Sex differences and early treatment of axial spondyloarthritis

Rusman, Tamara

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Tamara Rusman

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SEX DIFFERENCES AND EARLY TREATMENT OF AXIAL SPONDYLOARTHRITIS

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Tamara Rusman

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promotoren:	prof.dr. I.E. van der Horst-Bruinsma prof.dr. R.F. van Vollenhoven
copromotor:	prof.dr. M.T. Nurmohamed
promotiecommissie:	prof.dr. A.E.R.C.H. Boonen dr. A. den Broeder dr. F.A. van Gaalen prof.dr. D.M.F.M. Van Der Heijde dr. A.W.R. van Kuijk prof.dr. W.F. Lems dr. M.G.H. van de Sande

Voor mijn familie
en dierbaren

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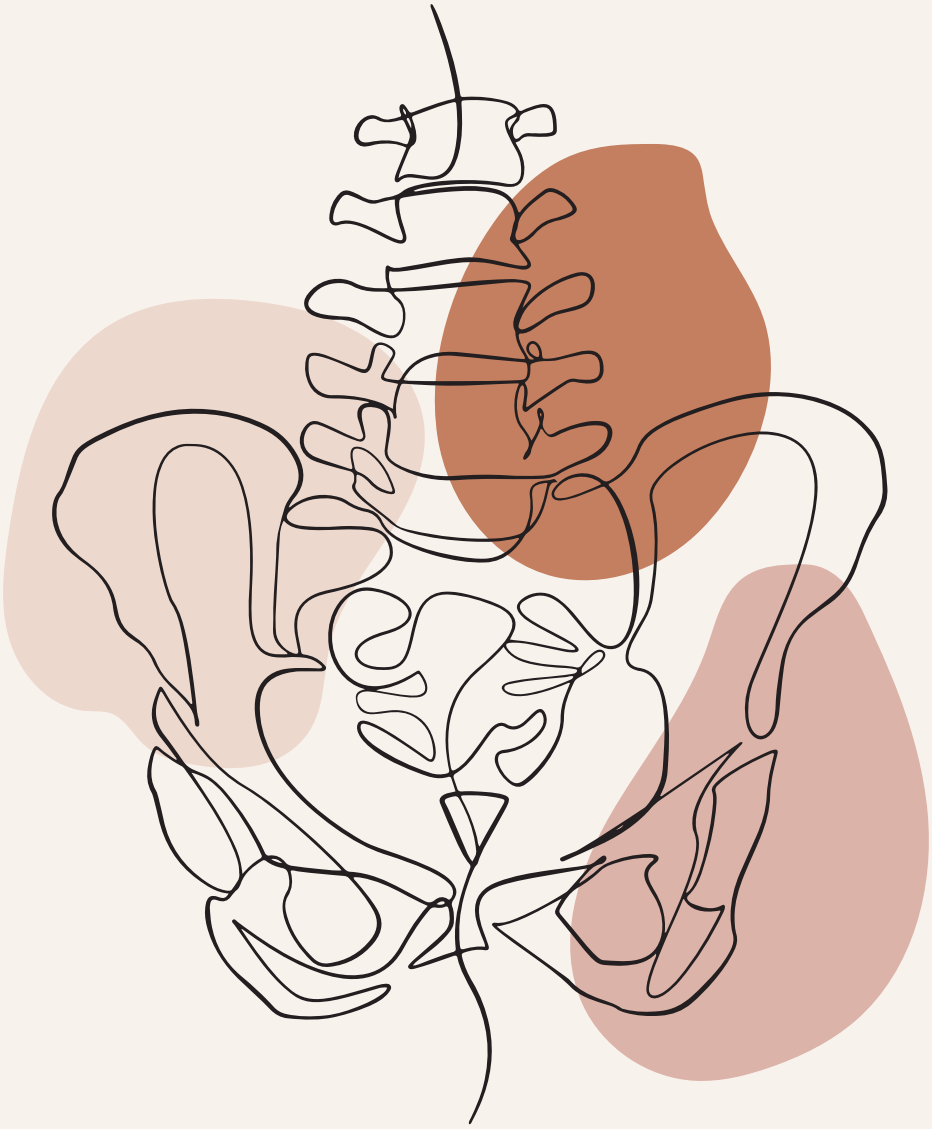

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

GENERAL INTRODUCTION

Axial spondyloarthritis (axSpA) is part of the disease spectrum spondyloarthritis (SpA) which comprises a group of inflammatory chronic auto-immune diseases with overlapping features, such as inflammatory back pain (IBP) and a strong genetic association with HLA-B27 (1, 2). SpA can be divided in two types: peripheral SpA, which is characterized by inflammation mainly of the peripheral joints, such as psoriatic arthritis and reactive arthritis, and in axial spondyloarthritis (axSpA) which is characterized by inflammation of the axial skeleton. The chronic inflammation of the axial skeleton can lead to new bone formation of the spine (syndesmophytes) and sacroiliac joints (SIJ, sacroiilitis) which eventually can result into ankylosing of the axial skeleton (bamboo spine) (3).

Clinical diagnosis and classification of axSpA

New bone formation causes radiographic changes of the sacroiliac joints which is the main characteristic of most familiar subtype of axSpA, called Bechterew's disease or ankylosing spondylitis (AS). AS is defined by the modified New York criteria as grade 2 changes bilateral or grade 3-4 unilateral of the SIJ on plain radiography (4-6). The other subtype of axial SpA is the group of patients who lack radiographic changes, called non-radiographic axial SpA (nr-AxSpA).

However, radiological progression is a slow process and symptoms related to axSpA often present many years before the structural radiological damage is visible on plain radiography (4). Therefore, AS is known for a large diagnostic delay, with an average a delay of 6-8 years, which consequently leads to delayed treatment in an early disease stage (7, 8). Women experience an even longer diagnostic delay compared to men (median 9-14 years vs. 5-7 years), although the age of onset is similar for men and women (9). Several explanations were put forward for the longer diagnostic delay among females, such as the differences in presenting symptoms as women present themselves more often with peripheral joint involvement and have a slower radiographic progression than men, but insufficient data are available on the possible causes for these observed sex differences in diagnostic delay (Chapter 1) (8, 10). Consequently, women fulfill the diagnostic criteria for AS later and therefore experience a longer diagnostic delay.

Symptoms related to axSpA are present many years before the actual diagnosis could be made, appropriate treatment strategies in especially nr-axSpA patients, both men and women, are often delayed because these symptoms are not recognized. In order to identify axSpA at an early stage of the disease, the Assessment of SpondyloArthritis international society (ASAS) defined the ASAS classification criteria which divide patients

with IBP in two groups: patients who meet the “clinical arm” and patients who meet the “imaging arm”. The “clinical arm” includes patients who are HLA-B27 positive with two additional SpA-features whereas the “imaging arm” refers to patients with active inflammatory lesions of the sacroiliac joints (SIJ) at Magnetic Resonance Imaging (MRI) and one additional SpA-feature (6, 11) (Figure 1). These new ASAS criteria were defined solely for study purposes, as the gold standard for making clinical diagnoses of axSpA by the rheumatologist are based on clinical and laboratory examinations and imaging, such as conventional radiological and MRI images.

Ten to 40% percent of patients diagnosed with nr-axSpA develop structural radiographic damage and progress to AS, of whom 5-14% within two years and 26% over a 15-years’ time period (12-15).

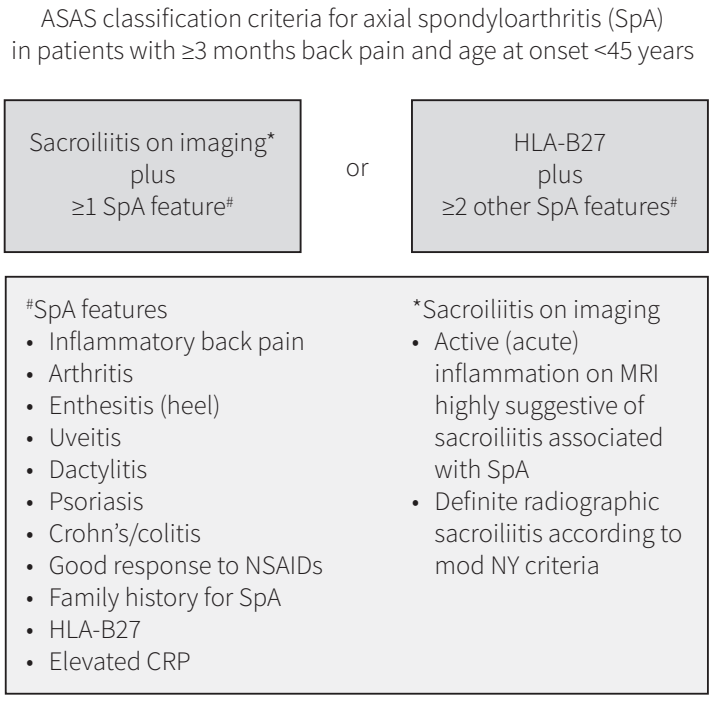

Figure 1. ASAS classification criteria for axial spondyloarthritis patients. Adapted from Sieper J et al. The assessment of spondyloarthritis international society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009 Jun;68 Suppl 2:ii1-44. Doi: 10.1136/ard.2008.104018

Clinical characteristics of AxSpA

The prevalence of axSpA is approximately 0.2% to 1.4% worldwide, depending on the prevalence of the HLA-B27 gene in a population (16). In Europe 0.25% of axSpA patients were diagnosed as AS, of whom men were two to three times more often diagnosed compared to women (16, 17). In patients with nr-axSpA, no sex differences were observed (18). AxSpA manifests itself at a young age, usually before the 40th year of life.

The main clinical symptom of axSpA is inflammatory back pain with a minimal duration of three months which, according to the ASAS definition, requires four of the five following criteria: age at onset <45 years, insidious onset, no improvement with rest, improvement with movement and night pain (2). Inflammatory back pain is more frequently observed in men compared to women (66% vs. 51%) (19).

In addition to spinal complaints, articular manifestations like arthritis and enthesitis occur in 30-50% of axSpA patients. Data on peripheral arthritis and enthesitis showed a higher percentage and more severe involvement in female patients (19-24). Extra-articular manifestations (EAM) are also very common, especially acute anterior uveitis (26-40%), inflammatory bowel disease (IBD) (7%) and psoriasis (9%), which add to the disease burden of axSpA patients. EAMs seems to have a higher prevalence in women, although some studies show conflicting results (8, 23, 25).

In addition to the articular manifestations, axSpA patients also have an increased risk of comorbidities like cardiovascular diseases and osteoporosis (26).

Patients diagnosed with AS have an 1.5 times increased cardiovascular (mortality) risk (27-30). Unfortunately, no systematically obtained data are available for sex differences in cardiovascular diseases.

Osteoporosis mainly occurs in AS patients with longstanding disease with a prevalence range of 19-50% (31, 32). Osteoporosis is typically seen as “women disease”, due to the high prevalence and number of fractures in post-menopausal women, compared to men at the same age (33). However, osteoporotic fractures have an unexpected high prevalence in young, male axSpA patients (34). This could imply a higher risk of undertreatment of osteoporosis (35, 36).

Inconclusive data on sex differences and their relation to the clinical presentation of axSpA especially in women, but also the scarcity of data for male patients diagnosed with osteoporosis, revealed an important knowledge gap.

Clinical instruments

Monitoring disease activity and progression in axSpA patients is mostly performed through patient reported outcomes (PROs), physical examination and radiological evaluation.

Disease activity is mainly monitored with the BASDAI (Bath ankylosing spondylitis disease activity index) questionnaire, which was developed in 1994 and includes six questions measured on an numeric rating scale (NRS) scale (0 – 10) on fatigue (1), pain (2), peripheral joints (3), entheses (4), intensity of morning stiffness (5) and duration of morning stiffness (6) (37). In 2009, a new disease activity measurement was developed, the ASDAS (Ankylosing Spondylitis Disease Activity Score) which combines three questions of the BASDAI, the patient global disease activity score and a value for systemic inflammation (C-reactive protein, CRP or Erythrocyte Sedimentation Rate, ESR) (38).

Physical function is in general monitored with the BASFI (Bath AS functional index) questionnaire, including ten questions (NRS 0 – 10) evaluating the level of ability to perform specific daily activities perceived by the patients (39). In 2009 a new tool for the measurement of physical function was developed, the AS performance-based index (ASPI), which is based on the BASFI questionnaire. The ASPI consists of tests based on daily physical activities and requires measurement of the performance time instead of the perceived performance of these activities by patients (40-43). The ASPI could be a promising measurement tool for the future.

For clinical studies, arthritis is reported by physical examination, by the 44-joint count for tender- and swollen joints. Enthesitis is usually evaluated by the MASES score (Maastricht AS Enthesitis score), which includes entheses of the sternum, pelvis and Achilles tendon (44). The spinal mobility is monitored with the Bath AS Metrology Index (BASMI score) (45).

To evaluate disease progression, radiological progression is monitored with conventional radiographs of the pelvis, cervical and lumbar spine once every two to five years. MRI imagines are made to detect inflammation of the SIJ with the intention to identify axSpA at an early disease stage before structural radiological damage has developed.

Treatment of axSpA

The first treatment strategy in patients diagnosed with axSpA is to start nonsteroidal anti-inflammatory drugs (NSAIDs), combined with physical therapy, regular exercises and lifestyle advises, including emphasizing the relevance of a healthy weight and to stop smoking. Patients who do not sufficiently respond to two different NSAIDs are eligible for a biological treatment (46). Currently, approved biologicals for axSpA are the tumour

necrosis factor inhibitor (TNFi) and the interleukine -17a inhibitors (IL-17a) (47-49). TNFi are effective in 40-60% of both nr-axSpA and r-axSpA patients and IL-17a inhibitors showed comparative results (although, up to now, no head-to-head comparisons have been done) (50).

Although biologicals are proven to be effective in both nr-axSpA and r-axSpA patients, there were significant differences between men and women and their response to specific TNFi (51, 52). So far, studies on sex difference in treatment efficacy in AS are limited. Most of these studies have proven sex as important predictor for treatment efficacy, but only a few studies have focused on long longitudinal follow up of sex differences in TNFi response in AS (53, 54). Therefore, more data are needed to add to the body of evidence in clinical practice.

Biological treatment in patients with longstanding disease and established radiological damage is proven not effective in reversing already existing radiological damage (55, 56). However, new studies showed that treatment with a biological in an earlier disease stage might suppress the inflammation which triggers the additional bone formation (57-59). Nonetheless, no specific data are available regarding the optimal moment to start biologicals in patients with early axSpA symptoms. Recent studies identified raised C-Reactive Protein (CRP-)levels and a positive MRI of the SIJ as predictors for a good response to biologicals (60-63). Therefore, most clinical trials with biologicals were performed in early axSpA patients with strict inclusion and exclusion criteria among which the requirement of having a positive MRI and/or raised CRP-level.

Studies without these requirements are very limited, which made the indication for biological treatment in patients suspected of nr-axSpA, with low CRP-level and non-active lesions on MRI of the SIJ, a topic of debate. Especially because in clinical practice only a small number of axSpA patients present themselves with these characteristics and limited data are available.

OUTLINE THESIS

Part 1: Sex differences in axial spondyloarthritis

The first part of this thesis describes data on sex differences in AS patients. Inconclusive data are available on sex differences revealing an important knowledge gap considering their considerable influence on clinical disease presentation within the axSpA disease spectrum. Women under TNFi treatment also remain to have a higher disease activity over time, showed to be less responsive to TNFi and had a shorter time on drug compared to men (Chapter 2, 3 and 4). Therefore in **chapter 2** we reviewed the current literature on sex differences in ankylosing spondylitis in genetic and immunological processes, diagnosis, clinical disease presentation and treatment efficacy and time on drug. In **chapter 3** sex differences on time on drug were investigated more thoroughly in a peripheral hospital setting. In **chapter 4** we present results on sex differences in treatment efficacy and survival using the Amsterdam SpondyloArthritis cohort. **Chapter 5** describes the influence of TNFi treatment on bone mineral density and vertebral fractures in AS patients.

Part 2: Early detection and treatment in axial spondyloarthritis

The second part of this thesis describes outcomes of the prevention of the progression of very early symptoms into ankylosing spondylitis (PRevAS)- trial and one chapter on structural damage. The PrevAS-trial included patients diagnosed with chronic back pain, high disease activity (BASDAI ≥ 4) and a suspicion of nr-axSpA according to a diagnostic algorithm, known for the high probability to diagnose axSpA in a preradiograhic stage (64). Patients were randomized (1:1) to etanercept or placebo (n=40) for 16 weeks and followed thereafter without study medication up to three years (Chapter 8 and 9). Parameters on disease activity, MRI outcomes (up to 24 weeks), X-rays (up to three years) and the number of patients who were diagnosed with axSpA were assessed. In **chapter 6** early recognition of axSpA using MRI and the assessment of structural damage is described in patients diagnosed with inflammatory back pain and high disease activity, suspected of nr-axSpA. In **chapter 7** we describe the 24 week results of the PrevAS-trial, in which the efficacy of 16 week etanercept treatment on disease activity and MRI outcomes are discussed. **Chapter 8** elaborates on the disease activity scores available in nr-axSpA to monitor the disease progression and treatment efficacy in a letter to the editor. **Chapter 9** yields the three year follow up data of the PrevAS-trial in which we investigated for both treatment groups the disease activity, X-Ray outcomes and the number of patients who were diagnosed with a form of axSpA. In **chapter 10** the association between CRP-level and radiological progression is described according to data from daily clinical practice of the AmSpA cohort.

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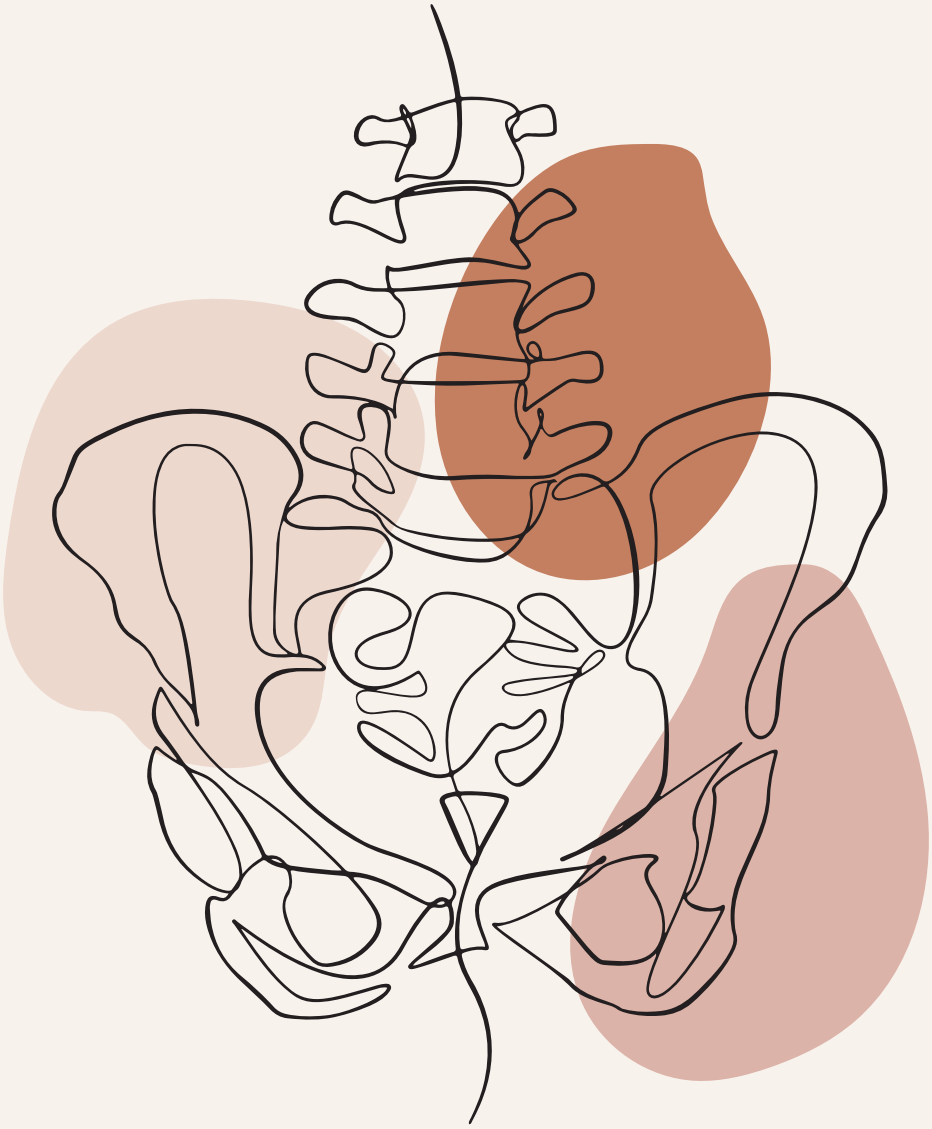
PART 1

SEX DIFFERENCES IN AXIAL SPONDYLOARTHRITIS



CHAPTER 2

SEX AND GENDER DIFFERENCES IN AXIAL SPONDYLOARTHRITIS: MYTHS AND TRUTHS

T. Rusman
R.E. van Bentum
I.E. van der Horst-Bruinsma

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ABSTRACT

Mounting evidence reveals evident sex differences in physiology, disease presentation and response to medication in axial SpA (axSpA). Unfortunately these data are often neglected in clinical practice and research. In this review, myths that still exist on diagnosis, disease manifestation and drug effectiveness were argued against data of the most recent literature. The aim is to increase awareness of sex differences in the clinical aspects of axSpA.

Keywords: spondyloarthritis, biological therapies, epidemiology, inflammation, sex differences, patient reported outcomes

Rheumatology key messages

- Women with axSpA have a longer diagnostic delay compared with males.
- Women with axSpA show significantly lower TNF inhibitor efficacy and drug survival compared with males.
- Men have a higher radiological progression, but the disease burden is similar for both sexes.

INTRODUCTION

Many rheumatic diseases show a clear sex difference in prevalence, often with female predominating, as in RA and SLE. In contrast, AS or radiological axial SpA (axSpA) is more frequently diagnosed in men compared with women (3:1), whereas non-radiographic axSpA has an equal sex distribution. This sex distribution might be explained by differences in disease course between the two sexes. Men with axSpA show a higher radiological progression (45 vs 33%) (1), whereas women show higher disease activity scores (mean BASDAI 3.2–5.9 vs 3.9–6.3) (1-6) and extra-articular manifestations (73 vs 82%) (1, 7, 8).

Before we start with the myths, a clarification is needed for the terms sex and gender. In essence, the term sex differences can be described as biological processes that differ between men and women (9). Gender refers to a person's self-perception as a man or woman and the behaviour they show during their life or the disease (coping style and disease perception) (7), but in some literature the word gender is also used to refer to physiological differences between sexes. This article aims to create awareness of the impact of sex differences in physiological, pharmacokinetics, disease presentation and treatment efficacy of biologics in axSpA.

Myth 1: Men and women with axSpA are physiologically the same

Sex differences in genes and immune modulation

Sex differences are observed not only in sex chromosomes, X and Y, but also in gene expression, immune modulation and physiological processes between men and women with axSpA. The most important genetic predisposition in axSpA is the association with the HLA-B27 allele. There are indications that women with axSpA are found to be less often positive for the HLAB27 allele compared with males (1), which might explain the different presentation of axSpA in men and women, such as radiological progression (10-15). The presence of the HLA-B27 allele is associated with a greater chance for a positive MRI of the SI joints (16). In addition, HLA-B27 was also found to be a predictor for having a positive treatment response and better drug survival on biologics (17-20).

In addition, there are sex differences in other less familiar gene expressions. An interesting study on genetic expression in AS revealed that 1522 unique genes were expressed in men and 291 genes in women compared with healthy controls (21).

A study considering the ANKH gene, which encodes a protein that is involved in osteogenesis and plays a role in ankylosis in AS, showed that different loci of the ANKH

gene were expressed in men and women with AS (22). Furthermore, in multiplex AS families, a specific tissue-non-specific alkaline phosphatase (TNAP) haplotype, which interplays with the ANKH gene in ossification, was associated with AS in men but not in women (23). These genetic predispositions in men might explain the higher radiographic progression and higher prevalence of AS in men compared with women.

Immune processes are also influenced by sex hormones. Testosterone decreases TNF-a production but increases the production of anti-inflammatory IL-10 (24). Oestrogens increase the cell-mediated and humoral immune response and production of IL-1, IL-6 and TNF-a (25), which contributes to increased inflammatory values. Interestingly, syndesmophyte development in men was associated with significantly higher IL-18 levels, whereas in women IL-6 was significantly elevated (26).

In AS, IL-17A and Th17 cells were elevated in male patients but not in female patients (15). However, the same study did not reveal sex differences in the components of the Th1 axis.

Pain mechanisms

Sex hormones also influence other physiological processes, such as pain transmission. Testosterone increases the pain threshold, whereas conflicting results were found for oestrogen and progesterone (27). Accumulating data reveal that pain sensation fluctuates with hormonal changes, especially in women during the menstrual cycle, in contrast to men who have more stable hormone levels over time (28, 29). Besides the influence of hormones, women have a greater number of pain receptors and a different expression of these receptors, for instance, in the opioid receptors (29). This could explain the overall higher pain sensitivity in women compared with men, which might contribute to higher pain scores reported for patient questionnaires by women with rheumatic diseases.

Body composition

In addition, sex differences in body composition influence the immune modulation indirectly, especially due to fat disposition. Women have greater deposits of subcutaneous fat (SAT), whereas men have more visceral fat (VAT), which is located intra-abdominally (30).

Interestingly, adipose tissue acts as an endocrine organ, secreting not only adipokines, which can act as pro-(leptin) or anti-(adiponectin) inflammatory, but also cytokines, such as the pro-inflammatory cytokine TNF-a (31). One study reported that female patients with higher disease activity scores [Ankylosing Spondylitis Disease Activity Score (ASDAS) and BASDAI] had a significantly higher percentage of body fat (BF) or fat mass index (FMI) (32). In contrast, men in this study had significantly higher disease activity scores

(ASDAS and BASDAI) when they had low BF or FMI (32). In addition, several studies have reported an association between a high BMI and a lower TNF inhibitor (TNFi) treatment response (33, 34). In one study a significant correlation was observed between BMI and the inflammatory marker CRP in female AS patients only (4).

Truth: Besides many sex differences in physiological processes, studies in axSpA have also revealed sex differences in gene expression and body composition. In addition, women with axSpA have different pain mechanisms and hormonal influences that might contribute to higher DASs compared with men.

Myth 2: axSpA is a predominately male disease

Sex differences in axSpA

AxSpA encompasses non-radiographic axSpA (nraxSpA) without radiographic changes and AS with radiological signs of sacroiliitis as classified according to the modified New York criteria (35-37). For many years AS was considered a predominantly male disease. The initial studies showed a male:female ratio of 10:1 (38), but subsequently this ratio has decreased to 3:1 (39). Recent studies report an even further decline in the male:female ratio among patients with axSpA in Switzerland, from 2.57:1 in 1980 to 1.03:1 by the end of 2016 (40). In contrast with AS, no sex differences have been encountered in the prevalence of nr-axSpA (41).

Delay in diagnosis

Currently, the average delay to diagnosis in AS is 6–8 years (42-44). Although the age of onset of AS is similar for men and women (2, 22, 23), women have a significantly longer delay in diagnosis compared with men (median 9–14 vs 5–7 years) (45, 46). These data were confirmed by a recent meta-analysis covering 42 studies and 23 889 patients (32.3% women), revealing a significantly longer diagnostic delay in female patients compared with males (8.8 vs 6.5 years) (47). So far, only one study has revealed a longer diagnostic delay in men compared with women (9.9 vs 6.3 years) (48). A longer diagnostic delay was found to be a negative predictor for a positive biologic treatment response (49, 50).

Several explanations were put forward for the longer diagnostic delay among females, such as the differences in presenting symptoms, including more enthesitis-related complaints instead of inflammatory back pain, more prominent widespread pain and a lower prevalence of radiographic changes (43, 45). Importantly, patients with widespread pain, which occurs in at least 25% of female axSpA patients, are sometimes misdiagnosed as fibromyalgia, as it has some overlapping symptoms with axSpA (33). In fact, one study reported that widespread pain doubled the delay in diagnosis in women (43). An

additional explanation for the difference in diagnostic delay might be the physician's bias, because axSpA is considered to be a 'male disease' (43). Consequently, women who show more predisposing factors of axSpA [most importantly a positive family history and acute anterior uveitis (AAU)] might have an increased chance of being diagnosed.

AAU is one of the most important extra-articular manifestations of axSpA (51) and axSpA is the most common associated systemic disease in AAU; they also share the same genetic predisposition, the HLA-B27 antigen. AAU can be the first manifestation of axSpA. Approximately half of axSpA patients experience AAU before the onset of axSpA symptoms and, in addition, in patients presenting with AAU, 40% appear to suffer from undiagnosed axSpA (52-54). Male and female axSpA patients have about the same lifetime risk of developing AAU (30%) (34, 51, 55). However, males are more often diagnosed with SpA many years before AAU occurs, whereas the diagnosis in females is significantly more often made after the first attack of AAU (56). Therefore screening of AAU patients by a rheumatologist, especially in the case of back pain, could reduce the diagnostic delay, especially in women.

Pitfalls in diagnosis

In AS, radiographic changes of the SI joints, graded according the modified New York criteria, are mandatory for the diagnosis. However, some radiological changes of the pelvis are important for the differential diagnoses, especially in women (35). For example, iliitis condensans, with bilateral sclerotic lesions around the SI joints, is often accompanied by lower back pain and SI joint tenderness and occurs mainly in women after pregnancy (57, 58).

In addition. imaging of the SI joints by MRI, which can substantiate the diagnosis of non-radiographic axSpA by showing active bone marrow lesions, has some pitfalls as well (59). Recent studies revealed that other factors, such as intensive sporting activities and pregnancy, can induce SI bone marrow oedema as well. Some studies show that up to 1 year after delivery, bone marrow oedema of the SI joints still can be detected (60).

Truth: AxSpA is not a predominately male disease. Diagnoses of axSpA are often missed or misdiagnosed in female patients, resulting in long diagnostic delays. New referral strategies, such as the occurrence of AAU, might decrease the diagnostic delay in female patients. On the other hand, it is important to be aware of diagnostic pitfalls, especially with MRI of the SI joints, since bone marrow oedema up to 1 year after pregnancy could lead to overdiagnosis.

Myth 3: Men with axSpA have a worse disease outcome compared with women

Radiological progression

Probably the main reason why men are often considered to have worse disease is the association of male sex with a higher radiological outcome. Most studies have revealed that men are more likely to show worse hip involvement and higher BASRI spine and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) compared with women (10-15, 61, 62). However, it is important to note that severe radiographic deformities, including ankylosing, occur in both men and women (Figure 1). A few studies observed greater radiological progression of the lumbar spine in male AS patients, whereas in female patients this progression was observed mainly in the cervical spine. The fact that most female AS patients seem to have slower radiological progression might be an explanation for the relatively greater number of women diagnosed with nr-axSpA and the longer delay in diagnosis (63). Comparison studies between nr-axSpA and AS reveal an equal disease burden, independent of sex (64).

Extra-articular manifestations and disease manifestations

One of the reasons an equal disease burden is observed and a higher percentage of women are diagnosed with nr-axSpA could be the presence of extra-articular and other disease manifestations, such as enthesitis. Enthesitis was reported to occur more frequently, and be more pronounced, in female patients (1-3, 65-67) (Table 1). In addition, the absence of enthesitis was found to be a predictor for better biologic treatment efficacy (68), which might explain the lower efficacy in female patients.

Extra-articular manifestations seem to have a higher prevalence in women (1, 7, 8) (Table 1), although some studies show conflicting results (43, 61, 66). Some studies showed a higher prevalence of AAU in men (6, 56, 69), whereas a systemic literature review suggested a somewhat higher prevalence in females (33.3%, vs 28.5% in males) (34). However, the last study also included other types of uveitis, which could have compromised the results. Three studies, including a meta-analysis, suggested female patients are more likely to develop IBD compared with male patients (1, 8, 51). In addition, some studies reported a higher risk of psoriasis in female axSpA patients (8, 69).

