>848</td>
<td>30 (10–40)</td>
<td>20 (10–40)</td>
<td>40 (20–50)</td>
<td>20 (10–40)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PsGA, mm</td>
<td>938</td>
<td>72 (53–85)</td>
<td>76 (62–88)</td>
<td>68 (50–80)</td>
<td>74 (59–88)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pain, mm</td>
<td>937</td>
<td>67 (50–80)</td>
<td>72 (55–85)</td>
<td>65 (48–77)</td>
<td>68 (50–81)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Fatigue, mm</td>
<td>846</td>
<td>70 (52–83)</td>
<td>74 (55–85)</td>
<td>67 (50–80)</td>
<td>72 (54–85)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* No baseline radiograph of sacroiliac joints available. * Nr-axSpA versus AS. Chi square or nonparametric testing (Mann-Whitney U test) for continuous data. TNFi: tumor necrosis factor inhibitor; AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BMI: body mass index; MTX: methotrexate; CRP: C-reactive protein; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory response; nr-axSpA: nonradiographic axSpA; VAS: visual analog scale; PGA: physician’s global assessment; PsGA: patient’s global assessment.
Further, it is debated whether the TNFi treatment effects in AS can be extrapolated to nr-axSpA. In Denmark, patients with nr-axSpA and AS are approached similarly in daily practice: a clinical evaluation must ensure that the correct diagnosis has been made (based on ASAS or modified New York classification criteria), and ≥ 2 measurements of high disease activity (BASDAI ≥ 40 mm) and failure of 2 nonsteroidal anti-inflammatory drugs (NSAID) must be documented in DANBIO before TNFi treatment starts. The TNFi treatment is tax-paid and provided free of charge to individual patients. Thus, treatment with TNFi in nr-axSpA does not require elevated CRP or active inflammation on MRI at baseline, in contrast to the guidelines applied in some countries.

In accordance with previous studies, patients with nr-axSpA were more frequently women and had shorter disease duration. Further, they were more often HLA-B27–negative compared to patients with AS. In a Swiss cohort of nr-axSpA and AS patients, HLA-B27 positivity was present in 70% (nr-axSpA) and 84% (AS), nearly identical to the rates found in our study. However, the frequency of HLA-B27 positivity among patients with axSpA seems to vary among different cohorts.

In the early years (2005–2008), patients with AS dominated, in contrast to the later years (2012–2014), mirroring the gradual implementation of the ASAS classification criteria from 2009 and explaining why patients with AS more frequently received IFX (the first TNFi available).

Patients with AS had higher CRP and BASMI at TNFi treatment start, which may reflect more active inflammation and structural damage, respectively. In contrast, patients with nr-axSpA had higher subjective measures of disease activity compared to patients with AS. A similar tendency was observed in the Swiss cohort. However, 2 previous observational studies and several randomized trials found similar baseline BASDAI and VAS scores in nr-axSpA and AS. These differences between cohorts are difficult to account for, but may reflect national differences in the management of these patient groups and the selection of patients for biological treatment. The higher prevalence of women in the nr-axSpA group might also
contribute to higher scores in patient-reported outcomes\textsuperscript{36,37}.

In accordance with previous observational\textsuperscript{9,18,19,38} and randomized studies\textsuperscript{33,34,35}, we found that patients with nr-axSpA and AS had similar response rates after 6 months. Patients with nr-axSpA, however, had poorer treatment adherence and more often stopped owing to lack of effect in crude analyses, but not after adjustment for differences in baseline characteristics, which may be considered confounders (CRP, sex, BASFI, HLA-B27 positivity). Previous studies have shown conflicting results\textsuperscript{18,19}. Poorer treatment adherence has been demonstrated in female TNFi-treated patients with axSpA\textsuperscript{36,39}. Further, patients with nr-axSpA more often started treatment during recent years where more different TNFi were available, enabling more frequent drug switching\textsuperscript{40}. The association between HLA-B27 status and TNFi treatment outcomes has not been reported previously, to our knowledge. In early axSpA, HLA-B27 positivity is associated with younger age at disease onset\textsuperscript{11}, spinal inflammation, and radiographic changes\textsuperscript{41}. Thus, HLA-B27 may be linked to disease severity and outcomes potentially modifiable to TNFi treatment. It cannot be excluded that inconsistencies in the interpretation of radiographs and MRI\textsuperscript{16,42} may have resulted in misclassification of patients. Because no such misclassification is possible for HLA-B27, this might have had an effect on the statistical analyses. It was beyond the scope of our present study to explore this issue further, and our results reflect clinical routine, where images are read by local radiologists.