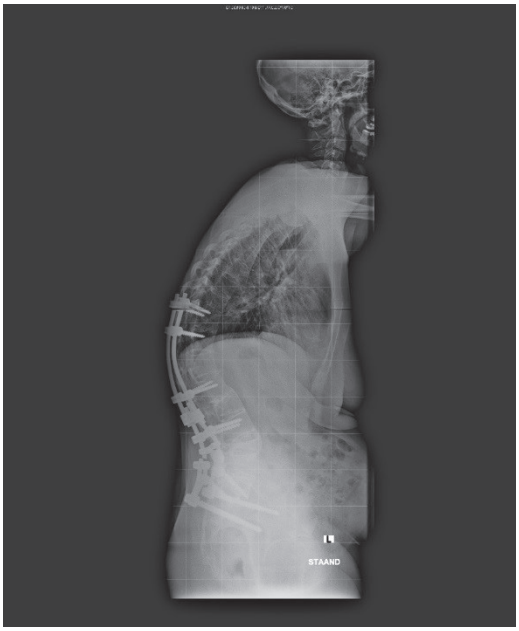

Figure 1. Woman, 47 years old, with long-standing AS

Comorbidity

Beside extra-articular manifestations, axSpA is also associated with an increased risk of comorbidities, such as cardiovascular diseases and osteoporosis (70). Unfortunately, cardiovascular diseases in axSpA has not been systematically studied for sex differences (Table 1).

Osteoporosis shows a prevalence range of 19–50%, especially in AS patients with longstanding disease, and can lead to immobilization due to vertebral fractures (71, 72). Osteoporosis is typically considered a woman's disease, due to the high prevalence and number of fractures in post-menopausal women compared with men of the same age. For example, at the age of 60 years, the risk in women is 44%, compared with 25% in men (73). However, in a relatively young male axSpA population with a short disease duration, 51% had a low BMD and 13–16% had osteoporosis(74). Another study revealed that male patients diagnosed with axSpA had a four times greater risk for low BMD compared with females (75). A study on osteoporotic fractures in relatively young axSpA patients (mean age 37 years, mean disease duration 7 years) reported at least one osteoporotic fracture in 15% of all patients (76). Most of these fractures were located at the thoracic spine, which is not included in the regular scoring method of the mSASSS. In relation to peripheral fractures, although women have a higher incidence of fractures, the risk

of undertreatment of osteoporosis and mortality after a hip fracture in men is much higher (77, 78).

Table 1. Extraspinal manifestations and comorbidities in axSpA

Manifestations and comorbidities	**Gender Differences**
Extraspinal manifestations	
AAU	No differences
Enthesitis	↑ in women
IBD	↑ in women
Psoriasis	↑ in women
Peripheral arthritis	↑ in women
Comorbidities	
Cardiovascular diseases	↑ in men and post-menopausal women
Osteoporosis	Equal risk, but underdiagnosis in (young) males

Table 2. Sex differences in disease activity, function and physical measures in axSpA

Disease activity at baseline	**Gender Differences**
BASDAI	↑ in women
ASDAS-CRP	No differences
CRP-levels	↑ in men
ESR-levels	No differences
Function	
BASFI	No differences
Quality of Life	
ASQoL	↓ in women
ASASHI	↓ in women
EuroQoL	No difference
SF-36	No difference
Physical	
BASMI	↑ in men
MASES	↑ in women

↑higher scores, ↓ lower scores. ASQoL: Ankylosing Spondylitis Quality of Life; ASASHI: Assessment of SpondyloArthritis international Society Health Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

Inflammatory laboratory values

Studies on sex differences in CRP levels showed significantly higher baseline levels in male patients compared with females (1, 5, 6, 66, 67), but the ESR was inconclusive for sex differences. A possible explanation for finding no clear differences in ESR levels could be the already different cut-off levels for normal ESR levels by sex (15 mm/h for males vs 20 mm/h females).

Disease activity and patient-reported outcomes

In both nr-axSpA and AS, women present themselves in general with higher disease activity, more pain and a worse quality of life (QoL) (Table 2). At baseline, before the start of biologics, BASDAI scores are significantly higher in female patients compared with males, especially the items total back pain, duration of morning stiffness and fatigue (1-3, 5, 6, 65, 66, 79-82). Interestingly, the ASDAS showed no sex differences (5, 6), which might be due to the fact that men show higher CRP levels, whereas women show higher scores on the other components of the ASDAS-CRP. Sex differences in QoL and overall well-being were inconsistent, depending on the validated questionnaire used. Significantly worse QoL scores were observed in female patients measured with the Ankylosing Spondylitis Quality of Life questionnaire, the Assessment of SpondyloArthritis international Society (ASAS) Health Index and the BAS-G (2, 3, 6, 66, 82). Other QoL questionnaires, such as the EuroQoL and the 36-item Short Form Health Survey revealed no (large) gender differences (1, 2, 6, 79). The BASFI showed no large sex differences, except one study that found a higher score in female patients (1) (Table 2).

Truth: Overall, men with axSpA show a higher rate of radiological progression compared with women, but severe ankylosis also occurs in female axSpA patients. Women with axSpA have, in general, higher disease activity scores and more peripheral manifestations compared with men. Comorbidities like cardiovascular events have not been studied for sex differences in axSpA, but osteoporosis, even with osteoporotic fractures, a manifestation mainly seen in post-menopausal women, has an unexpectedly high prevalence in young male axSpA patients.

Myth 4: No sex differences are present in efficacy and drug survival of biologics in axSpA

Sex differences in response and efficacy to biologic treatment

Two recent reviews (7, 83) described sex differences in treatment efficacy, but most clinical studies and safety trials are not powered to assess sex differences. For this reason, data from several randomized controlled trials (RCTs) on one biologic, etanercept, were pooled and analysed for sex differences, as the RCT studies separately included too few women

to perform the analyses. This study revealed a significantly lower treatment response at 12 weeks according to the BASDAI score in female patients compared with males (19.2 vs 23.4) (79) (Table 3). In addition, women also had a lower ASDAS-CRP response compared with men (68.4 vs 89.4%) at 12 weeks (5) (Table 3). Currently only two other studies have assessed disease activity for sex differences (83). A prospective cohort study including the TNFis etanercept, adalimumab, infliximab and golimumab revealed, according to adjusted longitudinal regression analyses for repeated measurements, a significantly higher mean BASCAI score for women (0.9) over a 5 year follow-up period. However, no significant sex differences were observed in the longitudinal analyses for mean ASDAS-CRP. A possible explanation could be because of the high CRP level in men and the higher scores on BASDAI components in women (84). However, assessment of the ASDAS-CRP clinical response revealed that men achieved the clinical response twice as often as women. The second study included the IL-17 blocker secukinumab and demonstrated no sex differences in treatment response at both 16 (46.9% for men vs 37.5% for women) and 52 weeks (61.7% for men vs 68.4% for women) (49). Besides differences in response and efficacy, male sex was found to be a predictor for improvement of function (69.9% for men vs 50.0% for women) (50).

Table 3. Sex differences in efficacy and time on drug in axSpA

Disease activity (mean)	**Differences *(range 6 – 60 months)***
BASDAI	Remains higher over time in females
ASDAS-CRP	No observed differences
CRP-level	Remains higher over time in males
ESR-level	No observed differences
Treatment response Differences (range 6-60 months)	
BASDAI50%	↓ in females
ASDAS-CRP*	↓ in females
ASAS20/40	↓ in females
Drug survival Differences (range 12 weeks -10 years)	
Time on drug	↓ in female patients
Switch	↑ in female patients

* clinical important improvement (ASDAS-CRP ≥ 1.1).
↑higher scores, ↓ lower scores.

Sex and gender differences in time on drug

In addition to treatment efficacy and response, the reviews also described a clear sex difference in drug survival. Most studies that investigated sex differences in biologic found a significantly lower time on drug in women compared with men, except for the

secukinumab study (5, 80, 85-89). The studies revealed a doubled risk for treatment failure in female patients. A recent study found that 31.1% of males experienced a treatment failure compared with 50.0% of females (50).

Biologics and peripheral manifestations

Although few studies have investigated sex differences separately, a greater number of studies have assessed sex as a possible predictor in relation to treatment efficacy and drug survival (49, 50). Studies including sex differences in their analyses also described several predictors for treatment efficacy and drug survival, such as presence of HLA-B27 antigen, being TNFi naive, short disease duration and absence of enthesitis (17, 18). Remarkably, these factors are less prevalent among female patients, as women are less likely to be HLA-B27 positive, more often have enthesitis and a longer disease duration and are less often biologic naive compared with men (1-3, 5, 47, 62, 65-67, 83, 90, 91). In addition, female patients have a greater fat mass, which is associated with a lower TNFi treatment response (92). This might be an explanation for the fact that women were found to have a shorter drug survival on biologics compared with men.

Truth: There is substantial evidence found in different studies indicating women have a significantly lower efficacy, response rate and drug survival for TNFis compared with men. Data on sex differences in other biologics, such as IL-17 inhibitors, are limited.

CONCLUSION

In axSpA, sex differences play a role in biologic processes such as immune responses, pain mechanisms and disease manifestations, such as involvement of the entheses, and disease course, such as radiological progression. Osteoporosis can be overlooked in men and pregnancies can hamper the diagnostic process with pelvis X-rays and MRI of the SI joints. Substantial sex differences were observed in lower TNFi efficacy and drug survival in women compared with men but remain to be determined in other biologics. In conclusion, it is of great importance to be aware of the sex differences in axSpA for diagnosis as well as treatment.

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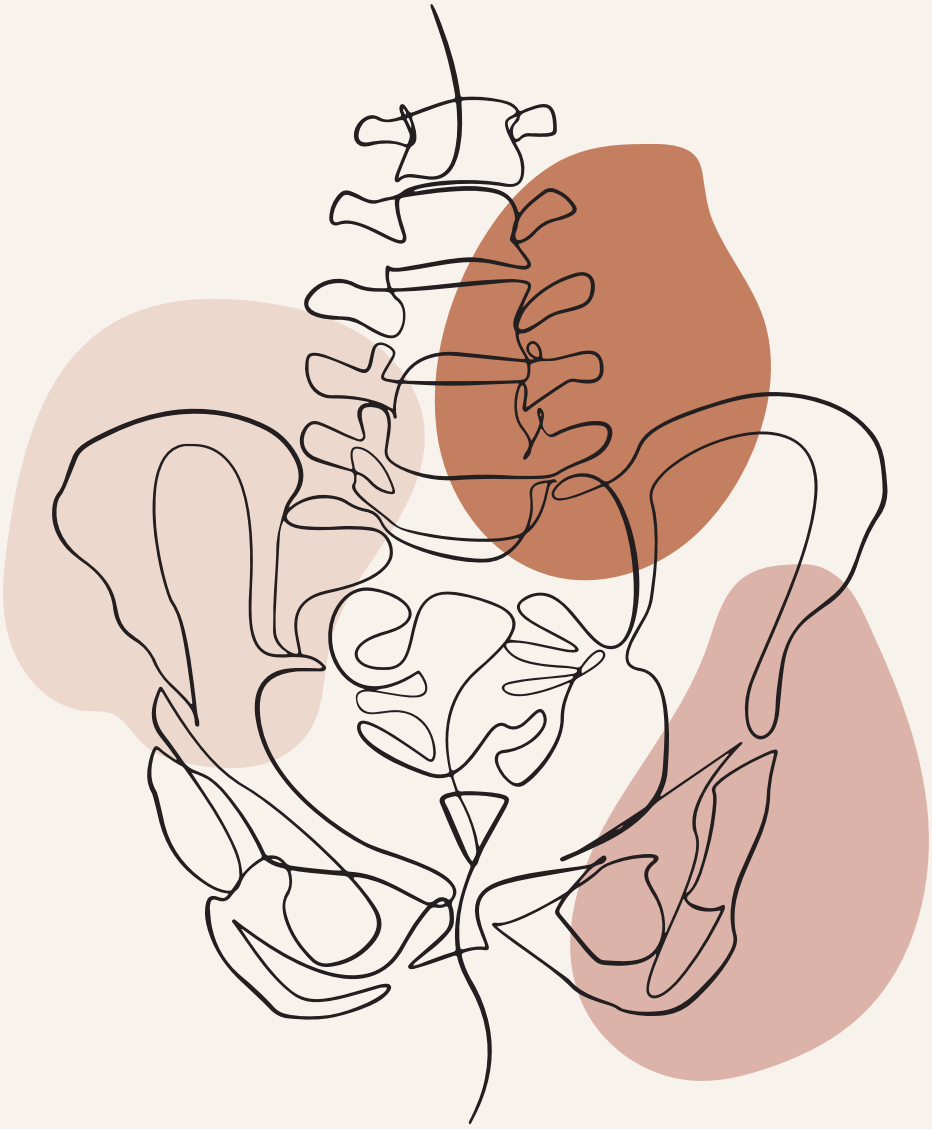

CHAPTER 3

GENDER DIFFERENCES IN RETENTION RATE OF TUMOR NECROSIS FACTOR ALPHA INHIBITOR TREATMENT IN ANKYLOSING SPONDYLITIS: A RETROSPECTIVE COHORT STUDY IN DAILY PRACTICE

T. Rusman
S. ten Wolde
S.M. Euser
T. van der Ploeg
O. van Hall
I.E. van der Horst-Bruinsma

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ABSTRACT

Aim

To assess gender differences in ankylosing spondylitis (AS) patients in relation to tumor necrosis factor alpha inhibitor (TNFi) drug survival and occurrence of adverse events in daily practice in a large peripheral hospital.

Method

Retrospective data were collected from AS patients treated with etanercept, infliximab and adalimumab between January 2004 and January 2014. Kaplan–Meier survival curves were conducted to describe the drug survival and occurrence of adverse events in time.

Results

Overall, 122 AS patients (60.7% male) were included over a 10-year time period, with a mean treatment period of 51 months (1–127 months). In total, 21 (17.2%) patients stopped the TNFi, mainly due to inefficacy (52.4%). Female patients showed a significant shorter treatment period compared to males (33.4 vs. 44.9 months). In addition, female patients switched more between TNFi compared to males (26.9% vs. 16.3%) and had a significantly higher risk at developing infections compared to male patients (26% vs.19%).

Conclusion

Females stayed on the same TNFi for a significantly shorter period compared to males (33.4 vs. 44.9 months) and the most important reason to stop or switch the drug was inefficacy. Moreover, females seemed to be more prone to infections during TNFi treatment than males.

Keywords: ankylosing, spondylitis, gender, survival, tumor necrosis factor.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease, which belongs to a spectrum of diseases named axial spondyloarthritis (SpA) with a prevalence of 0.1–1.4%.(1) AS manifests between the 15th and 40th year of life with a male to female ratio of 3 : 1.(2) The most characteristic symptom is inflammatory back pain. AS can lead to structural and functional impairments and work disability.(3) Treatment of AS mainly consists of non-steroidal anti-inflammatory drugs (NSAIDs) combined with exercise treatment.(4) In case of persistent disease activity, disease-modifying anti-rheumatic drugs (DMARDs) have limited effect on axial manifestations,(5) but tumor necrosis factor alpha inhibitors (TNFi) are very effective. Responses with TNFi were achieved in more than 60% of patients, and over a third of the AS patients achieved partial remission.(6-10)

However, these results indicate that 40% of the patients have an insufficient response to TNFi, which could be due to patient characteristics such as age and gender. A previous meta-analysis of several clinical randomized trials with etanercept revealed that female AS patients not only had a lower level of response (AS Disease Activity Score) to TNFi, but also showed a higher percentage of non-responders compared to male patients.(11) In addition, females stopped the TNFi more often compared to male AS patients.(12) The question arises whether these gender differences in response and non-adherence to TNFi are also found in daily clinical practice. Furthermore, the risk of side effects, such as infections, is well known and seems more prevalent in female AS patients.(13, 14)

In the Netherlands, all AS patients are treated in the same way according to the guideline of the Dutch Society of Rheumatologists,(15) but complex AS patients are mainly treated in academic hospitals. In addition, most clinical trials, which have stricter inclusion criteria for TNFi treatment are, mainly, conducted in academic centers, in contrast to the peripheral hospitals. Therefore, the AS population treated in general hospitals will differ from the university medical centers. Further, data on gender differences in infection rates during TNFi treatment in AS in daily practice in non-academic hospitals are lacking.(16, 17)

The primary aim of this study was to compare gender differences in long-term drug survival of TNFi treatment in AS patients in daily practice in a large peripheral center. The secondary aim was to assess the occurrence of side effects, such as infections and malignancies within this population.

MATERIALS AND METHODS

For this retrospective study, all AS patients (fulfilling the modified New York criteria)(18) in a large peripheral hospital, 'Kennemer Gasthuis', who received TNFi treatment between January 2004 and January 2014 were eligible. Patients classified as AS were selected from the hospital diagnoses registry and checked in the Hospital Pharmacy database for TNFi treatment. The diagnosis of AS was verified by an independent rheumatologist using the electronic patient records.

Data of patients on the TNFi etanercept, adalimumab and infliximab were included, since these biologicals were used for many years and sufficient data were available for a reliable analysis, in contrast to other types of TNFi. Patients were excluded when data on the start of treatment with TNFi were missing.

The following data were collected from the electronic patient files and the Hospital Pharmacy database: (i) patient characteristics (age, sex, disease duration, presence of human leukocyte antigen [HLA]-B27); and (ii) characteristics of TNFi treatment (dosage, type of TNFi used start/stop or switch date of the drug and the reasons for stopping or switching). In addition, data on side effects such as infections (including the use of antibiotics), the occurrence of malignancies and comedication (NSAIDs, DMARDS or phenylbutazone) were obtained.

Patients who used TNFi during the 10-year observation period (2004–2014) could have had multiple treatment episodes, since they could have switched between several TNFi. A treatment episode was defined as the start and stop date of a single TNFi treatment. For instance, patients who used in total of two types of TNFi had two starting dates and therefore two treatment episodes. The data for survival time were calculated per drug as cumulative treatment survival. Treatment interruptions and associated reasons for interruptions were recorded. In case of treatment interruptions > 6 months, the drug survival data were used until the date of treatment interruption.

Statistics

Kaplan–Meier survival curves were used to display the drug survival and adverse events during the treatment period of the patients. Log rank tests and Cox regression analysis were performed to compare the three treatments. To compare gender differences, independent t-tests and v2 tests were used. Possible confounders and effect modifiers, such as age and gender, were tested with a multiple Cox regression analysis. Based on the literature, risk factors for drug survival such as gender and age (≤ 40 years/> 41 years) were assessed along with side effects by comparison of the dichotomous variables.

RESULTS

Population

In total 223 consecutive AS patients (60.5% male) were identified from the hospital registration database, of whom 122 patients (54.7%) used TNFi (Table 1) and 95 patients did not (36 ((38%) female and 59 (62%) male). Six patients had insufficient data for follow-up.

Demographic baseline characteristics showed a male predominance (60.7%) and a mean age of 43.5 years (17–75 years; Table 1). More male patients were HLAB27 positive (83.6%). Significantly more female patients used infliximab (19.4%) and male patients used etanercept more often (65.2%; Table 1).

Table 1. Baseline characteristics of the included AS patients (N = 122), specified for gender

	Overall	Female	Male	P-value (if possible 95%CI)
Population, n (%)	122 (100%)	48 (39.3)	74 (60.7)	
Mean age in years (range)	43.5 (17 – 75)	43.7 (17 – 75)	43.4 (20 – 68)	0.88 (-4.8 – 4.1)
HLA-B27+ (%)	91.7	89.6	93.2	0.24
TNFi treatment, n (%)*				0.02*
Adalimumab	95 (59.7)	19 (28.4)	27 (29.3)	
Etanercept	46 (28.9)	35 (52.2)	60 (65.2)	
Infliximab	18 (11.3)	13 (19.4)	5 (5.4)	
Co-medication used, n (%)				0.69
NSAIDs	51 (41.8)	19 (39.6)	32 (43.2)	
DMARDs*	12 (9.8)	5 (10.4)	7 (9.5)	
Phenylbutazone	6 (4.9)	2 (1.6)	4 (3.3)	

Except indicated otherwise, values were presented as n (%); TNFI, tumor necrosis factor a inhibitor; HLA-B27+, presence of human leukocyte antigen B27; AS, ankylosing spondylitis; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs, methotrexate and sulfasalazine.
*Significant difference.

Drug survival

After starting TNFi treatment, the mean follow-up was 5.1 years (0.1–10.6 years). Censored data showed that 119 patients (97.5%) had 6 months of follow-up, 114 patients (93.4%) 1 year, 84 patients (68.9%) 3 years, 61 patients (50%) 5 years, 34 patients (27.9%) 8 years and four patients (3.3%) had 10 years of follow-up data.

The retrospective data analysis over 10 years showed the highest survival rate in etanercept (85.3% after 3.7 years), followed by adalimumab (76.1% after 2.6 years). Infliximab showed the lowest survival rate. However, if patients responded to the treatment, they stayed on the drug for a long time (4.7 years).

Of the 122 patients, 101 patients (82.8%) were still treated with a TNFi at the end of the observation time, of whom 90 patients were still on their first TNFi. In total, 21 patients (17.2%) stopped the treatment without starting a new one. Overall, 32 patients (26.2%) switched to another TNFi, of whom 20 patients continued the second TNFi (62.5%), four patients switched to a third TNFi (12.5%) and eight patients stopped the first TNFi treatment without starting a new one. Among the patients who started a third TNFi, three patients continued the treatment and one patient stopped the treatment with TNFi.

The most important reason for discontinuation was inefficacy (in 21 patients; 52.4%). The second reason was the occurrence of side effects, of which infections (mostly recurrent) were the most frequent. Malignancies were not reported. Furthermore, there were no significant gender differences in reasons for discontinuation.

Female patients had a significantly lower treatment survival: 33.4 versus 44.9 months ($P = 0.031$; 95%CI:1.1–22; Figure 1). At approximately 2.5 years of TNFi treatment a rapid decrease in drug survival was shown in female patients, while male patients stayed on treatment. Although not significant, females stopped TNFi more frequently compared to male patients (20.8% vs. 14.9%).

In total 32 patients (26.2%) switched treatment, of which female patients switched more frequently compared to male patients (26.9% vs. 16.3%). The most important reasons for switching in both males and females were inefficacy (72.7%) and side effects (21.2%).

Patients on etanercept showed the highest number of switches within the first 20 months (12%), while the number of patients on adalimumab and infliximab who switched were more dispersed. The most common switch was from etanercept to adalimumab (17.2%).

Logistic regression analysis indicated that being positive for HLA-B27 and the use of co-medication were predictors for switching.

During the three different TNFi treatments, 31 treatment interruptions shorter than 6 months and four treatment interruptions longer than 6 months occurred. Interruptions shorter than 6 months were mainly caused by mild infections, like ear, nose and throat infections.

Interruptions longer than 6 months were mainly caused by attempts to stop the drug permanently (in consultation between patient and physician), because the patients did not experience any disease-related symptoms any more, or because of pregnancy (one case).

In case of attempts to stop the drug, all three patients experienced an exacerbation of the disease after a median period of 8 months (6–10 months). The mean interruption duration was 7.7 months (6–10 months).

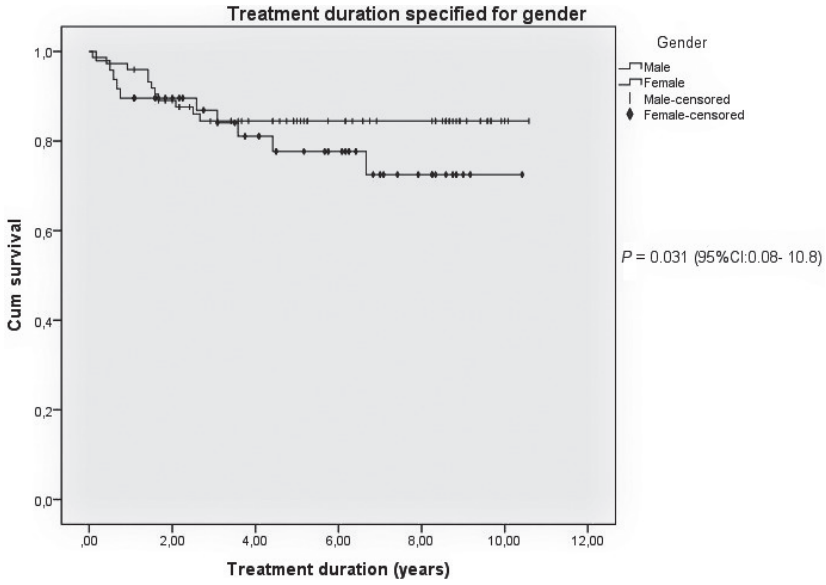

Figure 1. Kaplan–Meier survival curve for anti-tumor necrosis factor (anti-TNF) treatment duration specified for gender. Overview of treatment adherence, including switches, specified for gender.

Side effects

During the different treatment episodes, 40 infections (25%) were registered in 38 patients, of which 19 were marked as serious infections, because they necessitated antibiotic treatment (based on patient-reported outcome) mainly of the respiratory tract. In only one case hospitalization was needed due to a Staphylococcus aureus infection of a knee prosthesis.

Side effects which required the permanent discontinuation of TNFi treatment were mainly recurrent infections of the throat, nose and ears (patient-reported outcomes).

Some gastro-intestinal infections and skin reactions, mainly local reactions, but also a total body skin rash, occurred less often.

Both sex and age were risk factors associated with infection risk. Females had a 26.1% chance on developing infections compared to 18.7% for males (hazards ratio (HR) females 2.15; 95%CI: 1.1–4.0). The age group > 41 years showed a significantly higher risk for infections (HR 1.1; 95%CI: 1.0–1.1) compared to younger patients.

Although not significant, 15 out of the 36 patients (41.7%) using NSAIDs as co-medication developed an infection during TNFi treatment compared to 21 out of 75 patients (28%) who did not use NSAIDs. In this study no malignancies were diagnosed during TNFi treatment.

DISCUSSION

Analysis of AS patients treated with TNFi in a peripheral hospital in daily clinical practice showed that the majority of patients (81.3%) still used one of the three TNFi after 4 years. Interestingly, females showed a significantly shorter treatment duration compared to males (33.4 vs. 44.9 months) and switched and stopped the drugs more often.

Some studies found similar results on treatment discontinuation, but not with specific details about the gender differences in treatment survival as in our study. Several studies described female gender only as a baseline predictor for early TNFi treatment discontinuation.(12, 19, 20) However, these studies, as in our own study, could not give a clear answer for the exact reason for this gender difference in treatment survival.

In addition female AS patients switched more often (27%) to a second or third TNFi than male patients (16%), but this difference was not significant, most likely due to the low number of patients. This finding corresponds with the results of Glintborg et al., who also described that female patients switched between TNFi more often than male patients (33% vs. 22%). This might imply that TNFi treatment is less effective in female AS patients compared to male patients.(21) Overall, in this cohort 21% of the AS patients switched between types of TNFi, which is low in comparison to the DANBIO registry, where 30% of the 1432 patients treated with the same TNFi treatments switched. This discrepancy in switches could be explained by the smaller size of our study.(21)

However, these studies did not specifically assess gender differences. The most important reason found for switching in our study was inefficacy, which is in line with several other studies (21-23) and not related in this study to gender differences.

Interestingly, at baseline more female patients were treated with infliximab compared to male patients and infliximab had in this study the lowest survival rate of the three TNFi. We also found that females had a shorter treatment survival compared with males, which may imply an association between female gender and the lower survival rate of infliximab, but the number of patients in this cohort was too small to make reliable analysis of a probable causal relation.

Female AS patients showed an increased risk for infections during treatment compared to males. This finding corresponds with other studies in which female AS patients had a doubled increased risk of developing infections in comparison with males. [13, 14] This observation is in contrast with studies in the general healthy population, where male gender was described to be a risk factor for infections. (14, 24-28) There are no clear explanations for this result. Further investigation is needed to clarify the relation between AS, TNFi treatment infections and gender.

Overall, the majority (81.3%) of AS patients treated with TNFi showed a good drug survival over a long follow-up period (5.1 years), which was higher compared to other studies with the same TNF blockers (12, 29) which described 63% and 74% survival rates. Our higher drug survival rate could be explained by the difference in population size (842/243 vs. 122 patients) and the fact that our study was conducted in a peripheral hospital instead of a secondary referral center with probably a selection of less severe patients.

The most important reasons for drug discontinuation were inefficacy (52.4%) and side effects (47.6%), mainly due to mild infections, which corresponds with other studies on the same TNFi.(12)

Overall, the most important adverse events reported in this study were infections, which was expected since TNFi treatment increases the risk of mild infections.(10)

Another finding was that patients older than 40 years of age had a significantly increased risk of developing infections, although the reported effect was small, which corresponds with infection rates in many other studies.(30-32) Age was equally distributed for gender, so in this case gender was not considered a confounder.

The retrospective design was a limitation of our study, since the data collection was dependent on information used for clinical practice. However, the retrospective design was also a strength, since we had data access over a long follow-up period. Furthermore, the data were collected from a peripheral daily practice, instead of a more controlled

environment, like secondary referral centers, which provide, in our opinion, a different perspective of TNFi treatment use in AS patients.

It would be interesting for further research to collect more data on smoking and co-morbidities, which can make patients more vulnerable to infections, but even more important is to assess possible associations of infection rates with gender in order find strategies to increase TNFi drug survival.(33-38)

In conclusion, over a mean treatment period of 5.1 years with TNFi, female AS patients showed significantly shorter treatment periods compared to males (33.4 vs. 44.9 months) and permanently stopped the drug more often and seemed to be more prone to infections. Overall, the majority of AS patients (81%) continued TNFi for many years and the most important reason to stop treatment, in both males and females, was inefficacy.

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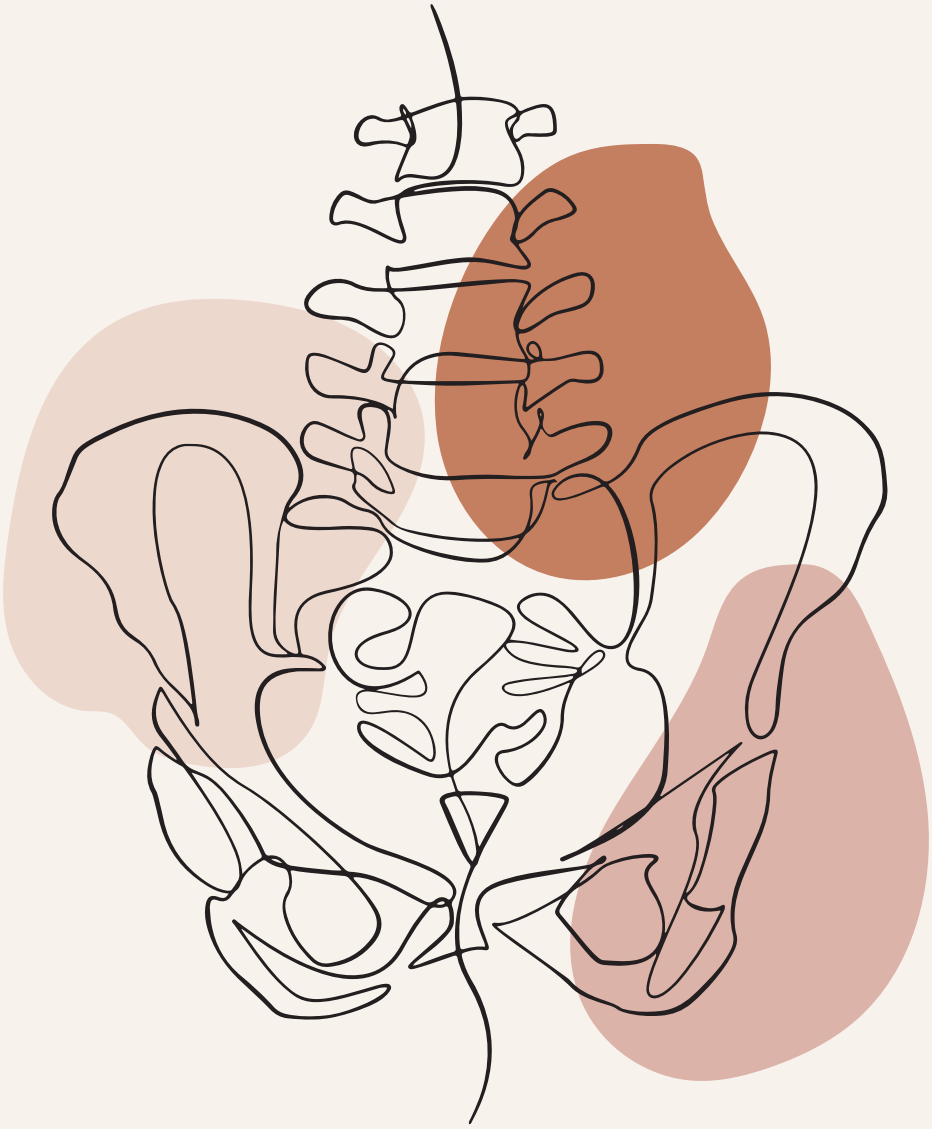

CHAPTER 4

DISEASE ACTIVITY IN WOMEN WITH ANKYLOSING SPONDYLITIS REMAINS HIGHER UNDER TUMOUR NECROSIS FACTOR INHIBITOR TREATMENT THAN IN MEN: A FIVE-YEAR OBSERVATIONAL STUDY

T. Rusman
M.T. Nurmohamed
S. Hoekstra
J.C. van Denderen
R.F. van Vollenhoven
M. Boers
M.M. ter Wee
I.E. van der Horst-Bruinsma

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ABSTRACT

Objective

To assess sex differences in response, level of disease activity, and drug survival in tumour necrosis factor inhibitor (TNFi)-naïve ankylosing spondylitis (AS) patients.