\textbf{Figure 2B.} Results stratified by diagnosis (AS/nr-axSpA) and HLA-B27 status (positive/negative). Median treatment duration (95\% CI): AS and HLA-B27–positive: 4.3 years (3.1–5.5); AS and HLA-B27–negative: 1.3 years [0.7–1.8; HR 2.04 (1.53–2.71)]; nr-axSpA and HLA-B27–positive: 2.2 years (1.0–3.3); nr-axSpA and HLA-B27–negative: 0.7 years [1.9–3.2; HR 1.74 (1.29–2.36)]. In a subanalysis including only HLA-B27–positive patients, patients with AS had significantly better treatment adherence than patients with nr-axSpA (p = 0.002). AS: ankylosing spondylitis; nr-axSpA: nonradiographic axial spondyloarthritis.
In the general population, the ratio of nr-axSpA to AS is about 1:15.43. In contrast, more patients in our study had AS than nr-axSpA. This difference may be explained, at least in part, by the selection of patients for biological therapy in routine care: Rheumatologists more often assign TNFi treatment to patients with AS 9. Further, the study included patients initiating TNFi before the ASAS criteria were implemented (2005–2009). One in 5 patients had unspecified axSpA (i.e., lacked radiographs of the SI joints at TNFi treatment start), and most of these started TNFi after 2009. This indicates that the clinicians seem to put more emphasis on MRI findings than on radiographic results after the introduction of the ASAS classification criteria.

In our present study, the majority of patients with nr-axSpA fulfilled the “imaging arm” of the ASAS criteria. Concerns have been raised regarding the “clinical arm” and the risk of erroneously diagnosing chronic mechanical back pain as nr-axSpA 27. Reassuringly, sensitivity analyses in which the clinical arm was excluded showed similar results for axSpA subgroups.

It has previously been shown that fibromyalgia (FM) occurs in 15%–20% of patients with axSpA 44 and that FM is associated with poorer TNFi adherence rates and higher disease activity scores 45. In a recent study, HLA-B27 positivity rates and imaging results were, however, similar in a cross-sectional cohort of axSpA patients with/without FM 45. It is possible that uneven distribution of FM among patients with nr-axSpA and AS in the present study affected the results, but we had no data to explore this further.

The strength of our study is that it includes a large nationwide cohort of patients treated in routine care with valid data from a clinical registry collected independently of treatment and subdiagnosis. Further, comprehensive data regarding several potential confounders were available, e.g.,

| Table 2. HR for stopping treatment. Univariate and multivariate Cox regression analyses (backwards selection) included a priori confounders. |
|---|---|---|---|
| **Univariate Analyses** | **Final Multivariate Model, Backward Selection** |
| HR (95% CI) | p | HR (95% CI) | p |
| **Diagnosis** | | | |
| AS | 1 | <0.0001 | — | — |
| Nr-axSpA | 1.41 (1.20–1.67) | | |
| **Sex** | | | |
| Men | 1 | <0.0001 | 1.52 (1.16–1.97) | 0.002 |
| Women | 1.72 (1.46–2.03) | 0.02 | — | — |
| **Disease duration, yrs** | | | |
| Age | 0.99 (0.98–0.99) | — | — |
| <45 yrs | 0.91 (0.77–1.07) | 0.2 | 1.05 (0.83–1.33) | 0.6 |
| ≥45 yrs | 1 | — | — |
| **TNFi start year** | | | |
| 2005–2008 | 0.58 (0.47–0.72) | <0.0001 | — | — |
| 2009–2011 | 0.82 (0.67–1.01) | | |
| 2012–2014 | 1 | — | — |
| **HLA-B27+** | 1 | <0.0001 | 1 | <0.0001 |
| **HLA-B27–negative** | 1.93 (1.61–2.32) | 2.15 (1.51–3.06) | |
| **TNFi drug type** | | | |
| Adalimumab | 1 | 0.10 | — | — |
| Etanercept | 1.01 (0.79–1.28) | — | — |
| Infliximab | 1.01 (0.82–1.23) | — | — |
| Golimumab | 1.35 (1.05–1.73) | — | — |
| **Smoking** | | | |
| Current | 1.52 (1.25–1.86) | <0.0001 | — | — |
| Previous | 1.34 (1.04–1.72) | — | — |
| Never | 1 | — | — |
| **Baseline BASDAI, mm** | 1.01 (1.01–1.02) | <0.0001 | 1.01 (1.00–1.02) | 0.002 |
| **Baseline BASMI, mm** | 0.99 (0.99–1.00) | 0.6 | — | — |
| **Baseline CRP ≥ 10 mg/l** | 1.52 (1.26–1.84) | <0.0001 | 1.36 (1.08–1.71) | 0.01 |
| **Baseline CRP > 10 mg/l** | 1 | — | — |

Similar results regarding effects of HLA-B27 and axSpA subdiagnosis were found when (1) applying multiple imputation of missing data; and (2) patients with nr-axSpA diagnosed according to the clinical arm were excluded.

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; nr-axSpA: nonradiographic axSpA.
smoking status, disease duration, HLA-B27 status, and baseline disease activity.

Current NSAID use is not registered routinely in DANBIO. Concomitant use of NSAID is known to have an effect on inflammation and outcomes\(^{46,47}\), so this might have affected our results. We were able to validate the diagnosis in about half of the Danish biologically treated patients with axSpA by a retrospective, voluntary review of the patient...
files. The withdrawal analysis revealed similar age and sex distribution among included and excluded patients, which indicate that selection bias was minimal and we therefore consider the results to be generalizable.

Patients with nr-axSpA had higher subjective disease activity at the start of first TNFi treatment, but had outcomes similar to patients with AS after adjustment for confounders. HLA-B27 positivity was associated with better outcomes irrespective of axSpA subdiagnosis.

ACKNOWLEDGMENT
Thanks to all the Danish departments of rheumatology for reporting to the DANBIO registry.

ONLINE SUPPLEMENT
Supplementary material accompanies the online version of this article.

REFERENCE LIST


CONCISE REPORT

A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry

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ABSTRACT

Objectives According to guidelines, a nationwide non-medical switch from originator (INX, Remicade) to biosimilar infliximab (Remsima, CT-P13) was conducted in Danish patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (AxSpA). We investigated disease activity before/after switching and retention rates in the DANBIO registry.

Methods Disease activities 3 months before and after switch and changes over time were calculated. flare was defined as change in 28 Joint Disease Activity Score (ΔDAS28) ≥1.2 (RA/PsA) or Axially elongated Spondylitis Disease Activity Score (ΔDASAS) ≥1.3 (AxSpA). Crude and adjusted retention rates were compared with a historic cohort of INX-treated patients.

Results Eight hundred and two patients switched (403 RA/120 PsA/279 AxSpA; 51% women, age (median IQR): 55 (44–66) years). Follow-up was 413 (339–442) days. Prior INX treatment duration was 6.8 (4.3–9.5) years. Disease activities were similar 3 months before/after switch. Crude 1-year CT-P13 retention rate (84.1 (95% CI 81.3 to 86.5)) was similar to the historic INX cohort (86.2 (95% CI 84.0 to 88.0), p=0.22). The adjusted absolute retention rates were 83.4 (95% CI 80.8 to 86.2) and 86.8% (95% CI 84.8 to 88.8), respectively (p=0.03). In total 132 patients withdrew (lack of effect: 71/132=54%, adverse events: 37/132=28%). Patients with previous INX treatment duration >5 years had longer CT-P13 retention.