Method

Consecutive AS patients, fulfilling the modified New York criteria, were included in a prospective cohort study at initiation of the first TNFi and followed until this medication was stopped (drug survival). Disease activity scores (AS Disease Activity Score using C-reactive protein (ASDAS-CRP), Bath AS Disease Activity Index (BASDAI), and CRP) were measured at 3, 6, and 12 months, and every subsequent year, up to 5 years. The response was defined by the ASDAS-CRP response criteria (clinically important improvement: ASDAS-CRP decrease ≥ 1.1). Analyses included regression methods for repeated measurements and survival analyses.

Results

Overall, 356 patients were included (34% women, mean ± sd age 46 ± 12 years), with a median disease duration of 12 (interquartile range 6;20) years. Women were less likely than men to achieve a clinically important response after 6 months of TNFi treatment (47% vs 64%; relative risk 1.4, 95% confidence interval (CI) 1.1;1.9, p = 0.02), despite a lack of sex differences in mean ASDAS-CRP levels over 5 year follow-up. Adjusted models for BASDAI over 5 years showed that women had a 0.6 point higher BASDAI score than men (β = 0.6 0.1;1.1 <0.02). Numerically, more women than men discontinued treatment over a period of 5 years (hazard ratio = 1.5, 95% CI 0.9;2.5, p = 0.15).

Conclusion

Female AS patients show a lower response to TNFi and a higher disease activity compared to men.

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease which can be divided into non-radiographic axSpA (nr-axSpA) and radiographic axSpA (or ankylosing spondylitis (AS)) (1). This study focuses on radiographic axSpA (AS) patients only. AS starts at a young age (15–40 years) and more often affects men than women (in a 3:1 ratio) (2).

Like many other medical treatments, the efficacy of tumour necrosis factor inhibitor (TNFi) has not been fully assessed for sex differences within the AS population, despite accumulating data on gender differences in physiological processes, such as renal and liver function and body composition, which may influence drug metabolism (3). In AS, our group previously documented significant sex differences in TNFi response in another patient population, both in efficacy and in time on drug (4, 5). Two review articles have confirmed that studies on sex differences in AS are limited in number and have a short period of observation (6, 7).

So far, only a few studies have focused on longitudinal follow-up of sex differences in TNFi response in AS, and only two studies had a long follow-up period, with a maximum of 10 years (5, 8, 9).

The primary aim of this study was to analyse sex differences in AS response to the first TNFi after 6 months, in TNFi-naive AS patients. The secondary aims were to assess sex differences in levels of disease activity and drug survival of TNFi over a 5 year follow-up period.

METHOD

Consecutive patients diagnosed with radiographic axSpA (according to the modified New York criteria (10), who had started their first TNFi, were included from the outpatient clinics of the VU University Medical Centre and Reade (Amsterdam, Netherlands). All data were registered in the Amsterdam Spondyloarthritis (AmSpA) cohort. Patients who had been previously treated with biologicals were excluded.

The study was initiated in January 2000 and included data on AS patients who started with infliximab, adalimumab, etanercept, or golimumab up to June 2018; data collection continued until December 2018. Patients on certolizumab were not included in this study because of the low number of patients and very limited follow-up data.

The study complied with the Declaration of Helsinki and was approved by the local ethics committees of the participating hospitals (approval number NL13486.029.06), and written informed consent was obtained from all participants before inclusion.

All included patients visited the outpatient clinic for screening at baseline (just before the start of TNFi treatment), at 3, 6, and 12 months, and every successive year up to 5 years' follow-up, after the start of the TNFi. In case of incomplete data during the 5 year follow-up, the corresponding reasons for missing data were reported. For patients who were lost to follow-up, additional information on drug status was retrieved from the patient files of the hospitals.

At baseline, demographics, medical history (i.e. year of AS diagnosis and disease onset (first symptoms)) and data on extra-articular manifestations (EAM) (uveitis, psoriasis, and inflammatory bowel disease) were collected.

Blood samples were obtained to determine the presence of the human leucocyte antigen B27 (HLA-B27) (baseline only), the level of acute-phase reactants, C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) (at every visit). Data on disease activity and function were obtained at every visit through validated questionnaires (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Global score (BASG), on pain and overall well-being through a numerical rating scale). A physical examination was performed at every visit to assess the Bath Ankylosing Spondylitis Metrology Index (BASMI) and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

Disease activity was assessed at every visit with the BASDAI and the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP). The definitions of the ASDAS-CRP clinical response are: 'clinically important improvement' (CII), with a decrease in the ASDAS ≥ 1.1 and 'major improvement' (MI) in the case of an ASDAS decrease ≥ 2.0, compared to baseline (11-13). In addition, the Assessment SpondyloArthritis international Society (ASAS) 20% and 40% response criteria were analysed (12, 13).

Drug survival was defined as the duration of treatment with the first TNFi, in months. Reasons for treatment discontinuation were treatment related (classified as adverse events (AEs); lack or loss of efficacy (LOE); low disease activity) or non-treatment related (pregnancy; other). Reasons for early censoring included loss to follow-up because of changing hospital, relocation, and lack of further follow-up data. In the case of missing

follow-up data, an effort was made to retrieve data on TNFi status from the patient files of the participating hospitals.

Statistical analysis

All data from the AmSpA cohort and the corresponding patients records from January 2000 to December 2018 were used for the analysis. In the case of missed visits, if continued use of the TNFi was documented in the patient record and the interval period between two visits was < 6 months, the first results after the interval were used in the analysis. If the interval was ≥ 6 months, or if there was reasonable doubt over continued treatment during the interval, only the data before the interval were used in the analysis (n = 20).

Demographic data at baseline were analysed cross-sectionally for possible sex differences, with chi-squared and Student's t-tests. Data were presented as mean ± standard deviation (sd) in the case of normally distributed outcomes, or median and interquartile range (IQR) in the case of skewed data. No distinction was made between different TNFi, since they are assumed to be equally efficacious in AS (14-17).

To assess sex differences in TNFi response according to the ASAS response criteria for ASDAS-CRP (CII), Student's t-tests, chi-squared tests, and longitudinal and linear regression analyses were performed.

To assess sex differences in disease status on TNFi treatment at several time points over a 5 year follow-up period, the mean ASDAS-CRP, BASDAI, BASMI, and BASFI values were analysed with the generalized estimating equation (GEE) analysis for sex to correct for repeated measurements over time in one patient. Post hoc, the 5 year mean of each of the six BASDAI questions was analysed with GEE, to investigate which of the components caused the sex differences. A regression coefficient (β) with 95% confidence interval (CI) expressed the difference in mean disease activity value between women and men over time. Age, disease duration, body mass index (BMI), pain, MASES, and CRP (except for ASDAS-CRP) at baseline were assessed as possible confounders in all the aforementioned outcome measures (checked for multicollinearity). Correlations between the MASES and BASDAI component 4 were checked with the Pearson correlation score. Continuous confounders were checked for linearity. An interaction term for time was added to the model to examine whether the sex effect was constant over time. If the interaction term was significant ($p < 0.10$), sensitivity analyses were performed.

Sex differences in time on drug were assessed with Kaplan–Meier survival curves and Cox regression analysis. The start date was defined as the date of the first injection with a TNFi

and the stop date as the last known date that the patient used the (first) TNFi. If a patient switched treatment to another TNFi, only data before the switch were used in the analysis.

Statistical analysis was conducted using SPSS version 26. All statistical tests were two sided, with a p-value of < 0.05 indicating statistical significance. No adjustment was made for multiple testing.

RESULTS

In total, 385 patients with AS were eligible for the study, of whom 29 (8%) were excluded since they were not TNFi naive (n = 25) or their prior treatment status was unknown (n = 4). This resulted in a baseline study population of 356 patients, with a mean ± sd age of 46 ± 12 years, of whom 121 (34%) were women (Table 1), with a mean BMI of 25.9 ± 4.8 kg/m2 . Most patients were HLA-B27 positive, and had long-standing disease and a history of EAM. At baseline, BASDAI was significantly higher, and BASMI significantly lower, in women (Table 1) compared to men. After 6 months of treatment, 47% of women and 64% of men fulfilled the ASDAS-CRP clinical response criteria of CII (relative risk 1.4, 95%CI 1.1;1.9, p=0.02). The difference was even more prominent at 3 months (46% vs 70%) and extended to both CII and MI. Limited data were available on the ASAS20 response after 3 and 6 months, which was reached by 24.4% (n = 87) and 31.1% (n = 73) of the patients, respectively. After 1 year, no further improvement was observed. No significant gender differences were observed, although the percentage of male ASAS20 responders at 6 months was higher compared to females (31.1% vs 21.5%). At 3 months, only 14.3% (n = 51) fulfilled the ASAS40 criteria. After 3 months of treatment, no additional ASAS40 responders were observed. No sex differences were found in ASAS40 responses.

Over the 5 year follow-up, the mean average BASDAI scores were higher in women than in men (Table 2). The adjusted model (which corrected for the confounders) showed 0.6 (95% CI 0.1;1.1, p = 0.02) higher BASDAI scores in women compared to men (Table 2). Sex differences on BASDAI levels were stable over time. No multicollinearity was observed between age and disease duration (variance inflation factor 1.3). Separate analyses of the BASDAI components revealed that all questions showed higher scores in women compared to men, not just the pain scores alone (Table 3). These differences remained after correction for the confounders CRP, disease duration, age, BMI, and MASES. No correlation was observed between the subjective BASDAI question 4 and the objective measurement MASES (Pearson correlation = 0.27).

Additional disease outcome parameters (mean ASDAS-CRP, BASFI, BASMI, and CRP) showed a significant mean improvement after 6 months and remained stable up to

5 years of follow-up (Table 2, Supplement S1). The mean BASMI scores were lower in women than in men (−0.6, 95% CI −1.2;−0.1, p = 0.03) at all time-points over a 5 year period (Table 2, Supplement S2). No sex differences were observed in mean ASDAS-CRP, BASFI, and CRP scores.

Table 1. Baseline characteristics of the included patients with AS, stratified for sex (N=356)

Demographical data	**Total population (n=356)**	**Men (N= 235)**	**Women (N= 121)**
	n	n	n
Age (years) (n =342)	46.4 ± 12.4	47.0 ± 12.2	45.2 ± 13.8
Age diagnosis (years) (n= 320)	32.1 ± 11.1	32.3 ± 11.7	31.7 ± 10.2
Disease duration (years) (n=318)	14.3 (6.0;20.3)	12.5 (6.0;21.0)	14.0 (5.0;20.0)
HLA-B27* (n=339)	276 (81.7)	178 (80.2)	99 (84.6)
Body Mass Index, (kg/m^2) (n=335)	25.9 ± 4.8	25.9 ± 4.4	25.8 ± 5.5
Extra-articular manifestations (EAM)			
Frequency (n=354)	269 (76.0)	171 (73.1)	98 (81.7)
Uveitis (n=350)	101 (28.9)	58 (25.0)	43 (36.4)
Psoriasis (n=353)	33 (9.3)	21 (9.0)	12 (10.1)
IBD (n= 354)	28 (7.9)	17 (7.3)	11 (9.2)
Concomitant drugs			
NSAIDs	196 (77.2)	121 (71.2)	56 (66.7)
DMARDs	22 (8.7)	14 (8.3)	8 (9.5)
Disease outcome			
ASDAS-CRP (n=275)	3.5 ± 0.9	3.5 ± 1	3.5 ± 0.9
BASDAI* (n=342)	5.8 ± 1.9	5.6 ± 1.9	6.2 ± 1.9
CRP (mg/L) (n=327)	7.0 (2.9;20.0)	8.0 (3.0;25.8)	5.0 (2.5;13.0)
ESR (mm/hr) (n=321)	18.0 (6.0;34.0)	16.5 (5.0;34.0)	18.0 (8.5;34.0)
BASMI* (n=317)	3.4 ± 2.2	3.7 ± 2.3	2.9 ± 1.9
BASFI (n=318)	5.3 ± 2.4	5.4 ± 2.4	5.3 ± 2.5
MASES (n=300)	0.5 (0.0;3.0)	0.0 (0.0;2.75)	2.0 (0.0;4.0)
Patient global well-being (VAS) (n=320)	6.3 ± 2.4	6.3 ± 2.3	6.3 ± 2.6
Patient pain (VAS) (n=310)	5.7 ± 2.6	5.7 ± 2.6	5.9 ± 2.6

Data are shown as mean ± sd, median *(interquartile range), or n(%).
HLA-B27*, presence of human leukocyte antigen B27; IBD, inflammatory bowel disease; NSAID, non-steroidal inflammatory drugs; DMARD, disease modifying anti-rheumatic drug; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR: erythrocyte sedimentation rate; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Function Index; MASES, Maastricht ankylosing spondylitis enthesitis score (0-13); VAS, visual analogue scale.
*p-value <0.05.

Table 2. Results of generalized estimating equation analyses for sex in mean disease status over time in ankylosing spondylitis.

Baseline up to five years follow up	β	95% CI	p
BASDAI			
Crude	0.9	0.4;1.3	<0.001*
Adjusted	0.6	0.1;1.1	0.02*
ASDAS-CRP			
Crude	0.1	-0.1;0.3	0.3
BASMI			
Crude	-0.8	-1.2;-0.4	<0.001*
Adjusted	-0.6	-1.2;-0.1	0.03
CRP-level			
Crude	-0.2	-0.5;0.0	0.08

Encoded male:0 and female: 1. All GEE analyses were checked for consistency over time by an effect-modifier check for follow-up time in the final model. β, regression coefficient; CI, confidence interval; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using C-reactive protein; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein. *Statistically significant ($p < 0.05$). BASDAI: disease duration, age, CRP–baseline, pain, body mass index (BMI)–baseline, and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)–baseline. BASMI: age, disease duration, CRP–baseline, pain, BMI–baseline, and MASES–baseline.

Table 3. Overview of the different Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) questions, by seks

Question BASDAI	Baseline (n=345)				GEE-analyses over 5 years					
					Crude model			Adjusted model		
	M	F	95% CI	*P*	B	95% CI	*P*	B	95% CI	*P*
1. Fatigue	6.6	7.2	-1.1;-0.1	0.05	0.9	0.4;1.4	0.001	0.7	0.1;1.4	0.02
2. Spinal pain	6.9	7.1	-1.1;-0.2	NS	0.8	0.2;1.3	0.004	0.6	0.01;1.2	0.05
3. Joint involvement	4.3	4.7	-1.1;0.3	NS	0.8	0.3;1.4	0.002	0.4	-0.2;1.1	0.18
4. Discomfort after pressure	5.2	5.6	-1.8;1.0	NS	0.9	0.2;1.6	0.01	0.9	0.2;1.5	0.01
5. Morning stiffness	6.7	6.8	-0.7;0.4	NS	0.7	0.2;1.2	0.01	0.4	-2.0;1.0	0.18
6. Duration morning stiffness	5.6	5.7	-0.9;0.5	NS	0.4	-0.1;1.0	0.1	0.2	-0.5;0.8	0.57

A significant difference is defined as $p < 0.05$; ns, non-significant. BASDAI scale: 0–10; GEE, generalized estimating equation; M, male; F, female; CI, confidence interval; β, regression coefficient. All components were checked for the following confounders: disease duration, age, C-reactive protein–baseline, pain, body mass index, and Maastricht Ankylosing Spondylitis Enthesitis Score. All GEE analyses were checked for consistency over time by an effect-modifier check for follow-up time in the final model.

Patient flow over 5 years of follow-up

A total of 214 patients (60%) remained on their first TNFi for 3 years and 161 patients (45%) for 5 years (Figure 1). The most important reasons for loss to follow-up were LOE (n = 38, 19.5%), AEs (n = 18, 9.2%), and relocation to other hospitals (n = 15, 7.7%) (Figure 1). No differences were observed between men and women: LOE, 21 men (17.9%) vs 15 women (19.2%); AEs, 10.3% vs 11.5%; and other reasons for loss to follow-up, 20 men (17.1%) vs 16 women (20.5%).

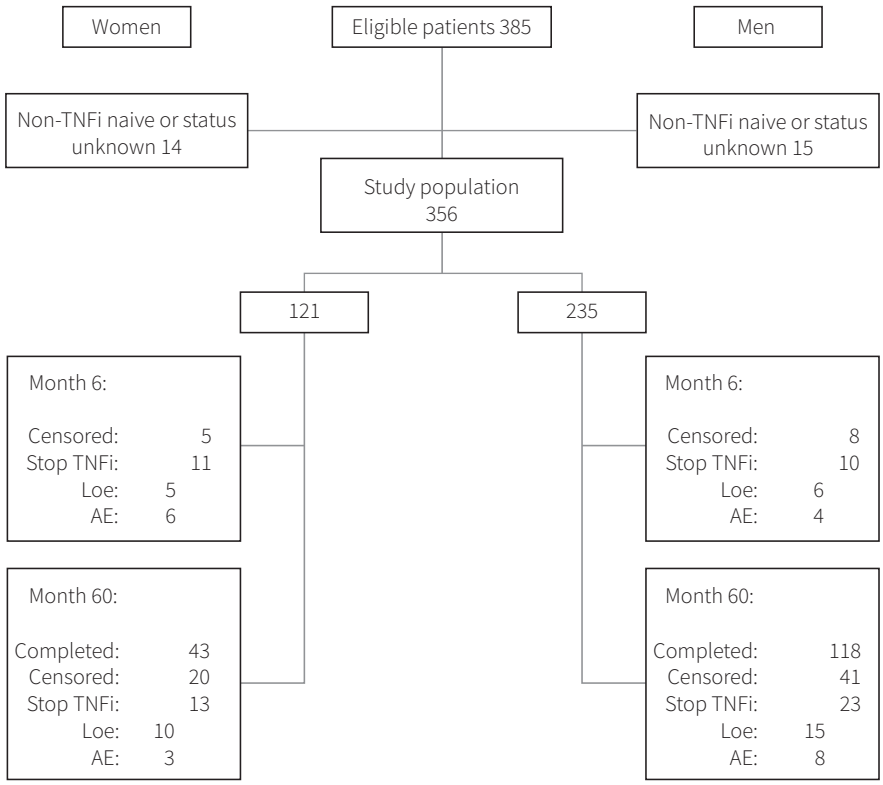

Figure 1. Flowchart of data availability over 5 years for patients in the Amsterdam Spondyloarthritis (AmSpA) cohort (N = 356). TNFi, tumour necrosis factor inhibitor; LOE, lack or loss of efficacy; AE, adverse event; censored, patients who were lost to follow-up without known treatment discontinuation.

Drug survival of the first TNFi

Overall, 131 out of 356 patients (36.8%) were lost to follow-up, of whom 74 patients had no treatment related reason for dropping out from the cohort (censored) (median treatment duration 32 months, IQR 12;48). Of the remaining patients who had a drug related reason for dropping out from the cohort (n = 57, 43.5%), median drug survival was

48 months (IQR 13;60). There were no significant sex differences in TNFi survival (women 49 ± 2 vs men 53 ± 1 months) (Figure 2). Numerically, women had an increased risk for TNFi discontinuation (hazard ratio (HR) 1.5, 95% CI 0.9;2.5, p = 0.15) compared to men.

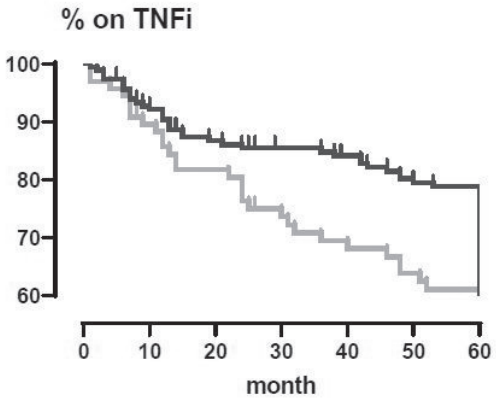

Figure 2. Time (in months) on the first tumour necrosis factor inhibitor (TNFi), by sex. Grey line, women; black line, men.

DISCUSSION

In this cohort of AS patients initiating TNFi treatment, women showed less response and overall higher disease activity in long-term follow-up. Although drug survival in months was similar between both sexes, women showed a numerically a higher likelihood of drug discontinuation compared to men.

Our observations confirm previous studies that revealed an average 20% difference in response rates between women and men in ASDAS-CRP response (4, 18).In addition, this study revealed a substantial sex difference in a longitudinal analyses for the disease activity score BASDAI. It has been hypothesized that women have, on average, higher BASDAI scores, mainly owing to higher levels of reported pain, but this study demonstrates higher values of all BASDAI components in women compared to men, not only pain. These elevated scores of BASDAI components in women correspond with the findings of one other study and additionally with results of the early stages of the disease (19). Of note, that study also included patients diagnosed with psoriatic arthritis and nr-axSpA and only cross-sectional analyses were performed instead of the longitudinal analyses in our study (20).

Reduced drug survival in women on TNFi was also described in two reviews (12, 13) describing one study including 122 comparable axSpA patients in a peripheral clinical setting (5). In our study, women had a numerically, but not significantly, higher risk (HR 1.5) than men of discontinuing their first TNFi treatment over a period of 5 years. Taking into account the relatively low number of patients included in the drug survival analysis (n = 57), this may be a reasonable explanation for not finding a significant difference in drug survival between men and women.

Our study substantially contributes to the scarce literature on sex differences in TNFi response in AS because data were analysed at several time points in daily clinical practice over such a long follow-up period. Only two studies (both by Glintborg et al) assessed data over comparable follow-up periods, but they used survival curves and logistic regression analyses (8, 9) and no longitudinal regression analyses such as GEE. These two studies found comparable results considering sex differences. In addition, only three studies included a larger study population than our study (440, 603, and 1283 vs 356) (4, 9, 18). However, one of these studies included pooled data from several randomized controlled trials, which is different from our prospective observational cohort design.

Possible explanations for sex differences in treatment efficacy include differences in drug metabolism, owing to differences in renal and hepatic function, weight, length, and body composition (3). It has also been suggested that the higher proportion of body fat in women increases the levels of TNF-α and decreases the efficacy of TNFi (21). The lack of sex differences in mean average ASDAS-CRP scores may be explained by the higher CRP levels in men which raise the ASDAS-CRP values, whereas the other ASDAS components, such as back pain, peripheral pain, and duration of morning stiffness, are higher in women. An alternative hypothesis suggests that women are more likely to suffer from widespread pain than men (22). However, this study revealed no higher global pain scores in women (mean ± sd 5.9 ± 2.6) compared to men (5.7 ± 2.6). Improvement of function (BASFI) and BASMI after the start of TNFi was comparable between the two sexes, although the BASMI scores remained higher in men with AS compared to women, which corresponds with other studies (9, 23, 24).

Our study has a few limitations. Only AS patients who fulfilled the modified New York criteria were included in this study, which could be seen as a limitation, since TNFi are not limited as treatment for this axSpA subgroup. However, we believe that our study results showed a reliable overview of AS patients in clinical practice, which is in our opinion a valuable addition to already existing data. As with any observational study, missing data and loss to follow-up increase the risk of bias. Loss to follow-up occurred similarly in women and men, which, in our opinion, did not compromise the results.

GEE analyses were used in this study to handle the missing data and strengthen our longitudinal findings on disease activity levels and the observed differences between men and women by calculating the mean of the disease activity scores over all the follow-up measurements, which we checked in the final GEE model for consistency over time by adding an interaction term for follow-up time to the model (25).

Another possible weakness could be the selection bias at inclusion, since we have no insight into whether every eligible patient was approached for possible study inclusion. However, our demographic data correspond very well with the patient populations of the previous studies, and thus were directly comparable.

CONCLUSION

This cohort study demonstrates a higher disease activity and lower response rate to TNFi in women with AS than in men. We suggest that more sex-specific treatment strategies in AS should be developed to optimize treatment for both sexes.

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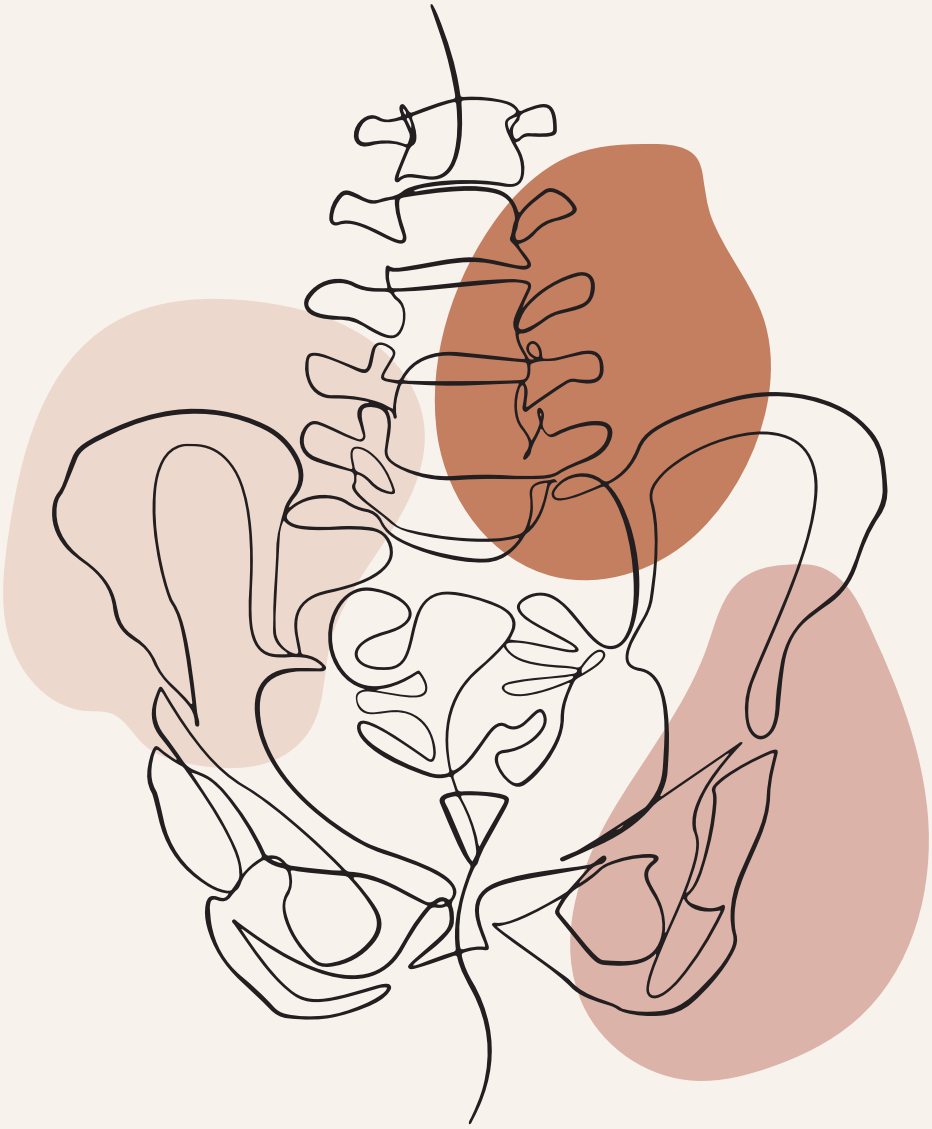

CHAPTER 5

LONG-TERM TREATMENT WITH TNF-ALPHA INHIBITORS IMPROVES BONE MINERAL DENSITY BUT NOT VERTEBRAL FRACTURE PROGRESSION IN ANKYLOSING SPONDYLITIS

K. J. Beek
T. Rusman
M.A.C. van der Weijden
W.F. Lems
J.C. van Denderen
M.Konsta
I. Visman
M.T. Nurmohamed
I.E. van der Horst-Bruinsma

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ABSTRACT

The aim of this cohort study was to evaluate the long-term effects of TNF inhibitors (TNFis) on BMD and the incidence of vertebral fractures (VFxs) in patients with ankylosing spondylitis (AS). Consecutive patients with active AS with TNFi treatment duration up to 4 years with available DXA scans and spine X-rays were included. BMD (classified according to the WHO criteria for osteoporosis) of the hip and lumbar spine, the VFx (classified as a Genant score ≥1/≥20% height loss), and radiological progression (modified stoke ankylosing spondylitis spinal score (mSASSS)) scores were obtained at baseline and at 4 years of TNFi treatment. Overall, 135 AS patients were included. At baseline, 40.1% of patients had low BMD of the hip and 40.2% of the lumbar spine. This decreased to 38.1% (p=0.03) with low hip BMD and 25.3% (p<0.001) of the lumbar spine BMD after 4 years of TNFi treatment. VFxs were present at baseline in 11.1% of the 131 patients, which increased to 19.6% after 4 years of TNFi treatment. A Genant score ≥2, was found at baseline in 3 out of 14 VFx (21.4%) patients, which increased to 7 out of 27 VFx (25.9%) patients after 4 years. All disease activity parameters—the ankylosing spondylitis disease activity scale, the C-reactive protein, the erythrocyte sedimentation rate, and the bath ankylosing spondylitis disease activity index—decreased significantly (p<0.001).The mean radiological progression (n=80) increased significantly from a median mSASSS of 4.0 (1.5 to 16.0) at baseline to 6.5 (2.1 to 22.9) after 4 years of TNFi treatment (p<0.001). Despite the improvement in BMD and the decrease in disease activity, we still found new VFxs, an increase in severity in the number and grade of VFxs, and radiographic progression during 4 years of treatment with TNFis in AS patients with long disease duration. © 2019 American Society for Bone and Mineral Research.

Keywords: Ankylosing Spondylitis; Bone mineral density; Vertebral fractures; radiological damage; TNF alpha inhibitors

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic rheumatic inflammatory disease that results in bone proliferation, mainly in the axial skeleton and sacroiliac joints. Recently, there has been interest in a contradictory feature concerning bone metabolism in AS patients. On the one hand, we see additional bone formation in the form of syndesmophytes, which can lead to ankylosis. On the other hand, there is bone loss or a decrease in BMD, which can subsequently lead to osteoporosis and osteoporotic vertebral fractures (VFxs). Most VFxs are overlooked in this group of patients because (1) no trauma is needed for this type of fracture, and (2) AS patients already experience back pain. The pain, as well as the burden of the disease, increases with the development of VFxs. Unfortunately, the pathogenesis underlying the impaired bone metabolism in AS patients remains unclear.

As described in a number of systematic reviews, the proinflammatory cytokine TNFa is involved in inflammation and bone loss.(47, 166) These studies showed a positive effect of TNFa-inhibitor (TNFi) therapy on pain and inflammation and reported lower disease activity compared with placebo.

TNFi treatment also shows a positive effect with respect to BMD, both of the hip and lumbar spine. (1, 2) In half of these studies bone formation was confirmed; in the other half no significant changes were found between the patient group and the control group. (3-8) It should be noted, however, that the effect of TNFi on BMD has only been measured with a maximum follow-up duration of 3 years.

In addition to osteoporosis, which has a prevalence rate of between 9.5% and 40% in AS patients, (9-11) VFxs are a serious problem for this group. VFxs lead to pain and loss of function and may contribute to kyphosis, which has a major impact on the quality of life. Previous research has shown that AS patients are not only at a higher risk to develop VFxs, but also show a high prevalence rate of VFxs, which varies between 10% and 45%. (12-17) In healthy individuals, VFxs are mainly seen as a complication of osteoporosis in postmenopausal women.

The occurrence of VFxs in AS is associated with lower hip BMD, older age and a more advanced disease status, more spinal radiographic damage, and an unhealthy lifestyle. (18, 19) So far, only two studies have examined the long-term effect of TNFis on the incidence of VFxs. Van der Weijden and colleagues (3) and Maas et al. (4) studied the effect of TNFi treatment on the incidence of VFxs with a subsequent follow-up duration of 2 and 4 years. From these studies, it can be concluded that despite the treatment with TNFis, the prevalence of VFxs still increased.

Because of the high disease burden associated with the development of VFxs, possibly related to decreased BMD (and to confirm the aforementioned studies), better insight is needed into the effect of TNFis on the development of VFxs. In addition, available data on the effect of TNFis on VFxs are scarce and not sufficient for drawing solid conclusions. Therefore, our aim here was to determine the long-term effect of TNFis on BMD and the incidence of VFxs in AS patients in combination with the radiographic progression.

PARTICIPANTS AND METHODS

Study population

All AS patients were recruited from the Amsterdam Spondyloarthritis Cohort at the VU University Medical Center and Reade. AS patients were only included if they fulfilled the modified New York criteria (20) and needed treatment with TNFis according to the Assessment of Spondyloarthritis International Society (ASAS) guidelines. (21, 22) Patients started with TNFi treatment if they failed at least two different nonsteroidal anti-inflammatory drugs and if they had a high disease activity score (bath ankylosing spondylitis disease activity index (BASDAI) score was >4). Switching between different TNFis was allowed if continuity was guaranteed. Patients were selected based on the availability of DXA-scans and radiographs at baseline and after 4 years of follow-up. Another inclusion criterion was the availability of signed informed consent. The study was approved by the medical ethics committees of the VU University Medical Center and Slotervaart/Reade. Written informed consent according to the new Declaration of Helsinki was obtained from all participants before inclusion in the study. The starting date of TNFi treatment varied from March 2003 to August 2014. No distinction was made between the different types of TNFis. Only TNFi-naive patients were included at baseline.