Conclusion In 802 arthritis patients treated with INX for median >6 years, a nationwide non-medical switch to CT-P13 had no negative impact on disease activity. Adjusted 1-year CT-P13 retention rate was slightly lower than for INX in a historic cohort.

BACKGROUND

As patents on the originator biological disease modifying agents (bDMARDs) expire, less expensive biosimilars are marketed – the first being CT-P13, Remsima. Due to their complex biochemical structure, a biosimilar drug is never an exact copy of the originator.1 Before marketing, the equivalence of CT-P13 compared with originator infliximab (Remicade, INX) was demonstrated in pharmacokinetic studies and randomised controlled trials (RCT).1-3 However, it is debated whether the biosimilars perform equally to the originator when INX-treated patients are switched to biosimilar in routine care, as small differences in immunogenicity potentially may influence tolerability and outcomes. Postmarketing observational studies contribute important knowledge regarding biosimilar effectiveness in clinical practice.1

In Denmark, public hospital owners provide bDMARDs via a tax-based system. A national guideline by May 2015 dictated a non-medical switch, that is, all patients treated with INX should switch to CT-P13 for economic reasons.4 The patients (and physicians) had no say in the matter. The potential implications of the switch were economic savings without loss of beneficial treatment outcomes.5 Thus, on marketing in Denmark, the costs of CT-P13 was 36% of that of INX. However, the experience with non-medical switching is limited and stem from open-label studies,6 small cohorts8–13 and the NOR-SWITCH trial.14

In the nationwide quality registry, DANBIO, treatment outcomes of Danish adult patients with inflammatory arthritis are monitored prospectively.15 The aims of the present observational study were to investigate the impact of the nationwide switch from INX to CT-P13 on (1) 3 months’ disease activity and flare rates and (2) 1-year retention rates.

METHODS

DANBIO covers >95% of adults with rheumatic diseases treated in routine care with bDMARDs. According to national treatment guidelines, disease activity and outcomes are monitored at
Table 1  Baseline demographics and clinical characteristics of the CT-P13 cohort and the subgroup of switch patients who withdrew from treatment during =1 year of follow-up stratified by diagnosis. Reasons for CT-P13 withdrawal are also shown

<table>
<thead>
<tr>
<th>Patients switched from INX to CT-P13</th>
<th>RA*</th>
<th>PsA</th>
<th>AxSpA†</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>403</td>
<td>120</td>
<td>279</td>
<td>802</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>281 (70)</td>
<td>58 (48)</td>
<td>73 (26)</td>
<td>412 (51)</td>
</tr>
<tr>
<td>Age, years</td>
<td>63 (51–71)</td>
<td>52 (44–61)</td>
<td>47 (39–55)</td>
<td>55 (44–66)</td>
</tr>
<tr>
<td>Number of comorbidities ≥1, n (%)‡</td>
<td>99 (25)</td>
<td>28 (23)</td>
<td>48 (17)</td>
<td>175 (22)</td>
</tr>
<tr>
<td>Biological treatment number, INX</td>
<td>1 (1–1)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>Concomitant methotrexate, n (%)</td>
<td>330 (82)</td>
<td>84 (69)</td>
<td>89 (32)</td>
<td>501 (62)</td>
</tr>
<tr>
<td>Concomitant oral prednisolone, n (%)</td>
<td>25 (6)</td>
<td>5 (4)</td>
<td>6 (2)</td>
<td>36 (4)</td>
</tr>
<tr>
<td>Start of disease remission, n (%)¶</td>
<td>191/309 (62)</td>
<td>55/92 (60)</td>
<td>42/199 (21)</td>
<td>288/600 (48)</td>
</tr>
<tr>
<td>Number of patients withdrawn from CT-P13 within =1 year of follow-up</td>
<td>76 (19)</td>
<td>11 (9)</td>
<td>36 (13)</td>
<td>123 (15)</td>
</tr>
<tr>
<td>Number of patients, n</td>
<td>403</td>
<td>120</td>
<td>279</td>
<td>802</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>281 (70)</td>
<td>58 (48)</td>
<td>73 (26)</td>
<td>412 (51)</td>
</tr>
<tr>
<td>Baseline CT-P13 dose, mg/kg</td>
<td>3.4 (3.0–4.5)</td>
<td>4.6 (3.1–5.1)</td>
<td>4.8 (3.7–5.1)</td>
<td>4.0 (3.1–5.0)</td>
</tr>
<tr>
<td>CT-P13 dose interval, weeks</td>
<td>8 (7–8)</td>
<td>7 (6–8)</td>
<td>8 (6–8)</td>
<td>8 (6–8)</td>
</tr>
<tr>
<td>Prior INX treatment duration, years</td>
<td>7.3 (4.9–9.8)</td>
<td>6.3 (3.8–5.3)</td>
<td>6.5 (3.9–9.3)</td>
<td>6.8 (4.3–9.5)</td>
</tr>
<tr>
<td>Prior INX treatment duration, years, mean (SD)</td>
<td>7.3 (3.6)</td>
<td>6.2 (3.4)</td>
<td>6.6 (3.5)</td>
<td>6.9 (3.6)</td>
</tr>
</tbody>
</table>

Subgroup of patients withdrawn from CT-P13 within =1 year of follow-up

<table>
<thead>
<tr>
<th>Number of patients, n</th>
<th>76</th>
<th>16</th>
<th>40</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n</td>
<td>56</td>
<td>11</td>
<td>17</td>
<td>84</td>
</tr>
<tr>
<td>Baseline CT-P13 dose, mg/kg</td>
<td>3.6 (3.0–4.6)</td>
<td>4.8 (3.0–5.5)</td>
<td>5.0 (4.6–5.5)</td>
<td>4.4 (3.1–5.2)</td>
</tr>
<tr>
<td>Concomitant methotrexate, n</td>
<td>52</td>
<td>12</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>Prior INX treatment duration, years</td>
<td>6.4 (3.5–9.8)</td>
<td>5.7 (2.6–9.6)</td>
<td>4.8 (1.8–6.6)</td>
<td>5.9 (2.9–9.2)</td>
</tr>
<tr>
<td>Number of comorbidities ≥1, n</td>
<td>26</td>
<td>4</td>
<td>5</td>
<td>35</td>
</tr>
</tbody>
</table>

Reasons for CT-P13 withdrawal, n=132

Lack of effect: 71 patients; adverse events: 37; remission: 5; cancer: 5; death: 2; several reasons: 3; other reasons (eg, pregnancy; surgery): 8; unknown: 1.

Statistics

Descriptive analyses were performed by SPSS 22 and SAS 9.4. Non-parametric statistics were used for comparisons. p values ≤0.05 were considered statistically significant.

Disease activity 3 months before switch (preswitch), at the time of switch, after 3 months (postswitch) and changes over time (∆preswitch and ∆postswitch) were calculated in each patient. Missing data at the 3 months’ visit were imputed with the 6 months’ visit. For patients who withdrew ≤3 months postswitch (n=18), data from the latest registered visit after baseline were carried forward.

Disease flare was defined as changes in 28 Joint Disease Activity Score (DAS28) ≥0.6 or ∆DAS28 ≥1.2 (rheumatoid arthritis (RA), psoriatic arthritis (PsA)), and ∆Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥1.3 (axial spondyloarthritis (AxSpA)). Remission was defined as DAS28 <2.6 and ASDAS <1.3, respectively.

Treatment retention among switchers was explored with Kaplan-Meier plots and log-rank tests. Univariable and multivariable Cox regression analyses and HR stratified by diagnosis (RA/PsA/AxSpA) were used to identify baseline predictors of CT-P13 retention (gender/age/methotrexate(yes–no)/CT-P13

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least biannually and when medication is changed.15 According to Danish legislation, registration and publication of data from clinical registries do not require patient consent or approval by ethics committees.