Data collection

At baseline, demographic characteristics were ascertained, such as sex, age, and ethnicity, and disease-related variables were obtained, such as disease duration, symptom duration, age of diagnosis, HLA-B27 status, infection parameters (C-reactive protein, erythrocyte sedimentation rate), disease activity scale scores (bath ankylosing spondylitis metrology index, BASDAI, bath ankylosing spondylitis functional index, ankylosing spondylitis disease activity score), and relevant comorbidities. Peripheral joint involvement was classified as peripheral arthritis and/or enthesitis. In addition, risk factors for osteoporosis were attained, such as comedication (bisphosphonates and corticosteroids), BMI, smoking, and alcohol use. Alcohol use was categorized according to the Dutch National Research Institute for Public Health and Environment (Rijksinstituut voor Volksgezondsheid en Mileu)(184) guidelines quantified per day (ie, in mild use:<one glass; moderate use: one to three glasses for men, one to two glasses for

women; heavy use: ≥three glasses for men, ≥two glasses for women). Menopause status was not included because it was not documented; it was also difficult to determine a cut-off value based on age. Current use of medication was also listed, including drugs that could influence BMD, such as antiosteoporotic drugs and corticosteroids. All data were collected at each follow-up visit every 3 months during the first year and from then on twice yearly.

BMD measurement

BMD was assessed in both the lumbar spine and the hip, defined as total proximal femur. These were assessed at baseline and at 4-year follow-up. In cases of total hip replacement or spondylodesis, patients were excluded if no sufficient data were available. BMD was measured by means of a DXA. There were two different DXA scans used: at Reade, the Lunar expert DPX-IQ (Oldelft, Delft, The Netherlands) and at the VU University Medical Center, the Hologic Delphi (Hologic, Marlborough, MA, USA). Longitudinal follow-up was performed on the same machine. T-score results were categorized according to WHO osteoporosis criteria to compare the results obtained from the two different machines: normal BMD(T-score:≥-1), osteopenia (–2.5<T<–1.0), and osteoporosis (T-score ≤ -2.5). (24)

Radiographs

Vertebral fractures

Lateral radiographs of the thoracic and lumbar spine were assessed by two observers (WFL and KJB). Both observers scored the VFxs in reverse chronological order in sets per patient. Scoring had been done by using the standardized semiquantitative method described by Genant and colleagues (25) in which the anterior, middle, and posterior heights of vertebras Th4 to L4 were determined. Height loss was classified as grade 0 (no reduction), grade 1 (mild fracture and 20% to 25% vertebral height decrease), grade 2 (moderate fracture and 25% to 40% vertebral height decrease), and grade 3 (severe fracture and >40% vertebral height decrease). A VFx was defined as a reduction in vertebral height ≥20%. Increase in severity was indicated by how many fractures had a score of ≥2 based on the Genant score at baseline and at 4 years of TNFi treatment.

Radiological progression

For determining the radiological progression, the modified stoke ankylosing spondylitis spinal score (mSASSS; range, 0 to 72) was used. Three blinded observers (IvdH, JCvD, and MK) scored lateral radiographs of the cervical and lumbar spines in chronological order in sets per patient. The vertebras, C2 to Th1 and Th12 to the sacrum, were evaluated for the presence of erosions, sclerosis, and squaring (1 point), syndesmophytes (2 points), and complete bridging (3 points). In case of missing vertebral corners (VCs), we used the

method of Wanders and colleagues. (26) That is if more than three scoring sites were missing, the radiographs were excluded. If three or fewer sites were missing, the mean of the other scoring sites was used as a substitue for the missing sites. To monitor the progression of syndesmophytes, we collected the frequencies at each time point. A syndesmophyte was defined as a VC score of 2 and higher.

Statistical analysis

Normally distributed continuous variables were reported as the mean with SD. Skewed continuous variables were presented as the median with the interquartile range (IQR). Categorical variables were presented as frequencies or percentages. The longitudinal effect of BMD was analyzed by a first categorization of T-scores according to the WHO osteoporosis criteria, after which frequencies were determined and a McNemar test was used. For the analysis of VFxs, the McNemar test was also used. The locations of the VFxs were presented in frequencies and percentages. Radiological damage (mSASSS) was analyzed by means of a paired t test (normally distributed) or nonparametric Wilcoxon signed-rank test (skewed). The interobserver variability of the mSASSS was analyzed by means of the intraclass correlation coefficient (ICC). For all analyses, the IBM SPSS statistics program version 22 (IBM, Armonk, NY, USA) was used.

RESULTS

Patient characteristics

In total, 135 AS patients were included and followed after starting with TNFi treatment, with a mean follow-up duration of 4.5 years. Because of missing data, we analyzed complete datasets (Figure 1). Demographic and clinical features were, for each dataset, comparable with the population at baseline (n=135; Table 1). Most of the patients (70%) were men with a mean age of 42.8 years and mean disease duration of 11.9 years.

Bone mineral density

At baseline, all 135 patients completed a DXA of the lumbar spine; 133 patients completed a DXA of the hip, of whom 5 patients had a bilateral total hip replacement. Four years after the start of TNFi treatment, 107 patients had a complete follow-up DXA. At baseline, 31.8% of the patients had osteopenia and 8.4% had osteoporosis in the spine (Table 2). At the hip, 36.4% of the patients had osteopenia and 3.7% had osteoporosis; 26 patients (26.0%) had decreased BMD of the hip and lumbar spine.

At follow-up, a significant decrease in the number of patients with low BMD of the lumbar spine was found, from 40.2% to 25.3% ($p<0.001$), as well as in the number of patients with low BMD of the hip, from 40.1% to 31.8% ($p=0.03$).

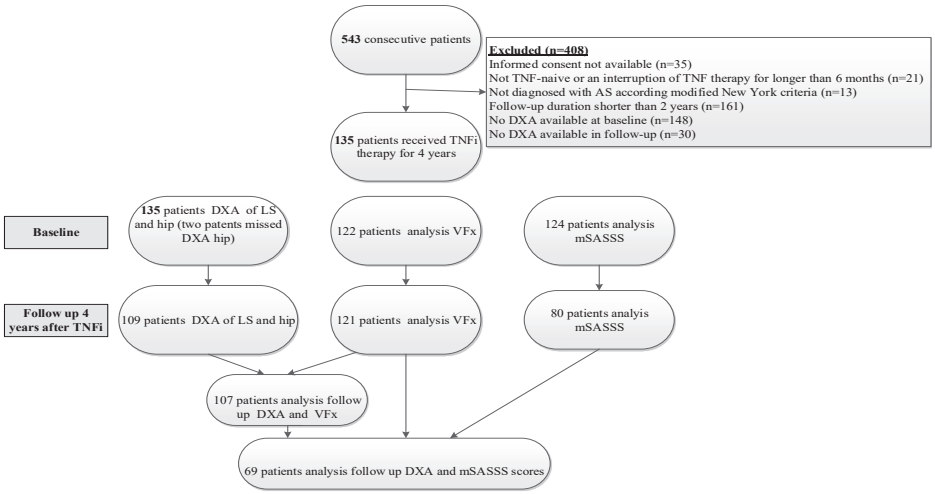

Figure 1. Flowchart of analyzed patients from the Amsterdam Spondyloarthritis Cohort. TNFi=TNF inhibitor; mSASSS=modified stoke ankylosing

Table 1. Baseline characteristics of AS-anti-TNF cohort (n=135)

Variables	Baseline	After 4 years of TNFis	p
Demographic variables			
Men, n (%)	95 (70.4)		
Age, years	42.8 (10.2)		
White, n (%)	109 (80.7)		
Disease-related variables			
Disease duration, years	11.9 (9.5)		
Symptom duration, years	16.5 (10.0-24.0)		
Age of diagnosis, years	32.0 (11.2)		
HLA-B27 positivity, n (%)	112 (83.0)		
BASMI, 0-10	3.6 (2.2)		
BASDAI, 0-10	5.4 (1.7)	3.3 (2.3)	<0.001
ASDAS CRP	3.45 (0.94)	2.05 (0.98)	<0.001
ASDAS ESR	3.23 (0.87)	1.89 (0.83)	<0.001
CRP, <10 mg/l	7.0 (2.5-26.0)	2.5 (1.9-5.5)	<0.001
ESR, <20 mm/hour	15.0 (6.0-32.5)	7.0 (2.0-17.0)	<0.001
Radiographic variables			
BMD lumbar spine	1.11 (0.20)		
BMD total proximal femur	0.93 (0.14)		

Table 1. (Continued)

Variables	Baseline	After 4 years of TNFis	p
T-score lumbar spine	−0.58 (1.5)		
T-score total proximal femur	−0.82 (1.0)		
Z-score lumber spine	−0.44 (1.4)		
Z-score total proximal femur	−0.59 (0.99)		
mSASSS	4.8 (1.6-22.2)		
BMD-related variables			
BMI, kg/m^2	25.5 (4.1)		
Smoking, n (%)	52 (39.1)		
Alcohol use, n (%)			
Non consumer	49 (36.3)		
Mild consumer	46 (34.1)		
Moderate consumer	20 (14.8)		
Heavy consumer	10 (7.4)		
Medication			
Etanercept, n (%)	107 (79.3)		
Adalimumab, n (%)	21 (15.6)		
Infliximab, n (%)	7 (5.2)		
NSAIDs, n (%)	108 (80.0)		
DMARDs, n (%)	11 (8.1)		
Corticosteroids, n (%)	7 (5.2)	1 (0.7)	
Bisphosphonates, n (%)	5 (3.7)	1 (0.7)	
Vit D/Calcium, n (%)	20 (14.8)	12 (8.9)	

Values are presented as number of patients (%), mean (SD) or median (interquartile range). TNFis=TNF inhibitors; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; BASMI=bath AS metrology index; BASDAI=bath AS disease activity index; ASDAS=AS disease activity score; IBD=inflammatory bowel disease; NSAID=nonsteroidal anti-inflammatory drug; DMARD=disease modifying antirheumatic drug.

Table 2. Bone Mineral Density measurement (Group A) at lumbar spine and hip

	Baseline[a,c] n=107 (%)	**After 4 years of TNFi[b,d] n=107 (%)**	**P values**
Low BMD LS	43 (40.2)	27 (25.3)	< 0.001
Osteopenia	34 (31.8)	25 (23.4)	
Osteoporosis	9 (8.4)	2 (1.9)	
Low BMD H	43 (40.1)	34 (31.8)	0.03
Osteopenia	39 (36.4)	31 (29.0)	
Osteoporosis	4 (3.7)	3 (2.8)	

Normal BMD=T-score:≥–1; osteopenia=–2.5<T<–1.0; osteoporosis=T-score≤–2.5.
LS=lumbar spine; H=hip; TNFis=TNF inhibitors.
[a]1 patient with spondylodesis; 4 patients with a total hip replacement.
[b]2 patients with spondylodesis; 5 patients with a total hip replacement.
[c]5 (4.7%) patients used a bisphosphonate.
[d]1 (0.9%) patient used a bisphosphonate.

In Table 3, results showing a significant increase in BMD (g/cm2) at the hip and the lumbar spine (p<0.001) are given. Disease activity (BASDAI), smoking, and use of alcohol were assessed as possible risk factors for lower BMD, but were found to not influence the outcome significantly; however, a high BMI (classified as ≥25 kg/m2) correlated with normal BMD at the hip and lumbar spine.

Table 3. BMD Values and Changes in BMD Between Baseline and During Follow-Up

			Bone increase	
BMD	**Baseline**	**After 4 years of TNFis**	**Absolute (p)**	**% of baseline**
Lumbar spine	1.11 (0.20)	1.11 (0.20)	0.08 (<0.001)	7.2
Total proximal femur	0.93 (0.14)	0.95 (0.13)	0.02 (<0.001)	2.2

Data are presented as mean (SD) unless stated otherwise. BMD values are presented as g/cm2. TNFis=TNF inhibitors

Vertebral fractures

After 4 years of TNFi therapy, 121 patients had a complete dataset on VFxs. The mean age of these patients was 48.0 years and 76.9% were men, which was comparable with the baseline group. Eighteen of the 84 men (21.4%) had a VFx after 4 years of TNFi therapy in comparison with 6 of the 37 (16.2%) women.

Most of the VFxs were located in the thoracic spine (Figure 2). At baseline, 3 VFxs (of 15; 20%) had a score of grade 2 or more; after 4 years of TNFi, 7 VFxs (of 29; 24.1%) had a

score of at least grade 2. At baseline, 4 of 13 (30.8%) patients with a VFx had low BMD of the lumbar spine and hip. At follow-up respectively, 4 of 21 (19.0%) patients and 5 of 21 (23.8%) patients with a VFx had a low BMD (Table 4).

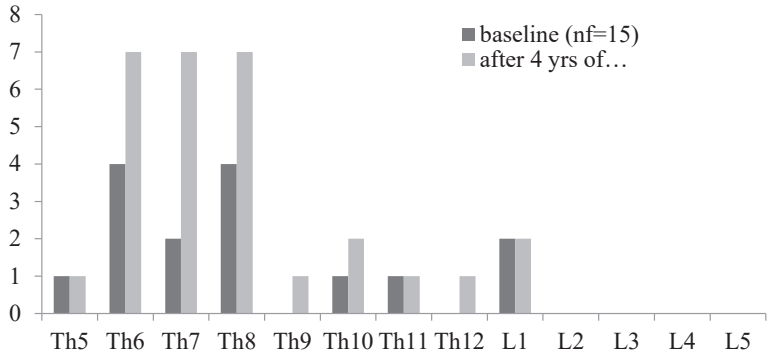

Figure 2. Location of vertebral fractures before and after TNFi treatment in patients with AS (n=121)
TNFi: TNF inhibitors; nf= number of fractures

Table 4. Number (%) of AS patients (n=107) with a VFx and Bone Mineral Density at hip and lumbar spine

	Baseline	**After 4 yrs of TNFi**
Patients with a VFx (n)	**13**	**21**
Low BMD; n (%)	H: 4 (30.8)	H: 5 (23.8)
	LS: 4 (30.8)	LS: 4 (19.0)
Normal BMD; n (%)	H: 8[a] (61.5)	H: 15[a] (71.4)
	LS: 9 (69.2)	LS: 16[b](76.2)

Normal BMD=T-score≥–1, osteopenia¼–2.5< T< –1.0; osteoporosis =T-score≤–2.5. AS¼ankylosing spondylitis; VFx=vertebral fracture;
LS=lumbar spine; H¼hip; TNFis=TNF inhibitors.
[a]1 patient had a total hip prothesis.
[b]1 patient had a spondylodesis

At baseline, the prevalence of patients with a VFx was 11.1% (15 of 131 patients), which means that 15 patients had at least one VFx, which increased to 19.3% (26 of 124 patients) at follow-up. The incidence of patients with a VFx was 0.02 or 2.0 events per 100 patients per year. The cumulative incidence at 4 years of TNFi treatment was 0.11.

Radiological progression

Data on radiological progression were available on 80 patients.ICCs were calculated between 0.85 and 0.99. The median significantly increased to 6.5 (2.1 to 22.9) after 4 years of TNFi treatment (p<0.001). This was a median increase of 2.5 mSASSS points in 4 years.

Comparison of mSASSS of patients with and without VFxs (n=69) showed that patients with VFxs had a significantly higher median mSASSS compared with patients without VFxs (Table 5).

Table 5. Radiological Progression (mSASSS) Categorized for Patients With or Without VFxs (n=69)

	Mean mSASSS (baseline)	Mean mSASSS (at 4 years)	P values
Patients with VFx	n=8	n=10	
	19.8 (0.6-49.7)	29.5 (5.9-56.6)	0.8
Patients without VFx	n=60[a]	n=58[a]	
	4.0 (1.5-15.4)	6.5 (2.0-21.1)	<0.001

Values for radiological progression presented in median and interquartile range. p values are based on a comparison between baseline and after 4 years of TNFi treatment with TNF inhibitors.
mSASSS¼modified stoke ankylosing spondylitis spinal score; VFxs= vertebral fractures.
[a]1 patient had a spondylodesis.

Table 6 shows the median mSASSS categorized for patients with normal and low BMD at the lumbar spine and hip. All median mSASSS increased in patients with both normal (p<0.001) and low BMD (p=0.09 and p=0.03, respectively) after 4 years of TNFi treatment. The number of syndesmophytes increased in every group over time. Increase in syndesmophyte formation was not related to BMDbecause patients with low and high BMD showed the same pattern. All X-rays of the lumbar spine of these patients were checked, but we could not find an association between lumbar syndesmophyte formation/ankylosis and (high) BMD of the spine.

Table 7 shows the number of patients who developed new syndesmophytes after 4 years of TNFi treatment per location. The total increase of patients with syndesmophytes was significant (p=0.004).

Table 6. Radiological Progression (mSASSS) Categorized for Patients (n¼469) With a Low and Normal BMD at Lumbar Spine and Hip and Number of Patients With Syndesmophytes in the Different Groups

	Mean mSASSS (baseline)	Mean mSASSS (at 4 years)	p-values	Number of patients with syndesmophytes (%) (baseline)	Number of patients with syndesmophytes (%) (at 4 years)
Low BMD (LS)	n=28	n=21	0.09	13 (46.4)	15 (71.4)
				CS: 3 (10.7)	CS: 6 (28.6)
	6.8 (1.8-21.4)	7.5 (3.5-26.8)		LS: 3 (10.7)	LS: 4 (19.0)
				Both: 7 (25)	Both: 5 (23.8)
Low BMD (H)	n=25	n=19	0.03	11 (44.0)	10 (52.6)
				CS: 2 (8.0)	CS: 4 (21.1)
	6.0 (2.0-21.7)	7.5 (3.0-27.5)		LS: 2 (8.0)	LS: 1 (5.3)
				Both: 7 (28.0)	Both: 5 (26.3)
Normal BMD (LS)	n=40[b]	n=47[a]	<0.001	14 (35.0)	21 (44.7)
				CS: 5 (12.5)	CS: 7 (14.9)
	3.3 (1.5-16.0)	6.5 (2.0-22.5)		LS: 3 (7.5)	LS: 4 (8.5)
				Both: 6 (15)	Both: 10 (21.3)
Normal BMD (H)	n=42	n=47[c]	<0.001	16 (38.1)	25 (53.2)
				CS: 6 (14.3)	CS: 9 (19.1)
	3.3 (1.5-16.0)	7.0 (2.0-22.5)		LS: 5 (11.9)	LS: 7 (14.9)
				Both: 5 (11.9)	Both: 9 (19.1)

Values for radiological progression presented in median and interquartile range. p values are based on a comparison between baseline and after 4 years of TNFi treatment. Normal BMD=(T-score:≥–1; osteopenia=–2.5<T<–1.0; osteoporosis=T-score≤–2.5.
mSASSS=modified stoke ankylosing spondylitis spinal score; CS= cervical spine; LS= lumbar spine; H= hip.
[a]1 patient had a spondylodesis.
[b]2 patients had a total hip prosthesis.
[c]3 patients had a total hip prosthesis.

Table 7. Number (%) of Patients With a Prevalent or New Syndesmophyte(s) per Location

Location	Baseline n=69	After 4 yrs of TNFi n=69	p
Total	28 (40.6)	37 (53.6)	0.004
Cervical Spine	8 (11.6)	13 (18.8)	
Lumbar Spine	7 (10.1)	9 (13.0)	
Both	13 (18.8)	15 (21.7)	

TNFis=TNF inhibitors

DISCUSSION

This prospective cohort study of AS patients treated with TNFis for 4 years showed a significant increase in BMD of the hip (p=0.03), as well as a decrease in disease activity. However, there was also a rise in the number of patients with a VFx, a higher severity rate of fractures, and a significant progression of radiological damage. These findings show a contradiction, with improvement of BMD, but a worsening of bone processes, indicated by an increase of fractures and in radiographic progression.

The improvement of BMD during TNFi treatment is in accordance with previous studies that have shown that bone loss is associated with inflammation.(9) TNF is not only decrease inflammation, but also reduce osteoporosis. The increase in the number of patients with normal BMD of 2.2% and 7.2% at the hip and lumbar spine, respectively, after TNFis is in accordance with previous studies, which show an increase of 1.8% and 6.8% in BMD, respectively, at the hip and lumbar spine. (3-8) It should be noted that the increase in BMD of the lumbar spine is higher in comparison with the increase in hip BMD, which might be attributed to additional bone formation by the development of syndesmophytes. However, in our study we did not find a difference in mSASSS between patients with normal and low BMD. The prevalence of syndesmophytes in patients with normal BMD was not higher in comparison with patients with low BMD, which makes a false-positive improvement in BMD based on the development of syndesmophytes unlikely.

Interestingly, despite the improvement in BMD, the number of VFxs and the severity of osteoporotic fractures increased. This observation is in accordance with two previous studies. Van der Weijden and colleagues (3) (n=49) showed that 12.2% of the AS patients had a VFx at baseline that increased to 30.6% of the patients after 2 years of etanercept treatment. In a study by Maas et al. (4) (n=105), 26% of the AS patients had a VFx at baseline, which increased over 4 years of TNFis with 20%. At baseline and follow-up, we found a lower percentage of VFxs compared with the aforementioned studies. We observed a VFx prevalence of 11.1% at baseline and 19.3% after 4 years of TNFi treatment. This difference can be explained by the difference in baseline disease activity, disease duration, smoking, a higher BMI, and lower BMD. (18, 19) However, the number of patients with VFxs in our study was too small to find a correlation with most of these risk factors. Interestingly, only a minority of the patients with a VFx had decreased BMD, and more than half of the patients with a VFx had normal BMD. The relationship between low BMD and the risk for VFxs remains unclear, but VFxs are common in the pathophysiology of osteoporosis. (13-18) The high prevalence of osteopenia/osteoporosis and VFx in relatively young, predominantly male AS patients is unexpected because these

manifestations usually occur in postmenopausal, older women. In the absence of an age- and sex-matched healthy control population to compare the prevalence of VFx in young males (mean age in our study was 42 years), we compared our data with more general studies. Lotters and colleagues (27) reported a prevalence of 8.9% spinal osteoporotic fractures in 1984 patients older than 50 years (529 male and 1455 female). In comparison, the prevalence in our study was much higher: 19.3% spinal fractures in 124 patients despite TNFis. The reason for the high prevalence of VFxs in our study can be explained by the high burden of inflammation during the long disease duration that might have induced an irreversible osteoporotic process before the start of TNFis. This is in accordance with our finding that patients with VFxs have higher radiographic scores (mSASSS) compared with patients without VFxs. The finding that patients still have VFxs despite the fact that BMD is improving and patients still develop syndesmophytes under TNFi treatment is contradictory. A possible explanation for this finding would be that in patients with VFxs, bone formation does occur, but is not of normal bone quality. This makes patients more susceptible to developing VFxs despite the restoration of bone. It could be that an earlier start of TNFi treatment may prevent the onset of decreased BMD and the occurrence of VFxs. Despite the positive effect of TNFis on both disease activity and BMD, the question remains as to whether TNFis can be combined with bisphosphonates to prevent the onset of VFxs. Viapiana and colleagues (28) showed a significant increase in lumbar spine BMD after 6 months of neridronate intravenously administered in comparison with infliximab. The long-term effects of bisphosphonates on increased bone formation of the spine, with the onset of new syndesmophytes, for instance, have not yet been studied.

The long disease duration in our patients (11.1 years) might also explain the high mSASSS at the start of the study, which predict an increase in radiological progression (mSASSS) despite treatment with TNFis. (29) Haroon and colleagues (30) showed that TNFi treatment only reduced radiographic progression when patients start therapy early, within 10 years after diagnosis, and continue their treatment for a longer time, but did not reduce radiographic progression in patients with a longer disease duration.

Our study is one of the first to investigate the long-term effect of TNFis on bone in AS patients,(167, 168) and confirms the results of Maas et al. (4) It is important to note that VFxs are often missed in daily clinical practice because X-rays of the thoracic spine are usually not performed because radiological progression (mSASSS) is only based on radiographs of the cervical and lumbar spines. We have demonstrated that most VFxs occur in the thoracic spine, not at the cervical and lumbar level, so this is another reason why they might have been missed in other studies. In a chest X-ray, which is performed more often, VFxs of the thoracic spine can easily be overlooked because of the over

projection of the heart and lungs. Moreover, back pain, which is a common feature of a spinal fracture, is often missed in AS patients because most already suffer from back pain resulting from the disease itself. In addition, our study is one of the few studies in which thoracic spine X-rays were given prospectively and scored systematically for osteoporotic VFxs.

Despite the interesting results, our study had a few limitations. First, the amount of missing radiological data might be considered as high. However, this can be explained by the fact that we chose to exclude more than three missing VCs from the radiographs. This occurred often in radiographs of the high cervical spine. In addition, when a patient has many radiological changes (high mSASSS), the treating practitioner does not expect any new changes and does not order cervical and lumbar spine X-rays. Second, this was prospective cohort study and no healthy, age- and sex-matched control group was available. It is important to note that in comparison with the prevalence of 8.9% osteoporotic VFxs in healthy, male controls at an age above 50 years, the prevalence of VFxs (19.3%) in our group of relatively young male AS patients (mean age of 42 years) was very high.

The results of our study have some clinical implications. In patients with AS who complain of (a different type of) back pain, osteoporotic fractures should be considered, despite the fact that the patient may be relatively young and male. In case of doubt, an X-ray of the thoracic spine is recommended as a diagnostic tool, as well as a DXA scan. A recommendation for future studies would be to replicate our results in larger groups of AS patients that would require systematic thoracic spine X-rays and scoring for osteoporotic fractures. In addition, the effects of TNFis on BMD and VFxs earlier in the disease should be examined and the role of bisphosphonates explored. Furthermore, other measurements of bone quality could be added, like the Trabecular Bone Score (TBS), which would provide data on bone microstructure. (31)

Overall, despite the improvement of BMD in the hip and the decrease in disease activity after TNFi treatment, we still found new VFxs, an increase in severity of VFxs, and radiographic progression during 4 years of treatment with TNFis in AS patients with long disease duration.We recommend the inclusion of thoracic spine Xrays in the follow-up procedures of AS patients to diagnose VFxs.

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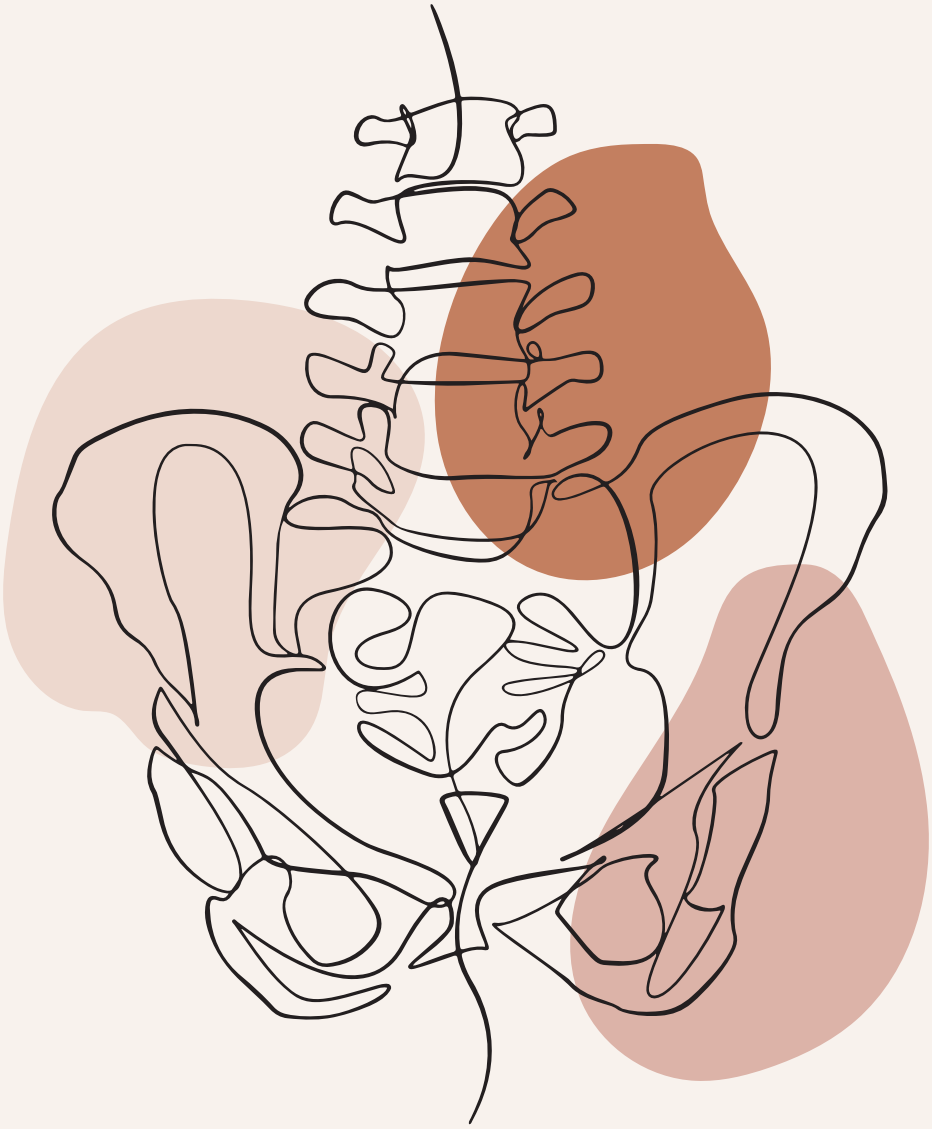
PART 2

EARLY DETECTION AND TREATMENT IN AXIAL SPONDYLOARTHRITIS



CHAPTER 6

PRESENCE OF ACTIVE MRI LESIONS IN PATIENTS SUSPECTED OF NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS WITH HIGH DISEASE ACTIVITY AND CHANCE AT CONVERSION AFTER A 6-MONTH FOLLOW-UP PERIOD

T. Rusman
M.L.B. John
M.A.C. van der Weijden
B.J.H. Boden
C.M.A. van der Bijl
S.T.G. Bruijnen
C.J. van der Laken
M.T. Nurmohamed
I.E. van der Horst-Bruinsma

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ABSTRACT

Objectives

The primary aim is to evaluate signs of inflammation on MRI of sacroiliac joints (SIJ)/spine in inflammatory back pain (IBP) patients suspected of nr-axSpA with high disease activity. Secondary aims are to describe the onset of new inflammatory lesions at MRI after 6 months and to evaluate gender differences in the presence of inflammation.

Method

Consecutively, patients with IBP with at least two spondyloarthritis features, high disease activity (BASDAI ≥ 4), and who were TNFi naïve, had a MRI of SIJ and spine. In the absence of active lesions, MRI was repeated after 6 months. MRI images were scored according to the Spondyloarthritis Research Consortium of Canada method.

Results

Sixty-nine patients were included (53% female), of whom 39% showed signs of inflammation at the first MRI: 30.9% of the SIJ, 19.1% of the spine and 2.4% at both sites, irrespective of the CRP levels. Males more often showed inflammatory signs at the MRI of the SIJ and spine compared with females (45.5% vs. 33.3%). Consistently, the median SPARCC score was higher in males: for SIJ 14.0 (IQR 2.3–25.0) and for spine 11.5 (IQR 8.5–25.6). Only one patient (4.7%) without baseline inflammatory signs showed active lesions of SIJ after 6 months.

Conclusions

Almost 40% of the IBP patients suspected of nr-axSpA, with high disease activity, showed inflammatory lesions on MRI of SIJ and/or spine, which occurred more often in males compared with females. In the majority (95.3%), an MRI without inflammatory lesions remained negative after 6 months despite high disease activity.

INTRODUCTION

According to "Assessment of Spondyloarthritis International Society (ASAS) classification criteria" (1), axial spondyloarthritis (axSpA) can be divided into two groups: patients with radiographic signs of sacroiliitis (ankylosing spondylitis, AS) and a group without radiographic sacroiliitis, the non-radiographic axial SpA (nr-axSpA) (1). Inflammatory back pain (IBP) is an important clinical symptom for axial involvement and is present in approximately 70% of patients diagnosed with axSpA (1, 2). Radiographic lesions usually develop several years after symptom onset, such as IBP, which can lead to a diagnostic delay of 5–10 years (3). This may result in subsequent undesired treatment delay, in particular in patients with nr-axSpA (3). A recent study revealed that approximately 5.1% of patients progress from nr-axSpA to AS in a 5-year period, especially in patients positive for the HLA-B27 antigen (3, 4). Active inflammatory lesions of the sacroiliac joints (SIJ), as defined by the ASAS group (1), contribute to an earlier diagnosis of axial SpA.

One of the challenges of the current ASAS classification criteria of axial SpA is the large contribution of a positive MRI of the SI joints. However, many patients with high disease activity do not show active lesions at the MRI of the SI joints; approximately 59–64% is MRI-negative (4, 5). Therefore, we selected patients with inflammatory back pain with at least two SpA features, who might be prone to develop axial SpA, and repeated the MRI procedure after 6 months in case of a negative MRI (absence of active inflammation). In order to increase the chance of a positive MRI, all patients had to have a high disease activity score and should be eligible for treatment with a biological, which is in contrast with previous studies. A previous study showed an association between male gender and the chance at a positive MRI in IBP patients, but data on gender differences are scarce (4).

Therefore, the primary aim of this study was to analyse the frequency of positive MRIs (both SIJ and spine) in IBP patients suspected of nr-axSpA with high disease activity. The secondary aims were to describe the progression of a negative MRI outcome at baseline after a 6-month follow-up, to describe the possible presence of structural lesions and to assess gender differences.

MATERIALS AND METHODS

Patients

Patients with chronic back pain were recruited from 2009 to 2014 at the rheumatology outpatient clinics of the VU University Medical Center (VUmc), Reade/the Jan van Breemen Research Institute in Amsterdam, the Netherlands, and by the website of the Dutch ankylosing spondylitis patient society ("Dutch axial spondyloarthritis foundation").

The study complied with the Declaration of Helsinki and was approved by our local ethical committee of the VU University Medical Center (approval number medical ethical committee 2009/206), and all patients signed an informed consent before screening.

Inclusion criteria

Patients were eligible if they were ≥ 18 years, fulfilled the Calin criteria of inflammatory back pain (195), (IBP, back pain with an insidious onset before the age of 45 years, chronic back pain persistence for at least 3 months, morning stiffness, improvement with exercise, pain at night). In addition, patients had to have at least two spondyloarthritis (SpA) features according to the ASAS axial SpA classification criteria. They had to be either HLA-B27 positive with at least ≥ 1 spondyloarthritis (SpA) feature or HLA-B27 negative with at least ≥ 2 SpA features.

SpA features were defined according to the European Spondyloarthropathy Study Group (ESSG) criteria: asymmetrical arthritis, alternating buttock pain, dactylitis, enthesitis of the Achilles tendon or the plantar fascia, presence or history of psoriasis, inflammatory bowel disease (IBD) or acute anterior uveitis (AAU), first- or second-degree relatives with AS/psoriasis/AAU/IBD, positive response to non-steroidal anti-inflammatory drugs (NSAIDs) and raised acute phase reactants, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (1).

In addition, they should be eligible to treatment with a biological with a high disease activity score (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4) and insufficient response to at least two NSAIDs (Figure 1).

Exclusion criteria

Patients were excluded if they had definite AS according to the modified New York criteria (7), had received biological treatment or showed contraindications for treatment with a biological (Figure 1).

Rationale inclusion and exclusion criteria

Inclusion criteria for this study were based on the algorithm of Rudwaleit et al. which had a high probability to diagnose AS early at the pre-radiographic stage in patients presenting with chronic back pain (8). IBP was indicated as a primary entry parameter for the assessment of patients with chronic back pain, since IBP is the key symptom of axial involvement. They calculated that a probability of at least 90% can be achieved if IBP plus two to three other features was present (9).

Data collection

The following patient characteristics were collected: age, sex, age onset of back pain, duration of back pain at baseline, IBP and SpA features, family history of SpA and presence of extra-articular manifestations (EAM), such as uveitis, inflammatory bowel disease (IBD) and psoriasis, and data on the use of NSAIDs were recorded. In addition, several disease activity–related scores were recorded: BASDAI, Bath Ankylosing Spondylitis Metrology Index (BASMI), tender (TJC) and swollen (SJC) joint count and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

All patients were screened by a clinician and tested for the human leukocyte antigen B27 (HLA-B27) if not previously determined, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels. At baseline, MRI scans of the SIJ and spine were made. Patients without signs of inflammation at baseline MRI ("negative spine and SIJ MRI") were invited for a second MRI after 6 months. Not all patients with a negative MRI had a second MRI because some patients refused or had already started with a biological due to high disease activity (N = 18).

MRI SIJ and spine

Imaging was performed using a Siemens MAGNETRON Sonata 1.5-T MRI device (Siemens Medical Solutions, Erlangen, Germany). T1-weighted sequences before administration of intravenous contrast (gadolinium) T1- weighted with fat suppression after intravenous contrast and short τ inversion recovery (STIR) images of the SIJ and spine were performed according to a standardized protocol in accordance with the recommendations of the European Skeletal Society of Radiology (ESSR). A detailed description of this protocol can be found in a previous article of our research group (10).

As in some patients, MRI was performed recently in another hospital before presentation at our centre; imaging was not repeated but imported into our system and revised.

MRI images of the SIJ and spine were scored by an expert radiologist of the OLVG for the presence of bone marrow edema (BME) according to the Spondyloarthritis Research Consortium of Canada (SPARCC) score for the SIJ and spine (11, 12). In addition, active sacroiliitis was scored according to the ASAS guidelines (13).

Positive MRI

A positive MRI SIJ was defined as a SPARCC score ≥ 2 (200). A positive MRI of the spine was defined as a SPARCC score ≥ 5. A maximum SPARCC score for the SI joints was 72 (199) and for the spine, 108 (11).

Active sacroiliitis on MRI

Active sacroiliitis on MRI was defined as positive if a sacral inter-foraminal bone marrow signal of the SIJ (or increased signal) on a STIR image was present, which was categorized as 0, normal signal and 1, increased signal.

Structural changes

A descriptive analysis was performed for the presence of structural changes, such as fat infiltration in the bone marrow, bone erosions, bone spur and ankylosing. The location of these structural changes was also recorded systematically by the expert reader in the VUmc.

ASAS classification criteria

The ASAS classification criteria, consisting of the imaging arm and the clinical arm, were published after the development and start of this study. According to the ASAS classification criteria, in the clinical arm, two SpA features were required in addition to a positive HLA-B27 status. According to the ASAS classification criteria, HLA-B27-negative patients were classified as axial SpA if they met the imaging criteria and one SpA feature (7).

RESULTS

In total, 70 patients were included in this study (Figure 1), of whom 37 (53%) were female. The mean age at baseline was 34 years (Table 1). The first symptoms of back pain occurred at 4.7 years before diagnosis of IBP, at a mean age of 29 years. In total, 37 patients (53%) were HLA-B27 positive, of whom 18 were female (48.6%) and 19 were male (51.4%). In one female patient, HLA-B27 typing was not performed.

At baseline, peripheral joint symptoms were present in 31% of patients; 42.9% presented with enthesitis, mainly of the Achilles tendon, 7% experienced anterior uveitis and 11% had psoriasis. A positive family history of AS was present in 30% of the cases. Thirty-one percent had a raised CRP level (≥ 5.0 mg/l), and there was no significant difference in CRP between patients with a positive or negative MRI. The baseline characteristics did not show significant gender differences.

NSAIDs were used by half of the patients (52.9%) at baseline of whom 16 patients (59.3%) in the MRI-positive group and 20 patients (47.6%) in the MRI-negative group.

Unfortunately, in one patient, only MRI images of the spine were available and not of the SI joints because they were performed in another centre. So complete scoring sets of the MRI scans of the SIJ were available in 69 instead of 70 patients. Some of the patients refused MRI scans of the spine, mainly due to complaints of claustrophobia, resulting in

a lower number of patients with baseline MRI of the spine (n = 47) compared with MRI of the SIJ (n = 69).

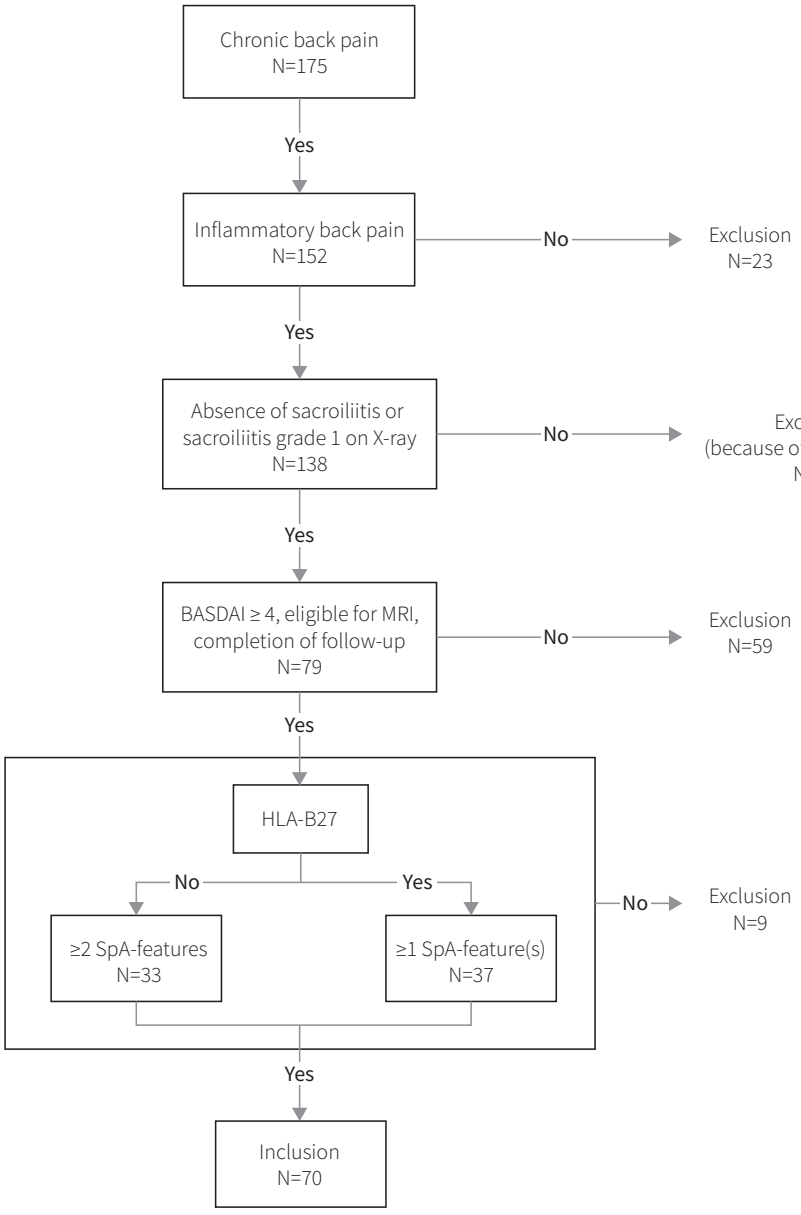

Figure 1. flowchart of the inclusions

AS, ankylosing spondylitis; HLA-B27, human leukocyte antigen B27; SpA, spondyloarthritis

Table 1. Patient characteristics of 70 non-radiographic axial SpA patients with high disease activity at baseline: comparison of positive and negative MRI SIJ and/or spine, stratified for sex

	Total (N = 70) M (n = 33)/F (n = 37)**	**Positive MRI (N = 27) M (n = 15)/F (n = 12)**	**Negative MRI (N = 42) M (n = 18)/F (n = 24**	***P* (95% CI)**
Demographics				
Male/Female (%)	47/ 53	55.6/44.4	18(42.9)/24(57.1)	0.3 (0.2;1.6)
Age (years)*	34 (8.6)	36.1 (8.1)	32.6 (8.8)	0.1 (-7.6;0.76)
	35.8(8.3)/32.1(8.7)	39.2(7.3)/32.3(7.6)¥	33.0(8.2)/32.4(9.4)	
Age onset back pain	29 (9)	30.9 (9.2)	27.4 (8.8)	0.1 (-8.0;1.1)
(years)*(N=68)	30.8(9.0)/26.8(8.8)	34.0(9.3)/27.5(8.1)	28.4(8.3)/26.7(9.4)	
Duration back pain	4.7 (4.3)	4.7 (4.5)	4.8 (4.3)	0.9 (-2.1;2.3)
(years)* (N=68)	4.3(3.6)/5.0(4.9)	4.9(3.9)/4.5(5.3)	3.9(3.5)/5.4(4.9)	
HLA-B27 positive (N=69)	36 (52.2)	13 (50.0)	13 (50.0)	0.7 (0.3;2.2)
	19(57.6)/18(50.0)	8(53.3)/5(45.5)	11(61.1)/12(50.0)	
NSAID use	37 (52.9)	16 (59.3)	20 (47.6)	0.3 (0.6;4.3)
	16(48.5)/21(56.8)	6(40.0)/10(83.3)¥	10(55.6)/10(41.7)	
SpA-features				
Number SpA-features*	3 (1.1)	3.0 (1.2)	3.0 (1.0)	1.0 (-0.5;0.6)
(mean)	2.9(0.9)/3.1(1.2)	2.9(0.9)/3.1(1.5)	2.9(1.0)/3.0(1.1)	
Arthritis	22 (31.4)	7 (25.9)	14 (33.3)	0.5 (0.2;2.0)
	10(30.3)/12(32.4)	5(33.3)/2(16.7)	5(27.8)/9(37.5)	
Alternating buttock pain	45 (64.3)	20 (74.1)	24 (57.1)	0.2 (0.7;6.2)
	18(54.5)/27(73.0)	10(66.7)/10(83.3)	8(44.4)/16(66.7)	
Dactylitis	5 (7.1)	2 (7.4)	3 (7.1)	1.0 (0.2;6.7)
	2(6.1)/3(8.1)	0/2(16.7)	2(11.1)/1(4.2)	
Thoracic pain (N=69)	45 (64.3)	16 (59.3)	29 (70.7)	0.3 (0.2;1.7)
	21(65.6)/24(64.9)	11(73.3)/5(41.7)	10(58.8)/19(79.2)	
Enthesitis	17 (24.2)	5 (18.5)	11 (26.2)	0.5 (0.2;2.1)
Achilles tendon	8(24.2)/9(24.3)	4(26.7)/1(8.3)	4(22.2)/7(29.2)	
Enthesitis	15 (21.4)	6 (22.2)	9 (21.4)	0.9 (0.3;3.4)
Plantar fascia	8(24.2)/7(18.9)	3(20.0)/3(25.0)	5(27.8)/4(16.7)	
Extra-articular symptoms				
Uveitis	5 (7.1)	2 (7.4)	3 (7.1)	1.0 (0.2;6.7)
	3(9.1)/2(5.4)	2(13.3)/0	1(5.6)/2(8.3)	
Inflammatory bowel	3 (4.3)	0	3 (7.1)	0.2 (0.9;1.0)
disease	2(6.1)/1(2.7)		2(11.1)/1(4.2)	
Psoriasis	8 (11.4)	5 (18.5)	3 (7.1)	0.2 (0.6;13.6)
	5(15.2)/3(8.1)	2(13.3)/3(25.0)	3(16.7)/0¥	
Enthesitis	29 (42.9)	10 (37.0)	19 (45.2)	0.5 (0.3;1.9)
	16(48.5)/13(37.8)	7(46.7)/3(25.0)	9(50.0)/10(41.7)	

Table 1. (Continued)

	Total (N = 70) M (n = 33)/F (n = 37)**	**Positive MRI (N = 27) M (n = 15)/F (n = 12)**	**Negative MRI (N = 42) M (n = 18)/F (n = 24**	***P* (95% CI)**
Family History				
Ankylosing Spondylitis	21 (30.0) 12(36.4)/9(24.3)	8 (29.6) 6(40.0)/2(16.7)	13 (31.0) 6(33.3)/7(29.2)	0.9 (0.3;2.7)
Psoriasis	12 (17.1) 3(9.1)/9(24.3)	5 (18.5) 1(6.7)/4(33.3)	7 (16.7) 2(11.1)/5(20.8)	0.8 (0.3;4.0)
Inflammatory bowel disease	6 (8.6) 1(3.0)/5(13.3)	2 (7.4) 1(6.7)/1(8.3)	4 (9.5) 0/4(16.7)	0.8 (0.1;4.5)
Uveitis	2 (2.9) 1(3.0)/1(2.7)	2 (5.6) 1(5.0)/1(6.3)	0	0.2 (1.0;1.1)
Other patient features				
BASDAI (N=61)*	5 (2) 4.8(2.0)/5.3(2.1)	4.9 (1.9) 4.4(1.8)/5.7(1.7)	5.3 (2.1) 5.1(2.1)/5.4(2.1)	0.5 (-0.7;1.4)
BASMI (N=48)*	1.8 (1.2) 1.8(1.3)/1.7(1.1)	1.7 (0.9) 1.8(1.0)/1.6(0.9)	1.8 (1.4) 1.8(1.5)/1.8(1.2)	0.9 (-0.7;0.7)
Schober (cm) (N=69)*	4.4 (1) 4.4(0.9)/4.4(0.9)	4.2 (0.9) 4.1(0.9)/4.3(1.1)	4.5 (0.9) 4.7(0.9)/4.4(0.9)	0.2 (-0.2;0.7)
SJC (N=68)*	0.2 (0.5) 0.3(0.2)/0.3(0.7)‡	0.2 (0.7) 0(0)/0.5(1.0)	0.1 (0.4) 0.06(0.2)/0.2(0.5)	0.5 (-0.4;0.2)
TJC (N=68)*	2 (4) 2.1(4.5)/1.8(3.2)	1.0 (2.2) 0.6(2.3)/1.6(0.9)	2.6 (4.5) 3.4(5.5)/2.0(3.7)	0.1 (-0.;3.2)
MASES (N=67)*	6.8 (7.4) 5.1(7.4)/8.3(7.2)	3.8 (4.3) 2.2(3.3)/5.8(4.8)¥	9.1 (8.4) 7.7(9.0)/10.1(7.9)	0.001 (2.1;8.4)¥
ESR (mm/hr) (N=67)*	10.7 (10) 7.2(9.4)/13.6(9.6)	11.1 (10.9) 8.8(12.1)/13.8(9.2)	10.3 (9.5) 5.8(6.4)/13.5(10.2)¥	0.8 (-5.8;4.3)
CRP (mg/L) (N=66)*	3.7 (5.5) 2.6(4.6)/4.6(6.1)	4.0 (6.0) 3.1(5.6)/5.1(6.5)	3.6 (5.4) 2.2(3.5)/4.8(6.2)	0.8 (-3.2;2.5)
CRP (mg/L) elevated (%)	22 (31.4) 9(27.3)/13(35.1)	9 (39.1) 5(33.3)/4(33.3)	13 (27.7) 4 (22.2)/9(37.5)	0.9 (0.4;3.0)

If not stated otherwise, all displayed values are listed in whole numbers with matching percentages in brackets. Parameters labelled with * are listed as mean value with standard deviation in brackets. Positive MRI means inflammation on MRI SIJ and/or spine at baseline. Negative MRI means no inflammation on MRI SIJ and/or spine at baseline. For some variables, sample size deviates from the original 70 patients. For these variables, the actual sample size is stated in brackets after the variable name. ‡ indicate a significant difference of p<0.05. HLA-B27: Human Leukocyte Antigen (B27); NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; SpA: Spondyloarthritis; IBD: Inflammatory Bowel Disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; SJC: Swollen Joint Count; TJC: Tender Joint Count; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein. M=male; F=female. CI: Confidence Interval

MRI at baseline

Overall, in 27 of 69 patients (38.6%), signs of inflammation were found at baseline MRI of the SIJ or spine whereas 42 patients (60.0%) had a negative MRI of both SIJ and spine (Table 2). Twenty-one out of 69 patients (30.4%) had a positive MRI of the SIJ, 9 out of 47 (19.1%) of the spine, of whom three patients (2.4%) had both. Male patients had more frequently a positive baseline MRI compared with female patients, 15 out of 33 male patients (45.5%) vs. 12 out of 37 female patients (33.3%) (OR = 0.58, 95% CI (0.2; 1.5), p = 0.26) (Table 1). Imaging of the SIJ was repeated in 21 of the 41 patients who had a negative baseline MRI (51.2%), of whom only one patient conversed, showing new inflammatory signs at follow-up. Imaging of the spine was repeated in 15 out of 28 patients with a negative baseline MRI of the spine (53.6%), of whom none showed new lesions after 6 months.

SPARCC score

Patients with a positive MRI at baseline showed a median SPARCC score of the SIJ of 10.0 (IQR 4.0–25.0) and for the spine of 10.0 (IQR 7.0–16.0). Although not significant, male patients revealed a higher median SPARCC score of the SIJ and spine compared with females, 14.0 (IQR 2.3–25.0) vs. 10.0 (IQR 6.5–22.5) and 11.5 (IQR 8.5–25.6) vs. 8.0 (IQR 5.5–14.5), respectively (Table 2).

Comparison of MRI outcomes

Only a lower MASES score was significantly associated with a positive MRI outcome in logistic regression analyses (β = −0.02, 95% CI (− 0.04; − 0.01), p = 0.004) (Table 1). Adjustment for sex, NSAID use at baseline and HLA-B27 status made no difference in the found association.

Structural changes

Overall, 17 MRIs of the spine and SI joints showed structural changes in 14 patients (20%), of whom 11 patients were male. The majority of these patients (N = 11) showed a combination of inflammatory and structural lesions in both the spine and SIJ. The most frequently recorded structural change was fat infiltration in both the spine (5 patients) and SIJ (1 patient). One patient had fatty infiltration in both the spine and SIJ (global fat infiltration). In the spine, fatty infiltration was found at several places, such as antero-inferior endplates, anterior corner and postero-superior endplate ranged L3–S1. Two patients showed doubtful erosions in the lower ilium. In addition, Schmorl's nodes were seen in three patients located in the Th8–Th12 region of the spine.

Importantly, even in patients with a negative MRI (N = 3), several structural changes were noted. In two patients, fat infiltration was observed in the spine, whereas one patient showed Schmorl's nodes at the superior endplates of Th8 and Th11.

Sacroiliitis on MRI according to the ASAS criteria

Sacroiliitis on MRI was present in 21 patients, of whom 11 patients showed unilateral and 10 patients bilateral sacroiliitis. Although not significant, more male patients had sacroiliitis compared with females, 37.5% vs. 21.6%, respectively.

ASAS classification of axial SpA

Twenty-six patients did not fulfil the nr-axSpA criteria, although the clinical presentation was highly suspicious of axial SpA. Twenty-three patients (52.3%) only fulfilled the "clinical arm". In addition, 21 of the 44 patients (47.7%) fulfilled the "imaging arm" of the ASAS criteria, of whom 11 patients also fulfilled the criteria for the "clinical arm". More male patients fulfilled the ASAS criteria imaging arm compared with females, 39.4% vs. 27.0%.

DISCUSSION

In 69 patients with IBP and at least two SpA features and a high disease activity, 39% of patients showed signs of active inflammation (BME) according to the SPARCC score on MRI scans, primarily of the SI joints (88%) and a few of the spine. Only one patient conversed from a negative MRI at baseline to a positive MRI of the SI joints after 6 months, whereas no new lesions of the spine were detected after follow-up. Structural lesions, mainly of the spine, were present in 20% of the patients, most often in combination with signs of active inflammation, both in the spine and SIJ, but also in three patients without BME.

The number of positive MRIs is comparable with that in other study results in IBP patients, which showed prevalence between 26 and 41% (4, 5). The difference might be explained by the fact that our population had a high disease activity and shows results that are comparable with baseline data from clinical trials with biologicals, showing positive MRIs in 67%, 54% or 48% of the axial SpA patients (15-17) However, in the SPACE cohort, which included patients with chronic back pain (> 3 months, < 2 years and onset < 45 years), a positive MRI of the SIJ was found in only 25% of the patients (203), which is much lower compared with our findings (39%). This difference can be explained by the high disease activity on our group, the presence of more SpA features, the addition of the MRI spine, which was positive in 19% of the patients with negative SIJ images, and the use of gadolinium, an intravenous contrast that enhances the quality of the MRI. The use of intravenous contrast in MRI scans of the spine and SI joints is a method that was

used in the past. In selected cases, when high STIR signal in the joint is the only finding, gadolinium-enhanced images may help to confirm the presence of synovitis. However, in our study, this was not the case and the use of gadolinium for the axSpA images is abandoned nowadays.

The level of inflammation, measured with the SPARCC score, showed a mean score of 10.0 for the SI joints and 10.0 for the spine. Comparison with other studies in nraxSpA showed contradictory results. Two studies showed comparable results: 7.2 and 7.4 for SIJ and 7.2 for spine (19, 20), whereas two others showed lower SPARCC scores: SIJ 4.7 and 4.9 and spine 4.3 and 4.6, respectively (15, 21). There were no demographical features or baseline data (e.g. disease activity) that could explain the differences with our study results.

Only one patient (4.7%) with a negative MRI at baseline conversed to a positive MRI after 6 months. Other studies showed comparable numbers, 4–15%, of conversion of negative to positive MRIs (4, 18). These low numbers of conversion of a negative to a positive MRI after a short interval period indicate that it is not efficient to repeat a MRI within 6 months. These results were confirmed by the SPACE cohort, which indicated that repetition of MRI scans at 3 months and 1 year was not useful (22).

Assessment of gender differences revealed that male patients, in general, more frequently had a positive MRI compared with females, 45.5% vs. 33.3%, respectively. In addition, the majority of patients with structural lesions was male (11/14 = 78.6%), which corresponds to a study by Maksymowych (23). These results are in line with the limited studies available assessing gender differences and MRI findings in nr-axSpA patients, which indicate that male gender, especially in the case of HLA-B27 positivity, is a predictor for a positive MRI outcome (4). Assessment of gender differences in the SPARCC scores in our study revealed that male patients had a higher median SPARCC score of the SIJ and spine compared with females, 14.0 vs. 10.0 and 11.5 vs. 8.0, respectively. Consistently, male patients also showed more often sacroiliitis at MRI, according to the ASAS definition, compared with females, 37.5% vs. 21.6%.

The question remained if MRI of the spine had an additional value to the MRI of the SIJ. In our own study, the number of positive MRIs of the spine was almost 20%. In addition, only three patients presented with a positive MRI of both the spine and SIJ. These results might indicate an additional value for the MRI of the spine. However, these numbers are in contradiction with a couple of other studies that assessed the diagnostic value of MRI of the spine (24, 25). Weber et al. revealed that the combined MRI (spine and SIJ) seemed to increase the percentage of identifications of nraxSpA patients and also showed false positive results in an equal percentage in the control groups (non-specific back pain and

inflammatory back pain patients). These misclassifications neutralized the additional diagnostic value of combined MRI in patients with nr-axSpA and seemed to have no contribution to the diagnosis (24, 25).

Our study included a unique population of patients suspected of nr-axSpA with a high disease activity (BASDAI ≥ 4). For this reason, our results differ slightly from those of other studies conducted in a population that fulfilled the ASAS criteria. However, the numbers of specific SpA features were too small to assess them for possible associations with a positive or negative MRI. In this study, we have used the ESSG criteria and BASDAI instead of the ASAS classification criteria and ASDAS response, which we would have chosen nowadays. However, the study was developed in a period (2004) when these classification criteria and outcome parameters were much less often used as they currently are. In addition, as we mentioned in the "Introduction", the MRI images of the SI joints are one of the major criteria in the ASAS classification criteria, whereas the primary aim of our study was to find out how often these images were positive in cases with a high risk at axial SpA. Considering the current debate around the value of all separate classification parameters in axial SpA, the MRI results of a slightly different group of back pain patients might help in the discussion around the added value of MRI in this group from a different perspective.

This study has several limitations. Apart from the inclusion criteria and disease activity parameters, which differ from the currently used criteria, we had only one assessor of the MRIs, who performed the SPARCC scores, and all MRIs were also assessed by the musculoskeletal radiologist of the university medical centre. In addition, we have not repeated the MRIs in all patients after 6 months, but only in those who did not show inflammatory lesions at baseline. Another limitation is the lower number of patients who underwent the MRI of the spine compared with the SIJ because they refused to undergo this procedure. However, the number of images of the SIJ is high enough to draw conclusions on the presence of inflammation in this group with high disease activity.

In summary, the results of this study show that in this specific group of patients with inflammatory back pain, a high BASDAI score and those who are either HLA-B27 positive and have one additional SpA feature or HLA-B27 negative with two additional SpA features have a number of positive MRI results of the SI joints. All patients with a positive MRI were included in a placebo-controlled trial with etanercept (the PREVAS study) of which the results will be presented soon. In our opinion, the MRI of the spine is of limited value in addition to the MRI SIJ for the assessment of disease activity and repetition of theMRI after 6 months of the SI joints, in case of absence of inflammation, is not warranted either.

In conclusion, almost 40% of the patients with inflammatory back pain and high disease activity showed inflammatory lesions on MRI of the SIJ and/or spine, which occurred more often in males compared with females. In most cases (95.3%), a MRI without inflammatory lesions remained negative after 6 months, which suggests that a second MRI scan after only 6 months is not valuable.

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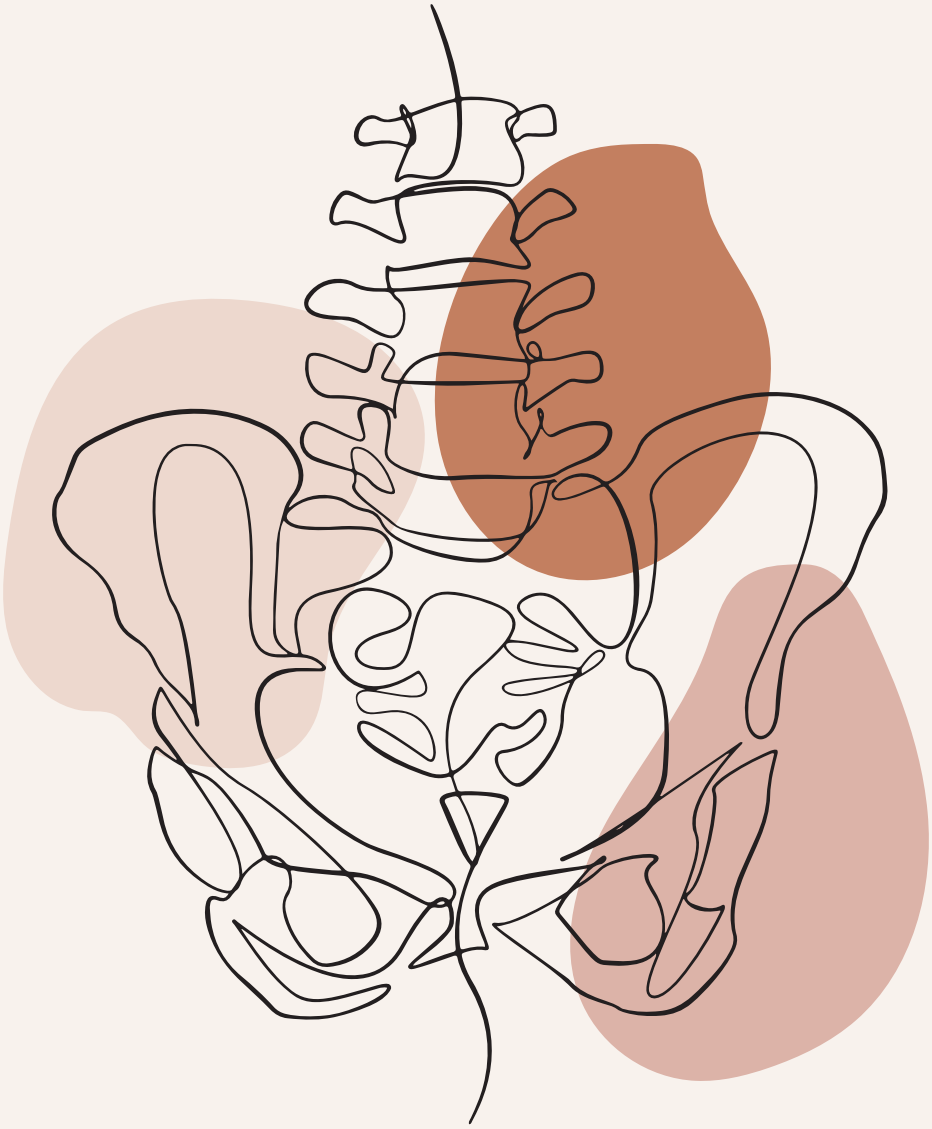

CHAPTER 7

IS TREATMENT IN PATIENTS SUSPECTED OF NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS EFFECTIVE? SIX MONTHS RESULTS OF A PLACEBO-CONTROLLED TRIAL

T. Rusman
M.A.C. van der Weijden
M.T. Nurmohamed
R.B.M. Landewé
J.J. de Winter
B.J.H. Boden
P.M. Bet
C.M.A. van der Bijl
C. van der Laken
I.E. van der Horst-Bruinsma

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ABSTRACT

Objective

To investigate the efficacy of 16-week treatment with etanercept (ETN) in patients with suspected nonradiographic axial spondyloarthritis (SpA).