Patients with inflammatory arthritis in DANBIO who had been followed since start of first bDMARD and who switched from INX to CT-P13 before 1 January 2016 were included (table 1). In addition, 28 patients from two hospitals, where the switch guideline was adapted later, were included. A time gap between planned INX and start of CT-P13 of 0–120 days was allowed to comply with differences in registration practice. All departments of rheumatology were invited to validate data regarding switch date, disease activities and reasons for CT-P13 withdrawal. Data were censored 9 September 2016.

The variables collected in DANBIO have been described previously.16 Predefined time windows were applied for visits on switch (=baseline) and 3 months preswitch/postswitch (see notes to table 2).

Through linkage by social security numbers, comorbidities were identified in national registries (hospitalisations and outpatient care 10 years back) and numbers (0–7) calculated.18
dose/CT-P13 interval/comorbidities (number) and baseline disease activity (patient’s global score/Bath Ankylosing Spondylitis Disease Activity Index score/ASDAS/DAS28)). Age and gender were forced into the model. Variables with p<0.1 on univariate analysis were included in the multivariate model (stepwise backwards selection).

The 1-year treatment retention was compared with that of a cohort of all patients in DANBIO receiving treatment with INX by 1 January 2014. Cox proportional hazards regression analysis was used to compare the crude 1-year retention rate in the two groups with a robust variance calculation implemented to account for repeated subjects. Multivariable Cox regression analysis with left truncation (1 year before start of CT-P13) and years since start of INX as timescale was performed to calculate HR for withdrawal adjusted for the following baseline variables - age/gender/diagnosis/methotrexate (yes/no)/comorbidities (number)/patient’s global score — and to calculate adjusted 1-year retention rates for INX and CT-P13.

RESULTS

We included 802 switch patients (table 1). The median (IQR) time gap between planned INX and first CT-P13 was 1 (1–1) day. In 76%, INX was the first biological drug. Follow-up time was 413 (339–442) days during which 16% stopped CT-P13, mostly due to lack of effect (71/132=54%) or adverse events (37/132=28%) (table 1 and online supplementary table 1).

Disease activity 3 months preswitch/postswitch was largely unchanged in the majority of patients (table 2) with no clinically meaningful differences observed. Flare rates preswitch/postswitch were similar (table 2).

The characteristics of the comparison and switch cohorts were similar (see online supplementary table 2). One-year crude retention rates (INX: 86.2% (95% CI 84.0 to 88.0) and CT-P13: 84.1% (95% CI 81.3 to 86.5), p=0.22) are shown in figure 1A. The adjusted absolute rates were 86.8% (95% CI 84.8 to 88.8) versus 83.4% (95% CI 80.8 to 86.2) (p=0.03), corresponding to an absolute difference of 3.4%. Consequently, CT-P13-treated patients had significantly higher relative risk of withdrawal than the INX cohort (HR 1.31 (1.02–1.68), p=0.03).

CT-P13 retention rate tended to be poorer for RA than for PSA and AxSpA (figure 1B). Duration of INX treatment (<3 years) was associated with poorer retention (figure 1C) as was not being in DAS28 remission at baseline (RA, figure 1D). Higher patient global score at baseline (RA (borderline significant),...
AxSpA), higher CT-P13 doses (AxSpA) and monotherapy (RA) were associated with poorer retention (table 3).