Methods

Tumor necrosis factor inhibitor-naive patients with inflammatory back pain with at least 2 SpA features and high disease activity (Bath Ankylosing Spondylitis Disease Activity Index score ≥4), without the requirement of a positive finding on magnetic resonance imaging (MRI) of the sacroiliac (SI) joint and/or elevated C-reactive protein (CRP) level, were randomized (1:1) to receive ETN (n = 40) or placebo (n = 40) for 16 weeks and subsequently were followed up for a further 8 weeks (to 24 weeks from baseline) without study medication. The primary end point was the Assessment of SpondyloArthritis international Society 20 (ASAS20) response at 16 weeks. Secondary end points included the Ankylosing Spondylitis Disease Activity Score (ASDAS) and changes in disease parameters, including the Bath Ankylosing Spondylitis Metrology Index (BASMI), CRP level, erythrocyte sedimentation rate (ESR), and Spondyloarthritis Research Consortium of Canada index scores (MRI of the SI joint), after 16 and 24 weeks.

Results

Patient characteristics at baseline were comparable between the ETN and placebo groups. At 16 weeks, there was no significant difference in the percentage of patients exhibiting ASAS20 response between the ETN group (6 patients (16.7%)) and the placebo group (4 patients (11.1%)) (relative risk 0.7 (95% confidence interval 0.2-2.2), P = 0.5). Only the ESR showed more improvement in the ETN group compared to the placebo group at 16 weeks (decreases of 2.2 mm/hour and 1.4 mm/hour, respectively), but the difference did not reach statistical significance. Between 16 and 24 weeks, without study medication, the BASMI, CRP level, and ESR had worsened to a greater extent in the ETN group compared to the placebo group, with the difference being significant for the CRP level.

Conclusion

This study shows that in patients with suspected nonradiographic axial SpA with high disease activity but without the requirement of a positive finding on SI joint MRI and/or elevated CRP level, treatment with ETN is not effective.

INTRODUCTION

According to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria, axial spondyloarthritis (SpA) can be divided in 2 groups: patients with radiographic signs of sacroiliitis (radiographic axial SpA; ankylosing spondylitis (AS)) and patients without radiographic sacroiliitis (nonradiographic axial SpA) (1). Despite the availability of these classification criteria, there is still a lack of understanding of disease presentation and progression, especially in patients with nonradiographic axial SpA (2-5).

Inflammatory back pain is present in ~70% of patients diagnosed as having axial SpA, and therefore is an important clinical symptom of axial involvement (5, 6). An algorithm described by Rudwaleit et al showed a high probability that AS could be diagnosed at the preradiographic stage in patients with chronic back pain with inflammatory back pain as the primary presenting symptom (7). Based on this algorithm, the probability that the patient has AS is at least 90% if inflammatory back pain plus 2 or 3 other features are present (8).

Currently, the ASAS classification criteria are widely accepted for use in clinical practice, although they were developed for the purpose of classification for study eligibility and not for clinical diagnosis (1, 9-11). In order to classify axial SpA at an early stage of the disease, the ASAS classification criteria divide patients in 2 groups: patients who meet the "clinical arm" and patients who meet the "imaging arm." The "clinical arm" includes patients who are HLA–B27 positive and have 2 additional features of SpA, and the "imaging arm" includes patients with active inflammatory lesions of the sacroiliac (SI) joints as seen on magnetic resonance imaging (MRI) along with 1 additional feature of SpA (1, 10).

In many reported studies, a positive SI joint finding on MRI has been one of the prerequisites for starting tumor necrosis factor inhibitor (TNFi) treatment in patients with nonradiographic axial SpA. The other criteria for starting TNFi therapy in nonradiographic axial SpA are unsuccessful treatment with at least 2 different nonsteroidal antiinflammatory drugs (NSAIDs) and increased C-reactive (CRP) levels in the setting of negative MRI findings (12, 13). Increased CRP levels, however, were found in only 30% of patients with nonradiographic axial SpA (9, 14), and in 59–64% of patients with nonradiographic axial SpA with high disease activity, inflammatory lesions of the SI joint are not detected on MRI. A patient population selected based on the ASAS classification criteria may therefore be different from the population seen in daily clinical practice (6, 14).

In addition, in several studies MRI has shown false-positive results of bone marrow edema at the SI joint (not related to axial SpA disease). This is the case in ~23% of healthy individuals, 57% of postpartum women, and in recreational runners, professional athletes, and military recruits undergoing physical training. In all of these cases the MRI component of the ASAS classification criteria was fulfilled (15-17).

In most studies a higher rate of response to TNFi was observed in nonradiographic axial SpA patients who had elevated CRP levels and/or MRI-detected inflammatory lesions compared to patients without these factors (13, 18-20). Only 2 randomized clinical trials on the efficacy of TNFi included patients with nonradiographic axial SpA without the abovementioned requirements (21, 22), 1 of which did not include an objective scoring method for MRI-detected SI joint lesions (21). Both studies revealed a significant difference in response according to the ASAS criteria for 40% improvement (ASAS40) (23) between the placebo group (12.5–15%) and the treatment group (36–54.5%).

Data are lacking on the indications for biologic treatment in patients with suspected nonradiographic axial SpA who have low CRP levels and do not have active lesions seen on SI joint MRI. Therefore, a double blind, placebo-controlled clinical trial with the TNFi etanercept (ETN) was initiated. The primary aim of this proof-of-concept study was to assess the short-term efficacy of TNFi treatment, according to the ASAS20 response over 16 weeks, in patients with inflammatory back pain and suspected nonradiographic axial SpA with high disease activity, regardless of the CRP level or the presence of SI joint inflammation seen on MRI. “Disease activity” was used in this study as terminology by default, since there is no validation for the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (24) in this patient group (25); we actually investigated the “level of symptoms” at 16 and 24 weeks. Secondary aims were to investigate the number of AS Disease Activity Score (ASDAS) (26) responders after 16 weeks, change from baseline in mean disease status, and the proportion of patients with inflammatory lesions of the SI joints seen on MRI at 16 and 24 weeks.

PATIENTS AND METHODS

Study population

Patients with chronic back pain and a suspicion of nonradiographic axial SpA were recruited from November 11, 2009 through August 29, 2014 at the rheumatology outpatient clinics of the VU University Medical Center (VUMC) and Reade/Jan van Breemen Research Institute, and via the website of the Dutch AS patient society (Dutch Axial Spondyloarthritis Foundation). Patients were eligible for inclusion if they were at least 18 years of age and fulfilled the Calin criteria for inflammatory back pain (27).

Patients were enrolled based on the algorithm of Rudwaleit et al (7), with at least 2 SpA features according to the European Spondylarthropathy Study Group classification criteria (28) if HLA–B27 negative, and at least 1 SpA feature if B27 positive. In addition, patients had to have a high disease activity score (BASDAI ≥4) and insufficient response to at least 2 different NSAIDs. Patients were excluded if they had definite AS according to the modified New York criteria (29) or had received biologic treatment in the past (Table 1). Detailed descriptions of the inclusion and exclusion criteria have been published previously (30). Because of a slow enrollment rate in the first study period, adaptations of the inclusion criteria were made in the second half of 2011, allowing patients without inflammatory lesions seen on MRI to be included in the study. The study was approved by the local ethical review board, and all patients provided written informed consent prior to screening.

Table 1. PrevAS study inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
Age ≥18 years	Diagnosis of radiographic axial SpA/AS according to the modified New York criteria (29)
Inflammatory back pain meeting the Calin criteria (27)†	
HLA–B27 positive with ≥1 SpA feature *or* HLA–B27 negative with ≥2 SpA features (1)‡	Previous treatment with a biologic agent
High disease activity score (BASDAI ≥4)	Contraindications to treatment with a TNFi
Insufficient response to ≥2 different NSAIDs	

* PrevAS = Prevention of the Progression of Very Early Symptoms in Ankylosing Spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; TNFi = tumor necrosis factor inhibitor.
† Back pain with an insidious onset before the age of 45 years, chronic back pain persistence for at least 3 months, morning stiffness, improvement with exercise, pain at night.
‡ Spondyloarthritis (SpA) features include asymmetric arthritis, alternating buttock pain, dactylitis, enthesitis of the Achilles tendon or the plantar fascia, presence or history of psoriasis, inflammatory bowel disease (IBD), or acute anterior uveitis (AAU), first- or second-degree relative with ankylosing spondylitis (AS)/psoriasis/AAU/IBD, positive response to nonsteroidal antiinflammatory drugs (NSAIDs), and increased C-reactive protein level (≥10.0 mg/liter) or erythrocyte sedimentation rate (≥15 mm/hour).

Treatment allocation and methods

The Prevention of the Progression of Very Early Symptoms in Ankylosing Spondylitis study was a randomized, double blind, placebo-controlled trial performed at VUMC (EudraCT number 2009-015515-40). Patients were randomly assigned (1:1) to receive ETN (25 mg twice weekly) or placebo. After 16 weeks, patients were followed up without study treatment for up to 3 years. Radiographs were obtained at baseline and after 1 year and 3 years of follow-up (only baseline data provided in the present report).

The study drug ETN was supplied by Pfizer. Placebo ETN was developed and validated at the clinical pharmacology department of VUMC. The study medication was labeled at the VUMC central pharmacy and distributed to the VUMC outpatient pharmacy department for dispensing to study subjects. The pharmacist randomized the patients and provided the masked study medication to the study personnel. All investigators, including the study physician and research nurse, remained blinded with regard to the treatment until the last patient had completed the study. The study drug was self-administrated twice weekly with a subcutaneous injection that contained 25 mg of ETN or placebo. The normally distributed injections of ETN, in a dose of 50 mg administered once a week, were not feasible for this study because the placebo could only be produced in a 25-mg formulation.

Patients were allowed to continue taking analgesics, NSAIDs, disease-modifying antirheumatic drugs (DMARDs), and/or oral glucocorticoids (≤10 mg/day). The dosage had to be stable for 2 weeks prior to the baseline evaluation in the case of NSAIDs and oral glucocorticoids, and 4 weeks in the case of DMARDs; during the study, the dosage could be reduced or the treatment temporarily discontinued. Patients were allowed to receive intraarticular glucocorticoid injections. Treatment with any cytotoxic drugs, investigational drugs, or agents targeted at reducing TNF was not allowed during the first 16 weeks. All concomitant medication used during the study or changes in medication dosage were reported during each study visit.

Assessments

All study personnel and patients were blinded with regard to the randomization schedule and to treatment assignments until the last patient had completed the 3-year follow-up. In order to prevent influencing the study visit assessments (due to events caused by the medication such as injection site reactions), assessors who were not involved in the study performed the physical examinations and evaluated laboratory results.

Data collection

Demographic data were recorded, and disease-specific variables were assessed, including disease duration (duration of back pain at baseline), inflammatory back pain, SpA features, family history and presence of extraarticular manifestations such as uveitis, inflammatory bowel disease (IBD), and psoriasis, and use of concomitant medication (NSAIDs, DMARDs). Questionnaires on pain, overall well-being (Bath Ankylosing Spondylitis patient global score (31)), and quality of life (Short Form 36 health survey (32)) were administered during each visit. In addition, physical examinations were performed during each visit, including assessments to determine the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (33) and swollen and tender joint counts (of 44 joints).

Time on study treatment (ETN or placebo) and compliance were determined. Compliance was calculated based on the number of injections taken divided by the number of injections expected. Safety parameters, such as adverse events, were registered during the follow-up visits. Safety analyses included all patients who had received ≥1 dose of study treatment.

Clinical efficacy parameters

Clinical efficacy was assessed based on the numbers of patients who met the ASAS20/40 response criteria and the ASDAS using the C-reactive protein level (ASDAS-CRP) response criteria (with clinically important improvement defined as a decrease in the ASDAS-CRP to ≤1.1 and major improvement defined as a decrease in the ASDAS-CRP to ≤2.0) (34) and based on the frequency of low disease activity (ASDAS-CRP <2.1) and inactive disease status according to the ASDAS-CRP criteria (ASDAS-CRP <1.3). Efficacy was measured throughout the first 16 weeks of treatment and at 24 weeks, i.e., 8 weeks after study-related treatment was discontinued. Other clinical outcome parameters were the Bath AS Functional Index (35), the Bath AS Metrology Index (BASMI (35)), global pain, and measures of inflammation, i.e., CRP (median value and proportion of patients with values exceeding the upper limit of normal (10.0 mg/liter)) and erythrocyte sedimentation rate (ESR).

MRI outcome measures

MR images were independently assessed by 2 expert readers (RBML and JJHdW), who were blinded with regard to treatment, patient characteristics, and sequence of the different MRIs. Potential reader discrepancies were resolved by consultation with a third reviewer (BJHB).

SI joint MRIs were assessed according to the ASAS definition (37, 38). To quantify the extent of and evaluate the changes in active inflammation seen on SI joint MRI, the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI Indices for Assessment of Spinal and SI Joint Inflammation in AS (SPARCC scores) (39, 40) were used. A score of ≥2 was considered an indicator of SI joint inflammation shown on MRI. The mean score from the 2 independent readers (or 3 readers if a third observer was needed) was used. Minimally important change in the SI joints was defined as a change in the SPARCC score of ≥2.5 (40). Intraclass correlation coefficients (ICCs) were calculated for change scores and presented as scores for absolute agreement.

Statistical analysis

The primary outcome measure of this trial was the ASAS20 response. It was assumed that 50% of the patients treated with ETN (intervention group) and 20% of the patients treated with placebo (control group) would experience an ASAS20 response. In order to

statistically support a real difference of 30%, 40 patients per arm were required ($\alpha = 0.05$, $\beta = 0.20$). Data were presented as the mean ± SD or, in cases of skewed distribution, as the median and interquartile range (IQR).

The analysis included the intent-to-treat population, with baseline, 16-week, and 24-week clinical outcome measurements. All patients who received at least 1 dose of the study drug were included in the intent-to-treat analysis. Data up to the last known data point for a study patient were included for analyses.

The primary outcome ASAS20 response and secondary outcomes ASAS40 and ASDAS-CRP response according to clinically important improvement and major improvement were assessed by chi-square test or, if the data were skewed, by nonparametric tests, such as the Mann-Whitney U test. Categorical data were assessed by chi-square test. Post hoc analyses were performed for ASAS20 and ASDAS-CRP response at 16 weeks, according to baseline CRP levels (normal CRP/elevated CRP (>10.0 mg/liter)), SI joint inflammation based on SPARCC score (yes/no), HLA–B27 status (positive/negative), sex (male/female), and NSAID use (yes/no). ICC between readers' scores for change in inflammation parameters on MRI, between baseline and 16 weeks and between 16 weeks and 24 weeks, was calculated. Relative risks (RRs) and 95% confidence intervals (95% CIs) were calculated.

All statistical analyses were performed using SPSS for Windows version 26.0. Two-sided P values less than 0.05 were considered significant.

RESULTS

Patients and baseline characteristics

One hundred six consecutive patients were screened for this 16-week placebo-controlled trial. Twenty-six patients (24.5%) did not meet entry criteria, and 80 were enrolled (40 in the ETN group and 40 in the placebo group) (Figure 1).

HLA–B27 status, number of SpA features, and other baseline patient characteristics were comparable between the ETN and placebo groups (Tables 2 and 3). The majority of the patients were female (63.8%). The mean ± SD age was 34.5 ± 9.6 years, and 60.0% (48 of 80) were HLA–B27 positive. NSAIDs were used by 67.5% and DMARDs by 11.3% (most commonly methotrexate (n = 3) and sulfasalazine (n = 3)). The median CRP level was 2.5 mg/liter (IQR 2.5–6.0). The mean ± SD BASDAI was 5.1 ± 2.4, and the mean ± SD ASDAS-CRP was 2.8 ± 1.1, which indicates moderate-to-severe disease activity. The median SPARCC-SI joint score at baseline was 0.0 (IQR 0.0–3.1).

Exposure and compliance

Within the 16-week double-blind period, 2 patients, both in the ETN group, discontinued the study (1 had an unrelated adverse event (AE) (streptococcal infection) and the other patient was lost to follow-up) and 78 (97.5%) completed the treatment. Compliance with the study medication, i.e., the percentage of patients who took the medication according to the study protocol in the first 16 weeks, was 72.1%. There were no significant differences between the 2 treatment groups. In the follow-up period without treatment (week 16 to week 24), 2 patients, both in the placebo group, discontinued (1 had a viral infection and the other found the study visits too burdensome), which resulted in an analyzable population of 76 patients (95.0%) at 24 weeks (Figure 1). No patients initiated or restarted ETN or another biologic treatment during the week 16–24 follow-up period without study medication.

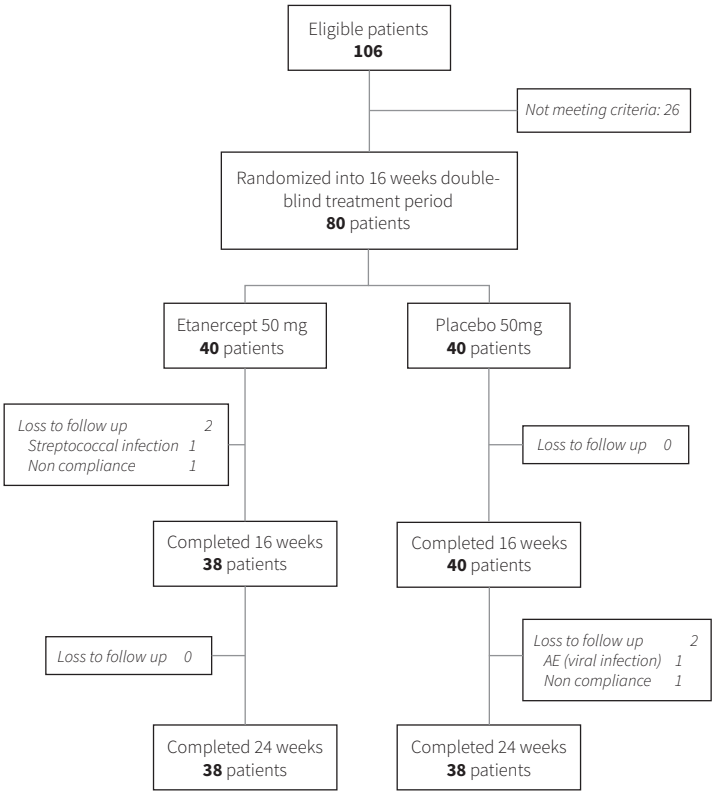

Figure 1. Flow chart showing disposition of the patients. AE = adverse event.

Clinical efficacy

At week 16, 10 of 72 patients (13.9%) had achieved an ASAS20 response: 6 (16.7%) in the ETN group and 4 (11.1%) in the placebo group. This difference was not statistically

significant (RR 0.7 (95% CI 0.2–2.2), P = 0.5) (Table 4). ASAS40 response at 16 weeks was achieved in 6 of 72 patients (8.3%): 3 (8.3%) in each treatment group. An ASDAS-CRP response (clinically important improvement and major improvement) was achieved in 12 of 62 patients (19.4%): 8 (25.0%) in the ETN group and 4 (13.3%) in the placebo group. This difference was also not statistically significant (RR 0.5 (95% CI 0.2–1.6), P = 0.2) (Table 4). Separate assessments of clinically important improvement and major improvement showed no significant differences between the 2 treatments at 16 weeks (RR 0.3 (95% CI 0.1–1.4), P = 0.1 and RR 2.1 (95% CI 0.2–22), P = 0.5, respectively) (Table 4). Low disease activity according to the ASDAS-CRP at 16 weeks was achieved in 30 of 70 patients (42.9%): 44.1% in the ETN group and 41.7% in the placebo group (RR:0.9 (95% CI 0.6–1.6), P = 0.8). Inactive disease according to the ASDAS-CRP was achieved in 13 of 70 patients (18.6%): 20.6% in the ETN group and 16.7% in the placebo group (RR 0.8 (95% CI 0.3–2.2), P = 0.7). During the first 16 weeks, both the ESR and the pain score showed more improvement in the ETN group than in the placebo group (mean ± SD change −2.2 ± 5.2 mm/hour versus −1.4 ± 7.4 mm/hour and −1.4 ± 2.7 versus −0.8 ± 2.7, respectively).

Table 2. Baseline demographic and clinical characteristics of the study population (n = 80)*

	Total	**Etanercept (n = 40)**	**Placebo (n = 40)**
Demographics			
Female	51 (64)	27 (68)	24 (60)
Age, mean ± SD years	34 ± 10	36 ± 10	33 ± 9
Clinical characteristics and extraarticular manifestations			
Disease duration, median (IQR) years	4.0 (2–9)	5.0 (2.5–14)	3.5 (2–8)
HLA–B27 positive	48 (60)	25 (63)	23 (58)
No. of SpA features, mean ± SD†	3 ± 1	3 ± 1	3 ± 2
Uveitis	15 (19)	10 (25)	5 (13)
Psoriasis	30 (38)	15 (38)	15 (38)
IBD	30 (38)	13 (33)	17 (43)
Concomitant medications			
NSAIDs	54 (68)	26 (65)	28 (70)
DMARDs	9 (11)	6 (15)	3 (8)

* There were no statistically significant differences between groups. Except where indicated otherwise, values are the number (%). IQR = interquartile range; DMARDs = disease-modifying antiinflammatory drugs.

† Spondyloarthritis (SpA) features include asymmetric arthritis, alternating buttock pain, dactylitis, enthesitis of the Achilles tendon or the plantar fascia, presence or history of psoriasis, inflammatory bowel disease (IBD), or acute anterior uveitis (AAU), first- or second-degree relative with ankylosing spondylitis (AS)/psoriasis/AAU/IBD, positive response to nonsteroidal antiinflammatory drugs (NSAIDs), and increased C-reactive protein level (≥10.0 mg/liter) or erythrocyte sedimentation rate (≥15 mm/hour).

Table 3. Baseline data on the disease outcomes assessed in the study population (n = 80)*

	Total	Etanercept (n = 40)	Placebo (n = 40)
ASDAS-CRP	2.8 ± 1.1	2.8 ± 0.8	2.8 ± 1.4
BASDAI, 0–10 NRS	5.1 ± 2.4	4.8 ± 2.2	5.4 ± 2.3
BASFI, 0–10 NRS	3.8 ± 2.5	3.8 ± 2.6	3.9 ± 2.4
CRP, median (IQR) mg/liter	2.5 (2.5–6.0)	2.5 (2.5–5.5)	2.5 (2.5–6.5)
CRP >ULN, no. (%)	9.0 (13)	6 (17)	3 (9)
ESR, median (IQR) mm/hour	6.0 (2.0–11)	8.0 (2.5–14)	4.5 (2.0–9.0)
$BASMI_{lin}$, 0–10 NRS	2.6 ± 1.1	2.4 ± 1.1	2.7 ± 0.9
MASES, 0–13	7.9 ± 3.1	7.9 ± 2.6	7.9 ± 2.6
SJC (44 joints), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
TJC (44 joints), median (IQR)	2.0 (0.0–5.0)	1.0 (0.0–4.0)	2.5 (0.0–6.8)
TJC >1, no. (%)	42 (53)	18 (45)	24 (60)
Patient global well-being, NRS	5.4 ± 2.4	5.2 ± 2.4	5.5 ± 2.5
Patient pain, NRS	5.2 ± 2.4	5.4 ± 2.5	5.1 ± 2.3
SF-36 PCS, 0–100 NRS	40.8 ± 6.6	40.6 ± 6.9	41.0 ± 6.4
SF-36 MCS, 0–010 NRS	40.0 ± 6.9	40.1 ± 7.0	39.9 ± 6.8
MRI			
SPARCC SI joint score (0–72), median (IQR)	0.0 (0.0–3.1)	0.0 (0.0–3.0)	0.0 (0.0–3.3)
SPARCC SI joint positive (≥2.0), no. (%)	18 (23)	8 (21)	10 (26)
ASAS positive, no. (%)	14 (18)	8 (21)	6 (15)
Conventional radiography			
BASRI (0–8), median (IQR)	0.3 (0.0–0.5)	0.3 (0.0–0.8)	0.1 (0.0–0.5)
BASRI positive (≥2.0), no. (%)	2 (3)	2 (5)	0 (0)
mSASSS (0–72), median (IQR)	2.0 (0.0–3.0)	2.0 (0.0–2.0)	2.0 (1.0–5.0)
mSASSS positive (≥2.0), no. (%)	41 (60)	23 (68)	18 (53)

** There were no statistically significant differences between groups. For all parameters except the swollen joint count (SJC) and tender joint count (TJC), data were not available from all 80 patients, as follows: For the Ankylosing Spondylitis Disease Activity Score using the C-reactive protein level (ASDAS-CRP), n = 67 (35 etanercept, 32 placebo). For the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), n = 78 (39 etanercept, 39 placebo). For the Bath Ankylosing Spondylitis Functional Index ($BASMI_{lin}$), n = 74 (38 etanercept, 36 placebo). For CRP, n = 69 (36 etanercept, 33 placebo). For erythrocyte sedimentation rate (ESR), n = 69 (33 etanercept, 36 placebo). For the Bath Ankylosing Spondylitis Metrology Index (linear measure) ($BASMI_{lin}$), (BASMI), n = 77 (38 etanercept, 39 placebo). For the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), n = 29 (9 etanercept, 20 placebo). For patient global well-being and patient pain assessments, n = 78 (39 etanercept, 39 placebo). For the Short Form 36 (SF-36) physical component score (PCS) and mental component score (MCS), n = 78 (39 etanercept, 39 placebo). For magnetic resonance imaging (MRI)–based Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac (SI) joint findings and positive diagnosis of spondyloarthritis according to the Assessment of SpondyloArthritis international Society (ASAS) criteria, n = 78 (39 etanercept, 39 placebo). For the Bath Ankylosing Spondylitis Radiology Index (BASRI), n = 77 (39 etanercept, 38 placebo). For the modified Stoke Ankylosing Spondylitis Spine Score (mSASS), n = 68 (34 etanercept, 34 placebo). Except where indicated otherwise, values are the mean ± SD. NRS = numerical rating scale; IQR = interquartile range; ULN = upper limit of normal.*

Table 4. Rates of treatment response at 16 weeks*

	Etanercept group, no. (%)	Placebo group, no. (%)	RR (95% CI)
Clinical response			
ASAS20	6 (17)	4 (11)	0.7 (0.2–2.2)
ASAS40	3 (8)	3 (8)	1.00 (0.2–4.6)
ASDAS-CRP response (CII and MI)	8 (25)	4 (13)	0.5 (0.2–1.6)
ASDAS-CRP (CII ≤1.1)	7 (22)	2 (7)	0.3 (0.1–1.4)
ASDAS-CRP (MI ≤2.0)	1 (3)	2 (7)	2.1 (0.2–22)
ASDAS-CRP (LDA <2.1)	15 (44)	15 (42)	0.9 (0.6–1.6)
ASDAS-CRP (ID <1.3)	7 (21)	6 (17)	0.8 (0.3–2.2)
Imaging response			
SPARCC SI joint MRI response (change ≥2.5)	8 (24)	7 (19)	0.8 (0.3–2.0)

** None of the relative risk (RR) values were statistically significant. For ASAS response, n = 72 (36 etanercept, 36 placebo). For ASDAS-CRP clinically important improvement (CII) and major improvement (MI), n = 62 (32 etanercept, 30 placebo). For ASDAS-CRP low disease activity (LDA) and inactive disease (ID), n = 70 (34 etanercept, 36 placebo). For SPARCC SI joint MRI response, n = 72 (35 etanercept, 37 placebo). 95% CI = 95% confidence interval (see Table 3 for other definitions).*

MRI findings

Reliability of results between MRI readers was confirmed by ICC analysis. ICCs at baseline, 16 weeks, and 24 weeks were 0.76, 0.72, and 0.70, respectively. Positive SI joint MRI findings according to the ASAS definition were observed in 14 of 78 patients (17.9%) at baseline, 7 of 72 (9.7%) at 16 weeks, and 9 of 73 (12.3%) at 24 weeks. Comparison of the percentage of patients with positive SI joint MRI findings by treatment group revealed no significant differences (at baseline 20.5% in the ETN group versus 15.4% in the placebo group, at 16 weeks 8.6% in the ETN group versus 10.8% in the placebo group, and at 24 weeks 14.3% in the ETN group versus 10.5% in the placebo group; RR (95% CI) 0.8 (0.3–2.0), 1.3 (0.3–5.2), and 0.7 (0.2–2.5), respectively).

Median SPARCC scores in the total study population were 0.0 (IQR 0.0–3.1), 0.0 (IQR 0.0–0.0), and 0.0 (IQR 0.0–1.5) at baseline, 16 weeks, and 24 weeks, respectively. Differences between groups were negligible and not statistically significant at baseline and 16 weeks. At 24 weeks, the difference in the change in SPARCC score (median 0.0 (IQR 0.0–1.0) in the ETN group versus 0.0 (IQR 0.0–0.0) in the placebo group) appeared statistically significant (P = 0.03). Positive SI joint MRI findings according to the SPARCC score (score ≥2.0) were observed in 18 of 78 patients (23.1%) at baseline, 10 of 72 (13.9%) at 16 weeks, and 9 of 73 (12.3%) at 24 weeks. Comparison of the percentage of patients with positive SI joint MRI findings according to SPARCC score by treatment group revealed no significant

differences (at baseline 20.5% in the ETN group versus 25.6% in the placebo group, at 16 weeks 8.6% in the ETN group versus 10.8% in the placebo group, and at 24 weeks 10.5% in the ETN group versus 14.3% in the placebo group; RR (95% CI) 1.3 (0.6–2.8), 0.9 (0.8–1.2), and 0.7 (0.2–2.5), respectively).

At 16 weeks, a minimally important change in the SPARCC-score (decrease of ≥ 2.5) had been achieved in 8 patients (23.5%) in the ETN group and 7 patients (19.4%) in the placebo group (RR 0.8 (95% CI 0.3–2.0), P = 0.7) (Table 4).

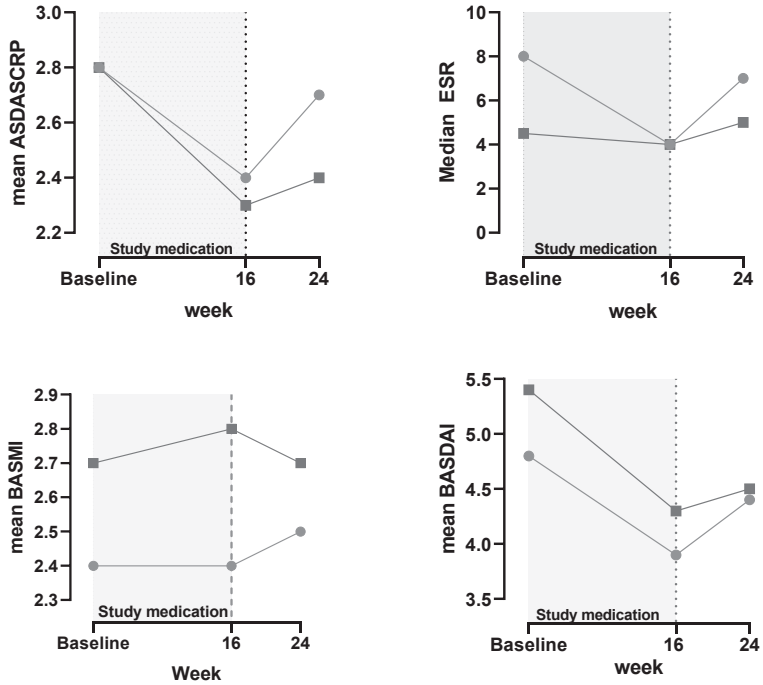

Figure 2. Disease activity by treatment group. Patients were treated for 16 weeks with etanercept (light gray circles) or placebo (dark gray squares). ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using the C-reactive protein level; ESR = erythrocyte sedimentation rate (mm/hour); BASMI = Bath Ankylosing Spondylitis Metrology Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.

Subgroup analyses

Fulfillment of the ASAS20 response after 16 weeks was not related to an elevated CRP level (≥10.0 mg/liter) or a positive finding on SI joint MRI according to the SPARCC score or ASAS definition, or to both an elevated CRP level and a positive finding on SI joint MRI. Of the 10 patients who had achieved an ASAS20 response at 16 weeks, 2 had an elevated CRP level at baseline: 1 of 4 in the placebo group (25.0%) and 1 of 6 in the

ETN group (16.7%). Comparison between patients with a positive finding on SI joint MRI according to the ASAS definition revealed no differences between treatment groups. Three patients with a positive finding on SI joint MRI according to the ASAS definition achieved an ASAS20 response: 1 of 4 in the placebo group (25.0%) and 2 of 6 in the ETN group (33.3%). Results were similar when a positive finding on SI joint MRI was assessed using the SPARCC score. In both the ETN group and the placebo group, only 1 patient with both an elevated CRP level and a positive finding on SI joint MRI achieved an ASAS20 response. In addition, ASAS20 response at 16 weeks was not influenced by sex, age, NSAID use, DMARD use, HLA–B27 status, or history of IBD, uveitis, or psoriasis.

Safety

At 16 weeks, AEs were reported in 30 of 78 patients (38.5%): 15 of 38 (39.5%) in the ETN group and 15 of 40 (37.5%) in the placebo group. Observed AEs were mainly diarrhea (20.0%), colds, and flu (both 10.0%). One patient was diagnosed as having a serious infection (streptococcal infection) and was withdrawn from the study. In 8 of 30 cases (26.7%) a possible relationship to the study drug was considered, and in 4 of 30 cases (13.3%) the AE was classified as being probably related to the drug. A higher proportion of patients in the ETN group had an AE that was possibly or probably related to the study drug compared to the placebo group (7 (50%) versus 5 (31.0%)). In 6 of 30 cases (20.0%), treatment for the AE was needed. Study drug was temporarily stopped in only 2 of the 30 cases (6.7%), both in the placebo group. At 24 weeks, 21 of 76 patients (27.6%) reported having had an AE; these were probably not related to study treatment since no patient received a biologic between week 16 and week 24. However, 1 patient experienced a viral infection that was serious enough for the patient to discontinue study participation. One patient experienced an exacerbation of IBD.

DISCUSSION

In this study, 16 weeks of treatment with ETN in patients with suspected nonradiographic axial SpA and reportedly high disease activity, but without the requirement of a positive MRI finding and/or elevated CRP level, did not result in significant improvement of disease activity compared to placebo. To date there have been only 2 other published placebo-controlled trials that included patients with nonradiographic axial SpA with high disease activity without the requirement of elevated CRP level and/or inflammatory lesions seen on SI joint MRI (21, 22). Both studies had a slightly higher proportion of HLA–B27–positive patients compared to our study (75% versus 60%). One study had a high percentage of patients with active MRI lesions at baseline (63% of the 46 patients) whereas the other had a lower percentage of patients with positive findings (32% of 200 patients), as in our study (23% of 80 patients). The numbers of patients with an increased CRP level are

difficult to compare between studies, as each study used a different definition of elevated CRP level, ranging from ≥6 mg/liter to ≥10 mg/liter.

In the earlier studies a significantly higher rate of ASAS20 response was observed in the groups treated with TNFi compared to placebo (54.5–71.1% versus 12.5–40.0%), which contrasts with our present findings. In our study, the frequency of improvement in disease activity scores (ASAS20 and ASDAS-CRP) was not significantly different in the ETN group compared to the placebo group. Comparison of the ASAS20 and ASDAS-CRP response within the ETN group showed a slightly higher percentage of responders according to the ASDAS-CRP (25%) than according to the ASAS20 (17%). This might reflect the influence of TNFi on CRP levels rather than on other outcome parameters.

In the study by Haibel and colleagues (21), the proportion of patients with positive SI joint MRI findings at baseline was much higher than was observed in the present study (63% versus 32%). Being HLA–B27 positive and/or having active inflammatory lesions seen on SI joint MRI at baseline were predictors of an ASAS20 response in previous studies (20, 21, 41, 42). Subanalyses by HLA–B27 status in our study revealed that B27-positive patients slightly more frequently had a positive SI joint MRI result according to the SPARCC score (26% versus 19%) and/or an elevated CRP level (≥10.0 mg/liter) compared to B27-negative patients. Due to the small number of patients in our study who had positive SI joint MRI findings at baseline, we were unable to detect differences in treatment efficacy between patients with and those without a positive SI joint MRI result and/or increased CRP levels. The relatively low number of patients with either a positive SI joint MRI finding (23%) and/or elevated CRP level (13%) at baseline in our study could be an explanation for the absence of an observed treatment effect in favor of ETN.

In addition, features of the patients included in this study might have more overlap with the "axial SpA group with peripheral signs," as described in a recent publication by Sepriano and colleagues (43), than with "pure axial SpA." This assumption is based on the low prevalence of positive SI joint MRI findings, high MASES scores, high number of patients with a tender joint count of >1 (52%), high proportion of female patients (64%), and high prevalence of psoriasis (38%) and IBD (38%), which are often associated with peripheral symptoms.

Our study cohort was relatively unique compared to most populations used in clinical trials of biologic treatments in axial SpA. With this unique study population some limitations emerged. For example, according to the algorithm described by Rudwaleit et al (7), many of the patients in our study population had a high probability (up to 90%) of developing a form of axial SpA, and this may be one of the reasons we did not

demonstrate significant results regarding efficacy of ETN treatment. A longer-term study (3-year follow-up) is underway, which should allow us to further characterize the disease progression in this population. Questions could be raised as to whether our inclusion and exclusion criteria captured patients with true nonradiographic axial SpA. Although our patients are typical of those commonly seen in clinical practice, published scientific data are scant. This study adds to the body of evidence and provides some direction with regard to prescription of TNFi treatment in this patient group. The terminology "disease activity" was used by default, although we realize the disease activity outcome measures used have not been validated for this study population, and what we actually measured was the "level of symptoms" (25). Another limitation is that we learned, during analysis of the data, that the study was underpowered to compare patients with versus those without a positive SI joint MRI finding and/or elevated CRP level, although the data were sufficient to analyze differences in disease activity between the 2 treatment groups. Furthermore, there was a long period of enrollment, due to the use of only one study center. The fact that we included only one center might, however, increase the reliability of the results by limiting the number of observers, and we have no reason to believe a faster enrollment rate would have influenced the study results.

In conclusion, the present results indicate that early treatment with ETN is not effective in patients with suspected nonradiographic axial SpA without the requirement of a positive MRI result or increased CRP level. It would be of interest to know whether our findings can be replicated in future investigations with comparable study populations and equal proportions of patients with and without positive SI joint MRI findings and elevated CRP levels.

Funding

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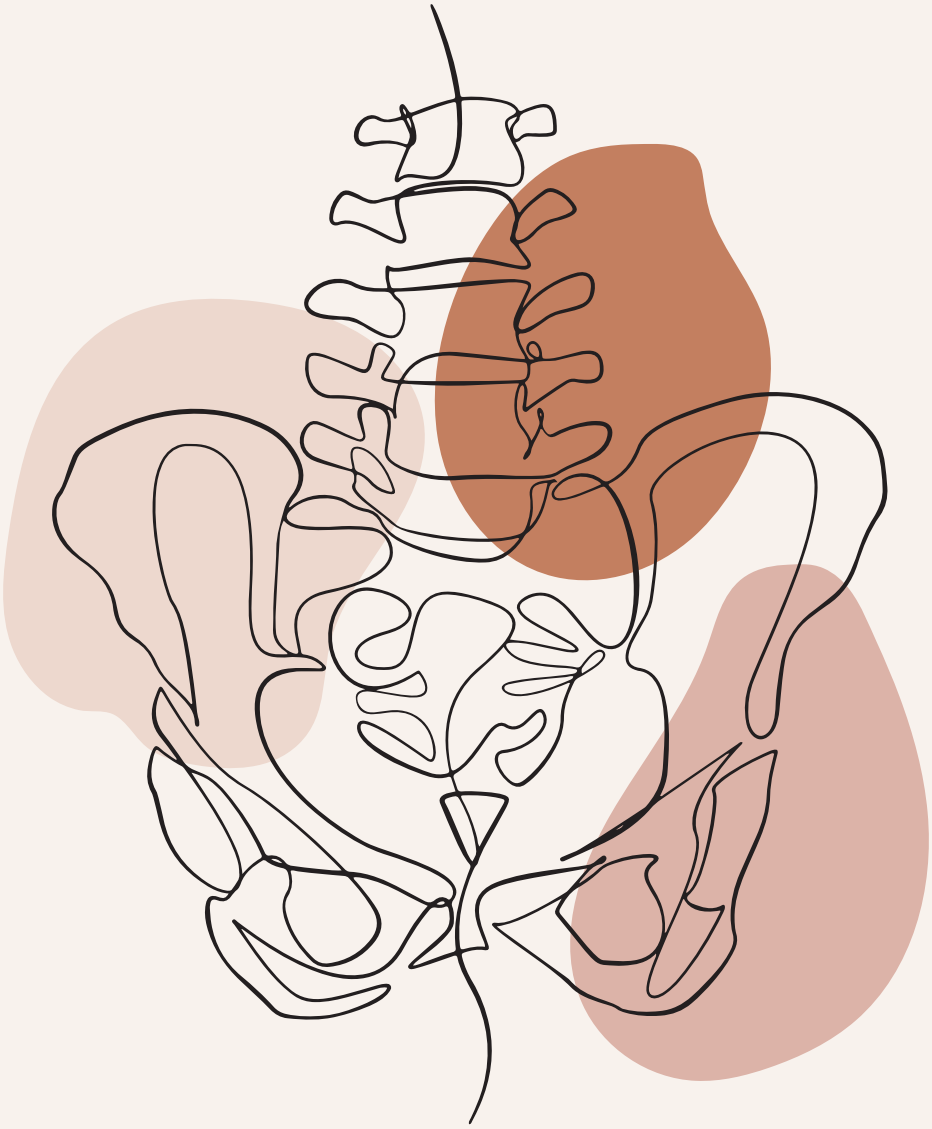

CHAPTER 8

DISEASE ACTIVITY SCORES IN NON-RADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

T. Rusman
M.A.C. van der Weijden
M.T. Nurmohamed
R.B.M. Landewé
J.J. de Winter
B.J.H. Boden
P.M. Bet
C.M.A. van der Bijl
C. van der Laken
I.E. van der Horst-Bruinsma

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TO THE EDITOR:

We would like to thank Dr. Mishra and colleagues for their comments on our article on the efficacy of treatment with etanercept in patients with suspected nonradiographic axial SpA. One of their suggestions was that the patients included were misdiagnosed, but we can confirm that the patients in our study did not have any of the comorbidities as suggested by the authors.

The main point of concern of Mishra and colleagues is that patients with a suspected diagnosis of axial SpA on the basis of the presence of several risk factors, such as inflammatory back pain plus at least 2 SpA features as well as high patient-reported disease activity (BASDAI ≥4) (1), as in our study, may not respond well to treatment with tumor necrosis factor inhibitors (TNFi) because objective signs of inflammation are lacking. As we have discussed in our article, we agree with the statement that the threshold for starting TNFi therapy, even in patients in whom a diagnosis of nonradiographic axial SpA is suspected but who have not been diagnosed as having nonradiographic axial SpA, is often too low. This, of course, may result in overtreatment and an increase in health care costs.

However, despite CRP being an attractive objective parameter for inflammation, many patients with axial SpA simply do not have raised levels of this inflammation marker, while they may have many severe manifestations of radiographic axial SpA (2). In addition, MRI of the sacroiliac joints can show bone marrow edema due to local inflammation, but these phenomena are also present occasionally in healthy individuals who actively participate in sports or in women who have recently given birth (3, 4). As the authors undoubtedly know, the other suggestions for objective disease parameters, such as swollen joint counts and abnormal findings on the modified Schober test of spinal mobility, are not suitable for evaluation of disease activity in axial SpA; arthritis is often absent, and results of the Schober test, most often found to be normal in patients with early disease, are not sensitive to change after treatment.

Our group therefore has developed a very interesting new tool based on physical performance measurements, the Ankylosing Spondylitis Physical Performance-based Index (ASPI), which is reliable, feasible for daily practice, and sensitive to change by treatment. We have recently published the Spanish translation, in addition to the English guidelines, which makes this new tool available for many rheumatologists around the globe (5).

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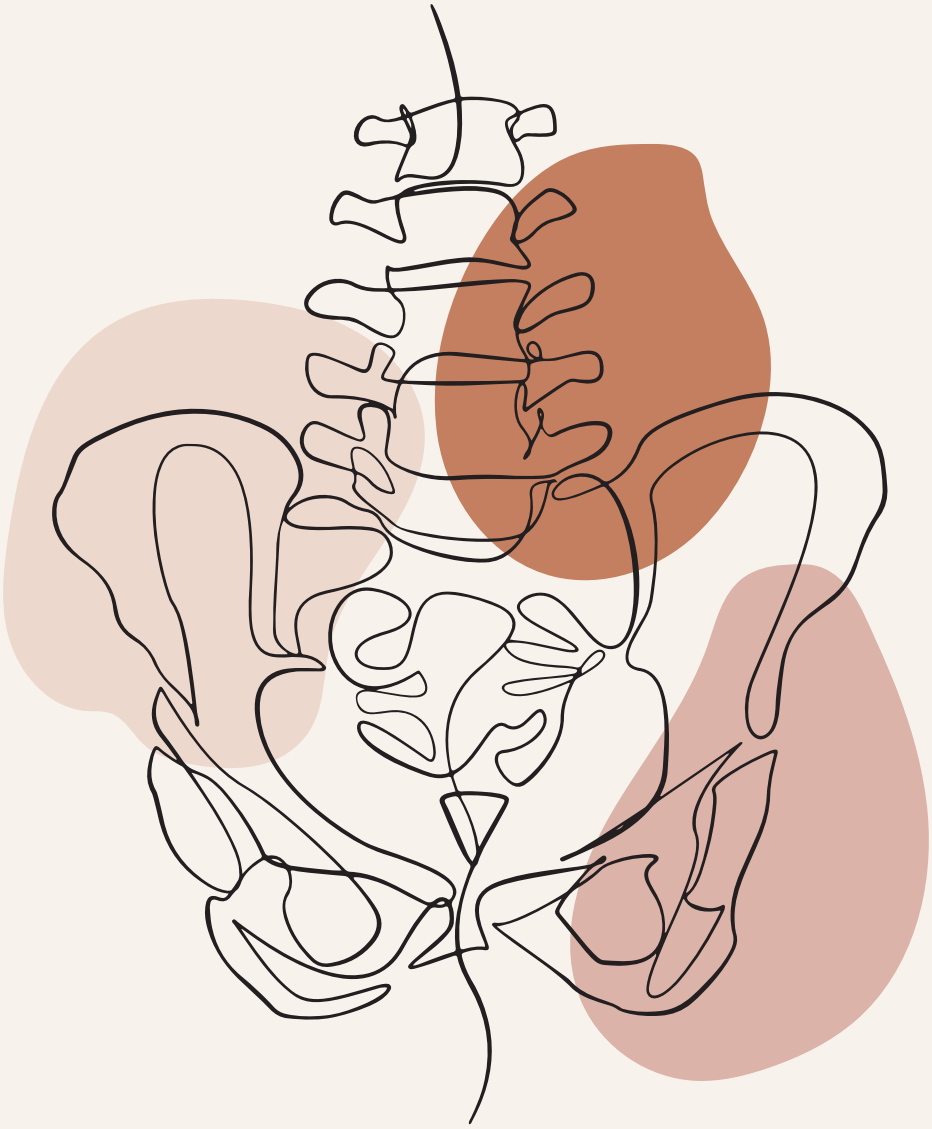

CHAPTER 9

DOES A SHORT COURSE OF ETANERCEPT INFLUENCE DISEASE PROGRESSION AND RADIOGRAPHIC CHANGES IN PATIENTS SUSPECTED OF NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS? THREE YEARS FOLLOW UP OF A PLACEBO-CONTROLLED TRIAL

T. Rusman
M.A.C. van der Weijden
M.T. Nurmohamed
J.C. van Denderen
R.B.M. Landewé
P.M. Bet
C.M.A. van der Bijl
C. van der Laken
I.E. van der Horst-Bruinsma

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ABSTRACT

Objectives

To study the long term effect of 16 weeks etanercept treatment at disease activity and radiographic changes in patients suspected of non-radiographic axial spondyloarthritis (nr-axSpA).

Methods

Eighty patients with inflammatory back pain (IBP) suspected of nr-axSpA, with a Bath ankylosing disease activity index (BASDAI) ≥ 4, received etanercept (n=40) 25mg twice weekly or placebo (n=40) for 16 weeks. They were followed without treatment restrictions after 24 weeks up to three years. Comparisons were made for biological exposure after 24 weeks (Yes/No) and change in BASDAI, AS disease activity score (ASDAS), Bath AS metrology index (BASMI), function and radiographic changes of the spine (according to the modified Stoke AS Spine Score (mSASSS)), sacroiliac joints (SIJ) (Bath AS radiology index (BASRI).

Results

After three years of follow up, 84% of the patients was diagnosed as SpA, predominantly axSpA. Biological treatment was started after 24 weeks in 30% of the patients. Disease activity scores after three years did not reveal significant differences between the initially randomization groups and for biological exposure with mean BASDAI scores over three years (mean difference: 0.9, 95% CI [-0.1;1.8], p=0.06) and ASDAS scores (0.3, 95% CI [-0.7;0.7], p=0.1). BASMI and function scores remained stable over three years. No differences in radiographic changes of the SI-joints or spine were observed over three years between the both groups.

Conclusion

A short course of etanercept in patients suspected with nr-axSpA did not affect disease activity, the chance at biological treatment nor radiographic progression after three years of follow-up.

Trial Registration

PREVENTION OF THE PROGRESSION OF VERY EARLY SYMPTOMS INTO ANKYLOSING SPONDYLITIS: A PLACEBO CONTROLLED TRIAL WITH ETANERCEPT (PrevAS study), Clinical Trials register - Search for eudract_number:2009-015515-40 and EudraCT number 2009-015515-40.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease characterized by inflammation of the axial skeleton and can be classified as radiographic (r-axSpA, ankylosing spondylitis (AS)) and non-radiographic axSpA (nr-axSpA)) based on the presence or absence of radiographic changes of the SI-joints (1,2). Radiographic changes usually develop many years after the first symptom onset and treatment with biologicals in an early disease stage is effective in lowering disease activity and the number of inflammatory lesions on MRI (1, 2). However, it is uncertain in which phase of the disease biological treatment might alter the course of the disease and radiographic progression.

Most randomized-controlled trials (RCT) so far were performed in patients with nr-axSpA who fulfilled the ASAS-classification criteria in combination with either a positive MRI of the sacroiliac joints (SIJ) and/or elevated C-reactive protein (CRP)-levels (3-6). Two of these studies investigated radiological progression on X-Rays (3, 6). Only one study was a RCT in patients with undifferentiated SpA but this study included non-steroidal inflammatory drug (NSAID) treatment instead of biological treatment (7). Therefore, data on the effect of biologicals at radiological progression in patients with high suspicion of developing axial SpA with high disease activity are lacking.

We recently reported our 24 weeks results of the prevention ankylosing spondylitis (PrevAS) study, a 16-weeks, double-blind placebo-controlled trial with etanercept in eighty patients with inflammatory back pain, suspected of nr-axSpA and a high level of symptoms (BASDAI>4) with an open label follow up. After six months of follow up, there were no significant differences between the ASAS20 response and change in inflammatory lesions on MRI-SIJ between the two treatment groups (8). The current study reports the three year outcomes of the PrevAS study, including both, clinical symptoms, radiological changes and disease progression.

PATIENTS AND METHODS

Population

A detailed description of the PrevAS study is published recently (9). In summary, consecutive patients with chronic back pain, suspected of nr-axSpA were eligible for inclusion if they were ≥ 18 years of age and fulfilled the Calin criteria of inflammatory back pain (10). In addition they had to be either HLA-B27 positive with at least one SpA-feature, or HLA-B27 negative with at least two SpA-features, according to the European Spondyloarthropathy Study Group (ESSG) criteria (11). Patients also were required to have a high level of symptoms (BASDAI ≥ 4) and insufficient response to at least two

NSAIDs. Subjects with definite AS according to the modified New York criteria (12) or who had received biological treatment were excluded.

Study design

The PrevAS study was a randomized, double blind, placebo-controlled trial performed at the Amsterdam UMC, location VU university medical center (VUmc) (EudraCT number 2009-015515-40). The study complies with the Declaration of Helsinki and was approved by the local ethical review board and all patients signed an informed consent before screening.

Patients were randomly assigned (1:1) to etanercept, twice weekly 25 mg, or placebo injections during the first sixteen weeks and followed up to three years, as was described previously. All study personnel and patients were blinded to the randomization schedule and to treatment assignments until the last patient had completed the three year follow up. Deblinding of the study medication was performed after all patients had completed the three years of follow up, or in case of an urgent medical need. After 16 weeks, treatment was initiated, if necessary, by the physician according to clinical judgement. All concomitant medication (biologicals, NSAIDs and disease-modifying antirheumatic drugs (DMARDs)) used during the study or changes in medication dosage were documented during each study visit.

Data collection

Study visits were performed at baseline and annually thereafter up to three years. Demographical and disease specific variables were assessed such as: sex, age, disease duration (duration of back pain at baseline), IBP- and SpA features, family history and presence of extra-articular manifestations (EAMs), such as uveitis, inflammatory bowel disease (IBD) and psoriasis, and data on the use of medication (biologicals, NSAIDs, DMARDs). Questionnaires on pain, overall wellbeing (Bath patient global) and quality of life (Short form health form (SF36)), were obtained during each visit. The clinical diagnosis (e.g. nr-axSpA, r-axSpA, peripheral spA or no SpA) after three years was made according to the physician's judgement.

Clinical outcomes

The level of symptoms was assessed with the BASDAI and ASDAS. Secondary clinical outcome measures were: Bath AS Functional Index (BASFI), Bath AS metrological index (BASMI) and inflammatory parameters (C-reactive protein (CRP) (median, upper limit of normal (10.0 mg/l) and Erythrocyte sedimentation Rate (ESR)- level).

Radiological outcomes

Radiological images of the sacroiliac joints (SIJ) and the cervical and lumbar spine were obtained at baseline and after three years of follow up. The X-rays were assessed independently by two expert readers (IvdH and CvD), who were blinded to the treatment of the patients, patient characteristics and sequence of the radiographs. Radiological scores, mean and change scores, were reported as the average of the two readers. A consensus meeting was organized to achieve agreement in case of a discrepancy in radiological scores between the two expert readers.

Radiographs of the spine were scored according to the modified Stoke ankylosing spondylitis spinal score (mSASSS: range, 0 to 72 (13)). A relevant change in mSASSS was defined as ≥1 non-bridging or bridging syndesmophyte defined as a score of two or three, respectively and syndesmophyte formation defined as a shift in score from zero or one to two or three reported by both readers (3, 6).

The radiographs of the SIJ's were scored according to the Bath ankylosing spondylitis radiology index (BASRI: range, 0 to 8). The mean score of both SIJ's was used for the BASRI-SIJ score (14). BASRI-SIJ was defined as "positive" with a ≥2 score bilateral or ≥3 unilateral according to the modified New York criteria (12). Change in BASRI-SIJ scores was defined as: a ≥ 1 point worsening or improvement in the BASRI-SIJ score in at least one SIJ, if the direction of the change was agreed on by both readers. No change was reported when there was a shift from grade 0 to 1 (in the worsened joint) or a shift from 1 to 0 (in the improved joint) (3).

Statistical analyses

Data were presented as mean values± (Standard Deviation) and as median (Inter Quartile Range) in case of skewed distribution. This analysis included the intention-to-treat population with baseline, one-, two- and three year clinical outcome measurements. All patients who received at least one dose of the study-drug were included in the intention-to-treat analysis.

Generalized estimating equations (GEE) assessed changes in disease activity (BASDAI and ASDAS-CRP) and physical functioning over time between the two treatment groups (biological exposure after 24 weeks), corrected for repeated measurements (unadjusted analyses). In all analyses DMARD initiation, study treatment group (ETN/PBO), elevated CRP-level and duration of biological exposure after 24 weeks were added as potential confounders for changes in disease activity. Follow-up time was assessed as possible effect modifier.

Proportions of patients with a relevant change (worsening or improvement) in radiological scores (mSASSS and BASRI-SIJ) were determined per treatment group (biological exposure after 24 weeks) at one and three years. The net percentage of patients with radiological progression per treatment group was defined as follows: the number of patients with radiological progression minus the number of patients with radiological improvement, divided by the total study population (15). To visualize the radiological progression between the two treatment groups a cumulative probability plot was generated for patients with ≥2 valid assessments. Overall agreement (positive and negative classifications) for the mSASSS and BASRI between the two expert readers were calculated. In case of skewed distribution non parametric analysis methods were used.

All statistical analyses were performed with SPSS for Windows V.26.0. A two-sided $p<0.05$ was considered statistically significant. P-value and 95% confidence interval (CI) were reported.

RESULTS

In total 80 patients were randomly assigned, of whom 40 patients received etanercept and 40 patients placebo in the first sixteen weeks and were followed up to three years. As previously reported, baseline data on demographics and disease activity status showed no differences between the etanercept and placebo group (8). Both groups had a mean age of 34.5 year (SD 9.6), 64% of included patients were female and 60% were HLA-B27 positive. At baseline, patients had a mean ASDAS-CRP score of 2.8 (SD 1.1), a BASDAI-score of 5.1 (SD 2.4) and a median CRP-level of 4.5 (IQR 2.5;6.0).

The dropout rates were similar for the two study treatment groups (ETN/PBO), with four patients during the first 24 weeks as described previously. At 24 weeks, 76 patients were still in study (8) and 65 patients completed the three year follow up. Between 24 weeks and three year follow up, 11 out of 76 patients (14.5%) dropped out, of whom seven patients were lost to follow up. Patients who were exposed to a biological after 24 weeks of the placebo-controlled study period, completed significantly more often the three year follow up compared to patients who were not exposed (95.8% vs. 75.0%, p=0.03). Reasons for lost to follow up were an operation, pregnancy, a protocol violation and one patient discontinued because the follow up visits were too much time consuming. For the other seven patients no data on the reasons for lost to follow up reason were documented.

Disease activity and function through three years

Both the mean ASDAS-CRP and BASDAI-scores remained stable over three years follow-up and no differences were observed in both BASDAI, ASDAS-CRP, BASMI and function (BASFI) scores between patients treated with ETN and PBO in the first 16 weeks of the placebo-controlled period through three years of follow up (Table 1). No biological treatments were initiated between 16 and 24 weeks of follow up.

Table 1. Clinical characteristics at the 1- and 3-year visit of the PrevAS study

	24 weeks, n=76				**1 year, n=72**				**3 year, n=65**			
	Etanercept		*Placebo*		*Etanercept*		*Placebo*		*Etanercept*		*Placebo*	
ASDAS-CRP	2.7	(0.9)	2.4	(1.0)	2.7	(1.0)	2.4	(0.9)	2.4	(1.0)	2.4	(1.3)
BASDAI (0-10) (NRS)	4.4	(2.6)	4.5	(2.7)	4.6	(2.5)	4.5	(2.4)	4.4	(2.4)	4.3	(2.1)
BASFI (0-10) (NRS)	3.7	(2.8)	3.6	(2.7)	3.8	(2.8)	3.5	(2.6)	3.6	(2.7)	3.2	(2.4)
$BASMI_{lin}$ (0-10)	2.6	(1.2)	2.6	(1.2)	2.5	(1.1)	2.6	(1.4)	2.9	(1.0)	2.9	(1.1)
CRP (mg/L) median (IQR)	2.5	(2.5; 8.5)	2.5	(2.5; 3.0)	2.5	(2.5; 6.0)	2.5	(2.5; 3.0)	2.5	(2.5; 3.0)	2.5	(2.5; 4.5)
CRP>ULN, n(%)	9	(22.5)	2	(5.0)	6	(15)	1	(3.0)	3	(9.4)	4.0	(14)
ESR (mm/hr) median (IQR)	7.0	(2.5; 14)	5.0	(2.0; 9.0)	7.0	(2.5; 13)	4.0	(2.0; 8.0)	4.0	(2.0; 9.0)	6.0	(3.0; 9.0)
Patient global well-being (NRS)	4.6	(2.9)	4.9	(2.8)	4.8	(2.7)	4.9	(2.8)	4.8	(2.9)	4.4	(2.6)
Patient pain (NRS)	4.6	(3.0)	4.7	(2.8)	4.8	(2.7)	4.6	(2.6)	4.8	(2.9)	4.4	(2.6)

Legend table 1: Except indicated otherwise, values were presented as mean with SD; SIJ: Sacroiliac Joints assessed as average by two independent readers NRS: Numerical rating scale. CRP ULN: upper limit of normal. IQR: Inter Quartile Range.
24weeks follow up: ASDAS: Ankylosing Spondylitis Disease Activity Score (n=71, etanercept n=36, placebo n=35); CRP: C-reactive protein (n=71, etanercept n=36, placebo n=35); ESR: Erythrocyte sedimentation rate (n=68, etanercept n=33, placebo n=35); BASDAI: Bath Ankylosing Spondylitis Disease Activity Index (n=76, etanercept, placebo n=38); BASFI: Bath Ankylosing Spondylitis Function Index (n=75, etanercept n=37, placebo n=38); BASMI: Bath Ankylosing Spondylitis Metrology Index (n=74, etanercept, placebo n=37); Pain (n=76, etanercept, placebo n=38); Patient global (n=76, etanercept, placebo n=38). 1 year follow up: ASDAS (n=62, etanercept n=30, placebo n=32); CRP (n=64, etanercept n=31, placebo n=33); ESR (n=66, etanercept, placebo n=33); BASDAI (n=68, etanercept, placebo n=34); BASFI (n=70, etanercept n=36, placebo n=34); BASMI: (n=70, etanercept, placebo n=35); Pain (n=71, etanercept n=36, placebo n=35); Patient global (n=70, etanercept n=36, placebo n=34). 3-year follow up: ASDAS (n=44, etanercept n=21, placebo n=23). CRP (n=60, etanercept n=32, placebo n=28); ESR (n=62, etanercept n=29, placebo n=33); BASDAI (n=59, etanercept n=29, placebo n=30). BASFI (n=58, etanercept, placebo n=29); BASMI (n=65, etanercept n=32, placebo n=33); Pain (n=60, etanercept, placebo n=30); Patient global: (n=60, etanercept, placebo n=39).

Comparison between patients exposed to a biological after 24 weeks and patients who did not showed the following results. GEE analysis for ASDAS-CRP showed no clinically relevant differences between patients who were exposed to a biological and patients who were not (mean difference crude model: 0.3, 95% CI [-0.7;0.7], *p*=0.1). Although non-significant, the crude GEE model showed a 0.9 higher BASDAI-score between patients exposed to a biological and patients who were not (mean difference: 0.9, 95% CI [-0.1;1.8], *p*=0.06). Follow-up time was an effect modifier (*p*=0.03) for the relation between biological exposure and non-exposure, meaning the results must be presented for each follow up moment separately (adjusted); year one (mean difference: 0.9, 95% CI [-1.4;3.2], *p*=0.5), year two (0.1, 95% CI [-1.8;2.1], *p*=0.9) and year three (-0.3, 95% CI [-1.7;1.2], *p*=0.7). Posthoc analyses showed patients in the biological exposure group had significant (p= 0.004) higher BASDAI scores at baseline compared to patients in the non-exposure group (6.2±2.4 vs. 4.6±2.2).

Both the BASMI score of mobility and function (BASFI scores) remained stable over three years of follow up (Table 1). The BASMI revealed no significant differences over time between patients who received a biological after the first 24 weeks and patients who did not. For function (BASFI score), a non-significant, mean difference of 0.8 higher function score was observed in patients with a biological treatment after 24 weeks compared to patients without a biological treatment. Analysis of follow-up time as possible effect-modifier for the relation between biological use and no biological use revealed a *p*-value of 0.05, indicating the results must be presented for each follow-up moment separately (adjusted); year one (mean difference: 0.01, 95% CI [-3.7;3.7], *p*=1.0), year two (-0.6, 95% CI [-3.2;1.9], *p*=0.6) and year three (-1.0, 95% CI [-1.0;3.1], *p*=0.3). As with the BASDSAI scores, posthoc analyses showed at baseline, numerically higher BASFI-scores in the biological exposure group compared to the non-exposure group (4.6±2.3 vs. 3.5±2.5).

Radiological progression

Overall agreement between the readers in the BASRI was reached in 100% of the cases at baseline, 89% after one year and 92% after three years. The overall agreement for the mSASSS scores was 53% at baseline, 57% at one year and 57% at three years.

The mean BASRI scores remained stable with median scores of 0.3 [IQR 0.0;0.5] at baseline, 0.0 [IQR 0.0;0.8] at one year and 0.3 [0.0-0.8] at three years. Median mSASSS scores showed no 'relevant' significant changes during follow up: at baseline 2.0 [IQR 0.0;3.0], at one year 2.0 [0.0;4.0] and at three years 3.0 [1.0;5.0] (Table 2).

A 'relevant' increase in the BASRI-score, as well as the mSASSS score was observed in only one individual patient (1.4%) after one and three years of follow up. In addition, a

'relevant' increase in the mSASSS score was observed in three patients (4.6%), of whom two new patients compared to one year follow-up, at three year follow up. Because of the low numbers, a probability plot could not be created.

Comparison of patients who were exposed to biologicals after 24 weeks during follow up, showed no differences in radiographic scores compared to patients who were not exposed.