DISCUSSION
This study of a nationwide non-medical switch in routine care included 802 patients with arthritis previously treated with INX for >6 years. Three-months' disease activity and flare rates were largely unaffected by the switch. One-year crude retention rate of CT-P13 was not statistically different from that of INX in a comparison cohort, and just reached statistical significance in adjusted analysis. To our knowledge, this is the first study of large-scale, non-medical switching in routine care with prospective data collection. Similar results of largely unchanged disease activity after the switch have been reported in smaller observational studies of <40 patients with inflammatory arthritis and inflammatory bowel disease, whereas few have reported negative outcomes. In the open-label extension studies of two RCTs (PLANETRA and PLANETAS), INX-treated patients switched to CT-P13 after 1 year (144 and 86 patients, respectively). These trials indicated similar safety, immunogenicity and efficacy between the two drugs. Preliminary data in a subgroup of patients in our study indicated that infliximab drug levels and presence of antidrug antibodies were unaffected by the switch. The NOR-SWITCH RCT, which examined non-medical switch of CT-P13 across indications, included 481 patients (198 with arthritis). Across diagnoses, the proportion of patients with flare in NOR-SWITCH was 26.2% for INX versus 29.6% for CT-P13. The higher flare rates might be explained by the different time periods (1 year in NOR-SWITCH and 3 months in the present), inclusion of patients with inflammatory bowel disease and the randomised controlled design of NOR-SWITCH. Retention rates were slightly lower in the CT-P13 cohort versus the historic INX cohort, with an adjusted absolute risk

Figure 1 (A–D) Kaplan-Meier plots of crude treatment retention rates among CT-P13 switch patients: (A) compared with a historic comparison cohort of INX-treated patients; (B) stratified by diagnosis; (C) stratified by duration of previous INX treatment; and (D) stratified by baseline DAS28 remission (yes/no) (only RA patients). AxSpA, axial spondyloarthritis; DAS28, 28 Joint Disease Activity Score; PsA, psoriatic arthritis; RA, rheumatoid arthritis.
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Table 3  Baseline variables associated with CT-P13 treatment withdrawal

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Univariate analyses</th>
<th>Final multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p</td>
</tr>
<tr>
<td>Gender, women versus men</td>
<td>1.26 (0.73 to 2.03)</td>
<td>0.4</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.01 (0.99 to 1.02)</td>
<td>0.4</td>
</tr>
<tr>
<td>Methotrexate use, no versus yes</td>
<td>2.27 (1.40 to 3.69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patient’s global score, mm</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0.049</td>
</tr>
<tr>
<td>DAS28</td>
<td>1.20 (0.99 to 1.46)</td>
<td>0.06</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.00 (0.99 to 1.02)</td>
<td>0.8</td>
</tr>
<tr>
<td>Longer CT-P13 interval, weeks</td>
<td>0.96 (0.82 to 1.13)</td>
<td>0.6</td>
</tr>
<tr>
<td>Higher CT-P13 dose, mg/kg</td>
<td>1.14 (0.94 to 1.38)</td>
<td>0.14</td>
</tr>
<tr>
<td>INX start year, 2000–2007 versus 2008–2015</td>
<td>0.83 (0.53 to 1.30)</td>
<td>0.8</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>1.36 (1.04 to 1.76)</td>
<td>0.025</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>p</td>
</tr>
<tr>
<td>Gender, women versus men</td>
<td>2.46 (0.86 to 7.08)</td>
<td>0.1</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.00 (0.96 to 1.04)</td>
<td>1.0</td>
</tr>
<tr>
<td>Methotrexate use, no versus yes</td>
<td>0.68 (0.22 to 2.12)</td>
<td>0.5</td>
</tr>
<tr>
<td>Patient’s global score, mm</td>
<td>1.01 (1.00 to 1.03)</td>
<td>0.2</td>
</tr>
<tr>
<td>DAS28</td>
<td>1.21 (0.79 to 1.85)</td>
<td>0.4</td>
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<tr>
<td>CRP, mg/L</td>
<td>0.99 (0.92 to 1.07)</td>
<td>0.9</td>
</tr>
<tr>
<td>Longer CT-P13 interval, weeks</td>
<td>0.84 (0.60 to 1.19)</td>
<td>0.3</td>
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<tr>
<td>Higher CT-P13 dose, mg/kg</td>
<td>1.11 (0.74 to 1.67)</td>
<td>0.6</td>
</tr>
<tr>
<td>INX start year, 2000–2007 versus 2008–2015</td>
<td>1.11 (0.42 to 2.98)</td>
<td>0.8</td>
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<tr>
<td>Number of comorbidities</td>
<td>0.93 (0.45 to 1.93)</td>
<td>0.8</td>
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<tr>
<td>Axial spondyloarthrits</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>p</td>
</tr>
<tr>
<td>Gender, women versus men</td>
<td>2.29 (1.22 to 4.29)</td>
<td>0.01</td>
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<tr>
<td>Age, years</td>
<td>0.98 (0.96 to 1.02)</td>
<td>0.15</td>
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<tr>
<td>Methotrexate use, no versus yes</td>
<td>1.36 (0.68 to 2.86)</td>
<td>0.4</td>
</tr>
<tr>
<td>Patient’s global score, mm</td>
<td>1.02 (1.01 to 1.03)</td>
<td>0.003</td>
</tr>
<tr>
<td>BASDAI</td>
<td>1.02 (1.01 to 1.04)</td>
<td>0.003</td>
</tr>
<tr>
<td>ASDAS</td>
<td>1.09 (0.76 to 1.56)</td>
<td>0.6</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.92 (0.84 to 1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Longer CT-P13 interval, weeks</td>
<td>0.69 (0.54 to 0.88)</td>
<td>0.002</td>
</tr>
<tr>
<td>Higher CT-P13 dose, mg/kg</td>
<td>1.66 (1.22 to 2.26)</td>
<td>0.001</td>
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<tr>
<td>INX start year, 2000–2007 versus 2008–2015</td>
<td>0.32 (0.16 to 0.65)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>0.67 (0.34 to 1.39)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Results from univariable and multivariable Cox regression analyses stratified by diagnosis.

Cox regression analyses stratified by diagnosis. Numbers are HR (95% CI). *p* Values <0.1 are marked with bold and the corresponding variables were included in multivariable analysis. Age and gender remained in the model irrespective of *p* value.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; DAS28, 28 Joint Disease Activity Score.

difference of 3.4%. This difference is not necessarily attributable to CT-P13, but could also represent a ‘nocebo-effect’, that is, negative expectations towards the drug29 or residual confounding.

In the present study =84% of patients were still on drug after 1 year, which was lower than in NOR-SWITCH (96%).11 This may reflect differences between ‘real-life’ patients and patients included in an RCT. Differences in study design (patients with arthritis in the current study versus patients from rheumatology/dermatology/gastroenterology in NOR-SWITCH) may also have contributed. The 14% 1-year withdrawal rate in our historic INX cohort illustrates that cessation of treatment also occurs after many years of treatment.28

CT-P13 retention rates across diagnoses were comparable. This is reassuring, as treatment of PsA with CT-P13 had not been investigated before marketing. Patients with RA who were on monotherapy were at increased risk of withdrawal, and there was a tendency towards poorer retention among women and patients with RA with more comorbidities. No new safety signals were detected for CT-P13.

The long average INX treatment duration of >6 years at the time of switching reflects that INX was not first-line bDMARD in Denmark prior to the switch.4 As longer treatment with INX was associated with better CT-P13 retention, extrapolation of our results to other cohorts of shorter treatment duration should be done with caution.

This study of a large cohort of real-life patients contributes important knowledge of postmarketing effectiveness of non-medical switching.1 The availability of historic DANBIO data enabled us to use the patients as their own controls regarding fluctuations in disease activity before and after switch, and to identify a historic INX cohort for comparison of retention rates. Limitations include incomplete data due to the observational study design, for example skin status and 66/68 joint counts in
PsA. We applied a time interval of 13 weeks around the baseline visit to reduce missing data at baseline, but in the majority of patients data were available within few days before/after the switch date.

In conclusion, a nationwide non-medical switch from INX to CT-P13 in 802 patients with inflammatory arthritis, who had previously been treated with INX for >6 years, had no apparent negative impact on disease activity. The adjusted retention rate during 1-year of follow-up was slightly reduced (3.4%) compared with a historic cohort.

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