Table 2. Radiological progression through three year follow up of the PrevAS study

Radiographic scores	**Baseline**				**1 year**				**3 year**			
	Etanercept		**Placebo**		**Etanercept**		**Placebo**		**Etanercept**		**Placebo**	
BASRI (0-8) (median, IQR)	0.3	(0.0; 0.8)	0.1	(0.0; 0.5)	0.5	(0.0; 1.0)	0.0	(0.0; 0.5)	0.5	(0.0; 1.2)	0.0	(0.0; 0.4)
BASRI positive (≥2.0) (%)	2	(2.5)	0	0	1	(2.8)	2	(5.7)	1	(3.1)	2	(6.1)
mSASSS (0-72) (median, IQR)	2.0	(0.0; 2.0)	2.0	(1.0; 5.0)	2.0	(0.0; 3.0)	2.0	(1.0; 5.0)	2.5	(0.3; 4.8)	3.0	(1.8; 5.0)
mSASSS positive (≥2.0), (%)	23	(68)	18	(53)	16	(52)	22	(69)	17	(61)	23	(77)

Legend table 3: Except indicated otherwise, values were presented as mean with SD; SIJ: Sacroiliac Joints assessed as average by two independent readers; IQR: Inter Quartile Range.
Baseline: mSASSS: modified stoke ankylosing spondylitis spinal score (n=68, etanercept, placebo n=34).
BASRI: Bath ankylosing spondylitis radiology index (n=77, etanercept n=39, placebo=38).
Year 1: mSASSS (n=63, etanercept n=31, placebo n=32); BASRI (n=71, etanercept n=36, placebo=35).
Year 3: *mSASSS (n=58, etanercept n=30, placebo n=28); BASRI (n=65, etanercept n=32, placebo=33).*

Clinical diagnoses after three years

Comparison of the final diagnoses after three years follow up, showed that out of the 80 patients 63 patients (79%) were diagnosed as axSpA, four patients (5%) with peripheral SpA, three patients (3.8%) with undifferentiated SpA, eight (10%) had no SpA diagnoses and two patients (2.5%) could not be analyzed due to an early drop out of the study (Table 3). Of the 63 axSpA patients, 62 (76%) were diagnosed as nr-axSpA and one (1.3%) with radiological axSpA (r-axSpA) according to the modified New York criteria (12). The peripheral SpA group included two patients (2.5%) with psoriatic arthritis (PsA) according to the CASPAR criteria (16), one patient (1.2%) with Crohn's disease (CD) and one patient (1.2%) without PsA or IBD.

Table 3. Clinical diagnosis for axSpA through three years follow up PrevAS study

Clinical diagnosis	n	(%)
Non-radiographic axial spondyloarthritis	62	(76.0)
Radiographic axial spondyloarthritis	1	(1.3)
Peripheral axial spondyloarthritis	4	(5.0)
Psoriatic arthritis	2	(2.5)
Crohn's disease	1	(1.2)
Non specified peripheral axial spondyloarthritis	1	(1.2)
Undifferentiated spondyloarthritis	3	(3.8)
No diagnosis	8	(10.0)
Missing*	2	(2.5)

Legend table 3
*Two patients dropped out the study before a clinical diagnosis could be made

Treatment changes between 6 and 36 months

Two patients dropped out in the first 16 weeks of the study and therefore no data regarding additional treatment initiation over the three years follow up were obtained. In the period between 6 and 36 months of follow up, 63 patients (69%) had initiated on average 3.8 (SD 3.6) new treatments (NSAIDs, DMARDs or biologicals). Through the different follow up periods over three years, new treatments were started at similar rates for the etanercept and placebo group and were similar in number and type of drugs for both groups. In total, twenty-four patients (30%) started with a biological after 24 weeks of follow up, of whom 11 out of 40 patients (27.5%) were part of the initial ETN group in the first 16 weeks and 13 out of 40 patients (33%) of the initial PBO group. Numerically, more women (n=19, 37%) initiated a biological compared to men (n=5, 17%). Numerical, more clinical diagnosis were observed for patients exposed to a biological compared to patients who were not exposed (87.5% vs.78.6%). The majority (39 patients (62%) started with NSAIDs, and in seven cases (8.0%) DMARD treatment was initiated (sulfasalazine or methotrexate). In five out of seven patients who started a DMARD, this treatment was combined with the start of a biological. All five cases were women diagnosed with nr-axSpA (n=3), PsA (n=1) and peripheral SpA (n=1). NSAID initiation in the third year of follow up was significantly associated with higher disease activity as measured with the ASDAS-CRP and BASDAI. The number of patients initiating a DMARD was too small for reliable analyses considering possible associations with disease activity or radiological progression.

DISCUSSION

A short course of etanercept treatment and exposure to biologicals after the placebo-controlled period in patients suspected of nr-axSpA did not alter the disease course, nor improved the severity of symptoms or radiographic progression compared with placebo after three years of follow up.

Disease activity scores did not differ between patients treated with etanercept or placebo during the first 16 weeks of the placebo-controlled trial, nor at 24 weeks follow up. Both treatment groups showed comparable disease activity scores (BASDAI: ETN 4.4 vs. PBO 4.5). After three years of follow up, despite the initiation of a biological in 30% of the patients, the disease activity of the whole group remained stable and similar mean disease activity scores were observed. Although comparisons for biological exposure after 24 weeks revealed no difference in disease activity scores (BASDAI and ASDAS), posthoc analyses revealed a significant difference in BASDAI values at baseline (6.2±2.4 vs. 4.6±2.2) and at one year (5.3±2.4 vs. 4.2±2.4) for patients who were exposed to a biological and patients who were not exposed. This finding indicates that biological treatment stabilized the disease activity in patients and could be an explanation for not finding a significant difference for biological exposure after 24 weeks through three years follow up.

Concerning radiological progression, no reliable conclusion can be drawn on the influence of a short course of etanercept in the first 16 weeks and biological exposure after 24 weeks, since the small number of included patients (n=80) and the low number of significant changes. 'Relevant' radiological progression was observed in only four patients, of whom three patients (4.6%) showed worsening in the spine (mSASSS (a relevant change (final score of 2 or 3)) and one patient in the SIJ (according to the BASRI score). These results are not in line with similar studies in early axSpA, that showed significant radiological progression over a two- and five year follow up period respectively (17, 18). Noteworthy is that the change in SIJ-scores at two years for the aforementioned study was only 0.1 (SD 0.8), which cannot be defined as a relevant change according to our study criteria (3). A reasonable explanation could be that only 20% of the patients in our study had a positive MRI of the SI-joint at baseline, which is rather low in comparison with other studies showing a higher percentage of radiological progression (37-63%) (17, 19). In addition raised CRP-levels (> 10 mg/L) at baseline, which is also considered a predictor for radiological progression, were only present in 13% of our patients (8, 18).

The clinical diagnoses after three years of follow up showed that the majority (84%) of this group of patients was diagnosed with axial SpA (79%) or peripheral SpA. Therefore,

the patients who were included in this placebo-controlled trial can be considered as very early SpA patients. The high percentage of nr-axSpA diagnoses is in line with the results from other studies (77.7% vs. 62-86%) (20, 21). However, in contrast with our study, these studies did not include clinical trials with biologicals. Despite this difference in study design, comparison between our baseline values (22) and those of the aforementioned studies showed comparable results for number positive MRIs (32% vs. 21-40%) and disease activity scores (BASDAI 5.1 vs. 4.5) reflecting a high disease activity and a slightly higher percentage of being positive for HLA-B27 (60% vs. 46-54%), which indicates a similar study population.

A strong point of this study is the three year follow up, in which all study personnel and patients were blinded to the randomization schedule until the last patient had completed the three year follow up. Blinding ensures an unbiased assessment of the evolution of clinical symptoms (and radiological progression) in this study group.

Limitations include the absence of MRI-imaging during the three year follow up. However, we do not believe that this jeopardized our study results as our previous publication including this population revealed a high number of negative MRIs (15). Based on previous publications that the chance that negative MRI's of the SIJ would become positive after three years is relatively low (6, 23-25). The effect of absence of follow up MRI's after three years is limited by the collection of radiographs of the SIJ and spine, which decreased the risk of missing cases of axSpA.

The main conclusion of this study is that early treatment with a short course of etanercept in inflammatory back pain patients initially suspected of nr-axSpA with a high symptom level was inefficacious, since disease activity remained high during the three year follow up for both treatment groups. No reliable conclusion could be drawn about the influence of etanercept on radiological progression, because only a low number of patients showed radiological progression. However, monitoring of this group patients seems necessary, since more than three quarters of the population developed clinical axSpa and a high percentage (30%) started a biological during follow up because of high symptom intensity.

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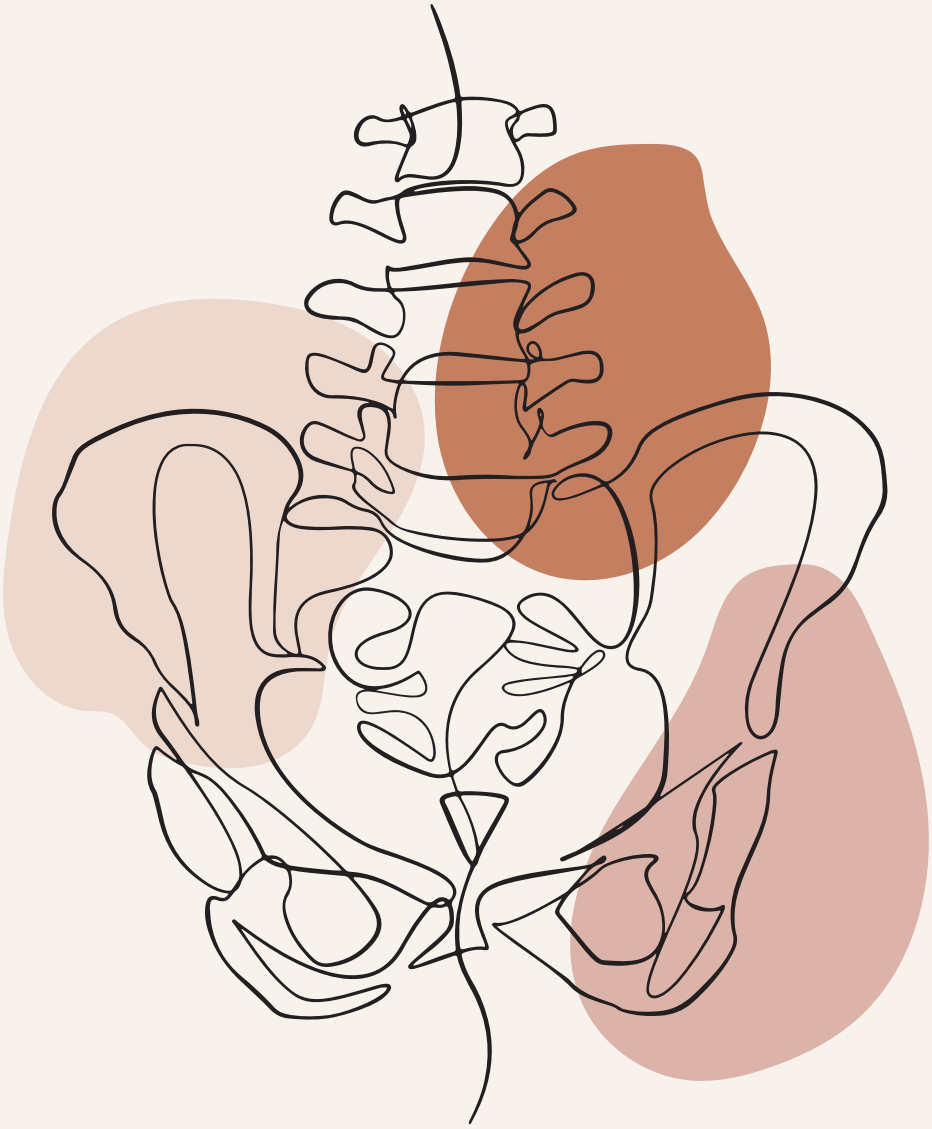

CHAPTER 10

LONG-TERM EFFECT OF TNF INHIBITORS ON RADIOGRAPHIC PROGRESSION IN ANKYLOSING SPONDYLITIS IS ASSOCIATED WITH TIME-AVERAGED CRP LEVELS

M. Konsta
G.T. Sakellariou
T. Rusman
P.P. Sifkakis
A. Iliopoulos
I.E. van der Horst-Bruinsma

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ABSTRACT

Objective

To investigate whether the impact of long-term treatment (> 3 years) with TNF inhibitors (TNFi) on radiographic progression in AS is associated with the level of acute phase reactants during therapy.

Methods

One hundred and one consecutive AS patients under TNFi (65 men; age: 41.6 ± 11 years (mean ± SD), with symptom duration: 17 ± 10 years) were included in this retrospective study. Lateral X-rays of cervical and lumbar spine, obtained before TNFi initiation, were compared to those obtained after a period of 7 ± 2.5 (range: 3–15) years. The levels of CRP and ESR were evaluated every 6 months. The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) assessed the radiographic damage. New syndesmophyte formation or ΔmSASSS-score/year ≥ 1 unit/year was defined as radiographic progression.

Results

Forty-seven patients (46.5%) showed radiographic progression. ΔmSASS-score/year was positively correlated with both, baseline CRP ($r = 0.35$, $P < 0.001$) and ESR ($r = 0.3$, $P < 0.01$), as well as with time-averaged CRP ($r = 0.3$, $P < 0.01$). Furthermore, ΔmSASS-score/year was significantly higher ($P < 0.0001$) in patients with syndesmophytes at baseline (0.9 (0.4–1.8), median (IQR)) compared to those without (0 (0–0.4)). In the multivariate logistic regression analysis, independent risk factors for spinal radiographic progression during TNFi treatment were the presence of syndesmophytes at baseline (OR: 14.7, 95%CI:4.9–44) and the time-averaged CRP > 5 mg/L (OR:7.6, 95%CI: 2.5–23). No gender differences were observed.

Conclusion

In AS patients with long standing disease, radiographic progression during TNFi treatment is significantly associated with higher levels of time-averaged CRP.

Keywords: Ankylosing Spondylitis, Radiographic progression, Time-averaged CRP, Baseline syndesmophytes

INTRODUCTION

Radiographic Axial Spondyloarthritis, also called Ankylosing spondylitis (AS), is a chronic inflammatory arthritis affecting the sacroiliac joints and spine associated with new bone formation and spinal fusion. Patients with AS suffer from significant pain and loss of function with associated work disability(1). Treatment with Tumor Necrosis Factor Alpha inhibitors (TNFi) has proven to be very effective for reducing symptoms of AS (2), but the impact on radiographic progression has been difficult to resolve. This is mainly due to the relatively slow rate of radiographic changes in AS, and the high variability between patients (3), (4).

Continuous TNFi therapy showed similar radiographic progression when compared with historical cohorts in AS at 2 years of follow-up (5), (6), (7), but less progression at 4 years (8), (9). However, a retrospective 8 years follow-up study, in only 22 AS patients, (10) as well as a recent meta-analysis (4) demonstrated a favorable effect in radiographic progression after 4 years with TNFi therapy. Confirming the afore-mentioned findings, a large prospective longitudinal observational study with 1.5 to 9 years of follow-up concluded that the beneficial effect of TNFi on radiographic progression is higher when started early in the disease course and when treatment is sustained for a longer period of time (11).

These findings triggered the debate about the effect of TNF-α blocking therapy and the relationship between disease activity and spinal radiographic progression in AS. Previews studies have shown that male gender, disease duration, HLA-B27 positivity, smoking, mSASSS score and presence of syndesmophytes at baseline, are associated with radiographic progression in TNFi naïve AS and axial SpA patients (12), (13). Besides the initial degree of structural damage, levels of inflammatory markers at baseline, specifically CRP, is associated with spinal radiographic progression in AS (9), (12), (14).

Moreover, structural change in AS is associated with both baseline and time-averaged levels of CRP in naïve (12), (15) and TNFi treated patients (15). Nevertheless, the studies regarding the effect of level of acute phase reactants on radiographic progression in AS patients treated with TNFi in daily clinical practice are scarce.

The primary aim of this study was to investigate whether the impact of long-term TNFi administration (i.e., > 3 years) on radiographic progression, in AS patients, is associated with the average level of acute phase reactants during the treatment. The secondary aim was to access independent predictors of progression, such as gender and smoking.

METHODS

Study population

Consecutive AS patients (fulfilling the modified New York criteria)(16), under long-standing anti-TNF treatment (≥ 3 years), were included in this retrospective study. The patients derived from the Amsterdam Spondyloarthritis cohort (AmSpA), Rheumatology Department of Veterans Administration Hospital and Rheumatology Unit of the First Department of Propaedeutic Internal Medicine of National and Kapodistrian University in Athens. Patients started TNFi (infliximab, etanercept, adalimumab, or golimumab) between January 2000 and March 2013. Written informed consent according to the new Declaration of Helsinki was obtained from all participants before inclusion in the study.

At baseline (before TNFi initiation), a verified medical history, physical examination, laboratory assessment, radiographs of spine and pelvis were obtained from all AS patients. The following patient characteristics were collected: demographics (i.e., gender and age), family history of AS (AS in first degree relatives), disease-related variables, such as time since diagnosis, symptom duration (time since symptoms onset), disease duration (time since disease diagnosis), and presence of enthesitis, peripheral arthritis, inflammatory bowel disease (IBD), psoriasis and uveitis. Disease activity was recorded at baseline by the Bath Ankylosing Spondylitis Metrology Index (BASDAI), and Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP/ESR). The functional capacity was evaluated by Bath Ankylosing Spondylitis Functional Index (BASFI).

Laboratory assessment included HLA-B27 antigen at baseline, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at baseline and every six months. All the patients were continuously under TNFi treatment during the follow-up period.

Spinal radiographic progression

Lateral X-rays of cervical and lumbar spine were made at baseline and in most of the patients repeated every two years, in order to assess the spinal structural damage. The radiographs obtained after 7 ± 2.5 years of TNFi treatment were compared retrospectively with the baseline ones. Radiographic progression was assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (17). Two trained assessors (IvdH and MK) scored radiographs independently. If a radiograph had ≤ 3 missing vertebral corners, missing scores were replaced by the mean score of the corresponding corners of the visible segments. Radiographs with > 3 missing vertebral corners were excluded from the scoring. The mean mSASSS of both readers was used for analysis.

New syndesmophyte formation (i.e., mSASSS of at least 2 at a vertebral level with a score of 0 or 1 at baseline) (18), or ΔmSASS-score/year ≥ 1 unit/year was defined as definite radiographic progression. As ΔmSASS-score/year was defined the difference between mSASSS at last visit and mSASSS at baseline, accounting for the time gap between radiographs (11). Excluded were patients with complete ankylosis of the spine.

Statistical analysis

Categorical variables were expressed as frequencies and/or percentages, and quantitative one as mean (SD) or median (IQR) according to the normality of data. Differences in baseline characteristics between males and females were evaluated by two-sample t-test for normally distributed variables, Mann-Whitney for skewed variables and Pearson X2 test for dichotomous variables. Spearman's coefficient was used for correlations between continuous variables. Time-averaged values of CRP and ESR were calculated as area under the curve, standardized for length of time interval (follow-up period). CRP levels > 5 mg/l and ESR > 12 mm/h were considered elevated.

Univariate and multivariate logistic regression analysis was applied to investigate possible risk factors for spinal radiographic progression (P-value < 0.05 was considered statistically significant). Inter-observer variability of the mSASSS was calculated by means of the intraclass correlation coefficient (ICC). All analyses were performed by STATA 12 software.

RESULTS

Out of the 208 eligible patients, fifty-eight had no cervical and/or lumbar spine X-rays at baseline (n = 48) and follow-up (n = 10), twenty-six received TNFi for less than two years, nine patients had many missing values of acute phase reactants (CRP, ESR) and fourteen (all male) had complete ankylosis at baseline (Figure 1). In total 101 of the 208 consecutive AS patients who started treatment with a TNFi were included in the analysis.

The baseline characteristics, stratified by gender, are summarized in Table 1. Most patients were males (65/101,64%) and 78% were HLA-B27 positive. The mean age was 41.6 ± 11 years (mean ± SD) and the median disease duration 6 years (IQR: 1-14) with a symptom duration of 17 ± 10 years. The mean duration of TNFi treatment was 7 ± 2.5 years (min:3 years, max:15years), and the median delay in starting biologics, estimated as the time interval between the onset of AS symptoms and the start date of the TNFi, was 15 years (IQR: 9–22).

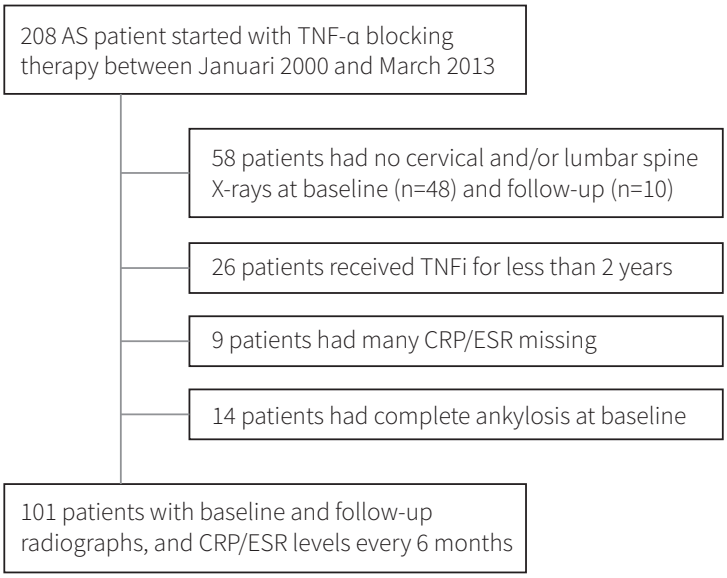

Figure 1. Flowchart of AS patients included in the analysis.

Most disease outcome measures were comparable between genders, (i.e., ESR, peripheral arthritis, and history of extra-articular manifestations (uveitis, psoriasis, IBD). At baseline, female patients scored significantly worse on disease activity (i.e. BASDAI), whereas a trend was observed of a higher baseline CRP in male patients and no gender difference was observed for the ASDAS-CRP. In contrast, male patients showed significantly more spinal radiographic damage (mSASSS and syndesmophyte formation) at baseline. There were no differences in radiographic progression between patients who continued their first TNFi or those who had to switch to another TNFi during the follow up period.

At follow up, forty-seven patients (46.5%) showed radiographic progression after 7 ± 2.5 years. Interobserver ICC for mSASSS scores was 0.92 [95% CI (0.85–0.99)]. Spinal change was evident in 38/65 men (58.5%) vs. 9/36 women (25%), $P < 0.01$. The rate of progression of the mSASS-score (ΔmSASS-score/year) was higher in males than females [0.6 (0–1.3)] vs. 0 (0–0.6)], mSASSS unit/year, ($P < 0.01$). Specifically, progression rate was significantly evident in cervical spine, in males compared to females [0.25 (0–0.8) vs. 0 (0–0.05) mSASSS unit/year, ($P < 0.01$)]. In contrast, no gender difference was observed in terms of time-averaged inflammatory markers CRP and ESR in relation to radiographic progression (Table 2).

Table 1. Baseline characteristics of 101 AS patients stratified by gender.

Patient characteristics	All, *n* = 101	Male, *n* = 65 (64%)	Female, *n* = 36 (36%)
Demographic variables			
Age (yrs), mean (SD)	41.6 (11)	42 (10.5)	41 (11.5)
Disease related variables			
Age at disease onset, mean (SD)	24.4 (8.6)	25.6 (9.3)	22.4 (7)
Time since diagnosis (yrs), median (IQR)	6 (1–14)	6 (1–14)	5 (1–13)
TNFi treatment delay (yrs), median (IQR)	15 (9–22)	15 (8.5–21)	15 (9–28)
Symptom duration (yrs), mean (SD)	17 (10)	16 (9.5)	18 (12)
HLA-B27–positive, (%)	73 (78)	45 (75)	28 (82)
AS in a first-degree relative, (%)	19 (20)	13 (22)	6 (18)
Enthesitis, (%)	87 (89)	54 (86)	33 (94)
Peripheral arthritis, (%)	44 (45)	26 (42)	18 (51)
Psoriasis, (%)	11 (11)	8 (13)	3 (9)
IBD, (%)	11 (11)	6 (10)	5 (14)
Uveitis (ever), (%)	37 (38)	20 (32)	17 (49)
Smoker (current), (%)	37 (37)	27 (42)	10 (28)
ESR, mm/h, median (IQR)	18 (10–34)	18 (9–38)	18 (10–32)
CRP, mg/L, median (IQR)	13.5 (5–33.7)	14.3 (6.7–37)	9 (3.7–22)
BASDAI, median (IQR)	6 (5–7.4)	5.7 (4.6–7)	6.5 (5.5–7.8)*
BASFI, mean (SD)	5.2 (2)	5 (2)	5.6 (2.2)
ASDAS-ESR, mean (SD)	3.6 (0.8)	3.5 (0.8)	3.7 (0.6)
ASDAS-CRP, mean (SD)	3.9 (0.8)	3.9 (0.9)	3.9 (0.8)
Radiographic damage			
mSASSS (range 0–72), median (IQR)	5 (1–19)	11 (4–26)	1.5 (0–3.5)**
Presence of syndesmophytes (yes), (%)	48 (47.5)	40 (62)	8 (22)**

AS: Ankylosing Spondylitis, IQR: interquartile range, IBD: Inflammatory bowel disease, ESR:erythrocyte sedimentation rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score. * $P < 0.01$; ** $P < 0.001$.

Table 2. Medication, inflammatory markers and radiographic progression of AS patients after 7 ± 2.5 years of follow-up.

	All, *n* = 101	**Male, *n* = 65 (64%)**	**Female, *n* = 36 (36%)**
Medications			
Current NSAIDS use, (%)	51 (55)	30 (49)	21 (66)
Current DMARD use, (%)	9 (9)	8 (13)	1 (3)
Current TNFi, (%)			
Infliximab	23 (23)	16 (25)	7 (19.5)
Adalimumab	19 (19)	13 (20)	6 (17)
Etanercept	47 (46)	31 (48)	16 (44)
Golimumab	12 (12)	5 (7)	9 (19.5)
Previous TNFi (yes), (%)	31 (31)	18 (28)	13 (37)
Inflammatory markers			
Time-averaged CRP mg/L, median (IQR)	4.7 (2.8–9.5)	5.6 (2.9–9.3)	4.5 (2.8–10.4)
Time-averaged CRP ≥ 5 mg/L, (*n*, %)	49 (48.5)	34 (52)	15 (42)
Time-averaged ESR, mm/h, median (IQR)	9.3 (5.7–16)	8.7 (4.2–14.5)	11.8 (6.2–17.6)
Time-averaged ESR ≥ 12 mm/h, (*n*, %)	45 (45)	27 (42)	18 (50)
Radiographic progression			
mSASSS (0–72), median (IQR)	10 (2–27)	18 (8–37)	2 (0–8)**
ΔmSASSS-score/year, median (IQR)	0.38 (0–1)	0.6 (0–1.3)	0 (0–0.6)*
ΔmSASSS-score/year (Cervical Spine), median (IQR)	0 (0–0.6)	0.25 (0–0.8)	0 (0–0.05)**
ΔmSASSS-score/year (Lumbar Spine), median (IQR)	0 (0–0.4)	0 (0–0.5)	0 (0–0.4)
Definite radiographic progression, (*n*, %)	47 (46.5)	38 (58.5)	9 (25)*

NSAID: Nonsteroidal AntiInflammatory Drug, DMARD: Disease–Modifying Antirheumatic Drug, TNFi: tumor necrosis factor inhibitor, IQR: interquartile range, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score. * $P < 0.01$; ** $P < 0.001$.

The ΔmSASS-score/year was significantly higher in AS patients with syndesmophytes at baseline [0.9 (0.4–1.8), median (IQR)] compared to those without [0 (0–0.4)], ($P < 0.0001$). Additionally, ΔmSASSS/year was positively correlated with both baseline and time-averaged CRP ($r_{baseline} = 0.35$, $P < 0.001$, $r_{time\text{-}averaged} = 0.3$, $P < 0.01$) and ESR ($r_{baseline} = 0.3$, $P < 0.01$, $r_{time\text{-}averaged} = 0.2$, $P < 0.05$).

In the univariate logistic regression, male gender and baseline radiographic damage (defined as presence of syndesmophytes at baseline X-rays) were associated with

radiographic progression (OR = 12.8; 95% CI = 4.9–33) (Table 3). Moreover, smokers were more likely to progress (OR = 3.3; 95% CI = 1.1–10.2). In contrast, concomitant NSAIDs' use reduced the odds of radiographic damage (OR = 0.4; 95% CI = 0.18–0.95). All markers of inflammation (i.e., baseline CRP > 5 mg/L, ASDAS-CRP/ESR, time averaged ESR, time averaged CRP > 5 mg/L) were significantly associated with progression of structural changes.

In the multivariate model, independent risk factors for spinal radiographic progression during TNFi treatment were the presence of syndesmophytes at baseline (OR: 14.7, 95%CI: 4.9–44) and time-averaged CRP above 5 mg/L (OR: 7.6, 95%CI: 2.5–23).

Table 3. Univariate and Multivariate logistic regression analyses for spinal radiographic progression over 7 ± 2.5 years.

Variable	Univariate analysis	Multivariate model
	OR (95% CI)	OR (95% CI)
Male vs. Female	4.2 (1.7–10.4)**	
Age, years	1.02 (0.9–1.05)	
NSAID use	0.4 (0.18–0.95)*	
Smoking	3.3 (1.1–10.2)*	
HLA-B27	0.7 (0.25–1.8)	
TNFi treatment delay > 10years	1.6 (0.6–3.8)	
Baseline CRP, (mg/L)	1.005 (0.9–1.01)	
Baseline CRP ≥ 5 mg/L	6.3 (1.9–20.2)**	
Baseline ESR, (mm/h)	1.02 (0.9–1.04)	
Baseline ESR ≥ 12 mm/h	2.5 (0.99–6.3)	
Baseline BASDAI	1.06 (0.8–1.35)	
Baseline BASFI	0.95 (0.8–1.2)	
Baseline ASDAS-CRP	2.6 (1.4–4.9)**	
Baseline ASDAS-ESR	1.9 (1.03–3.7)*	
Time-averaged CRP ≥ 5 mg/L	5.6 (2.4–13)***	7.6 (2.5–23)***
Time-averaged ESR, mm/h	1.05 (1.003–1.09)*	
Time-averaged ESR ≥ 12 mm/h	1.9 (0.87–4.3)	
Presence of syndesmophytes	11.5 (4.5–29)***	14.7 (4.9–44)***
Baseline mSASSS	1.08 (1.03–1.11)***	

OR: odds ratio, CI: confidence interval, NSAID: nonsteroidal antiinflammatory drug, TNFi: tumor necrosis factor inhibitor, ESR:erythrocyte sedimentation rate, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, mSASSS:modified Stoke Ankylosing Spondylitis Spinal Score. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

DISCUSSION

In AS patients with long standing disease, treated with TNFi in daily clinical practice, the higher levels of inflammation, measured by time-averaged CRP levels, were significantly associated with higher spinal radiographic progression on long term. To the best of our knowledge, this is the first study to show the impact of sustained elevated acute face reactants, during treatment with TNFi, on structural damage, in AS patients with established disease and long symptom duration (> 10 years). In our study, only time-averaged CRP and the presence of syndesmophytes at baseline have been demonstrated as independent prognostic factors for radiographic progression.

Before TNFi initiation, all AS patients had high disease activity and about half of them (47%) had syndesmophytes, which means that this group had a high risk at radiographic progression. According to literature review, the proportion of syndesmophytes at baseline varied from 30% in 'early' AS (< 10 years symptom duration) (12), 47–58% in AS patients with a variable disease activity status (13) to 55–61% in AS patients with active disease before initiation of TNFi (9), (10). In accordance with previous studies, we found in the univariate analysis, that male gender, smoking status, elevated baseline CRP levels, ASDAS (both CRP/ESR) and NSAIDs use, were significantly associated with radiographic progression (12), (18), (19), (20). We acknowledge, however, that the calculation of the recommended NSAIDs index was not applicable during data collection. Additionally, radiographic progression was significantly more prominent in the cervical segment than in the lumbar segment, which was evident in previous studies from OASIS cohort (13), (21).

Our results were similar with previous findings of Park et al. (22), who, in contrast to our study, examined the radiographic progression of patients with early AS (i.e., symptom duration < 10 years) for shorter follow-up period (2–4 years). Moreover, they included patients under NSAIDs, besides those under TNFi. According to their findings, the presence of syndesmophytes at baseline and time-averaged CRP level were associated with increased odds of progression (OR of 5.71 and 3.02, respectively), which are consistent to ours. Nevertheless, no difference regarding treatment regime (TNFi vs. NSAIDs) on radiographic progression was observed.

A five-year, sex-stratified prospective study from Sweden showed that that presence of baseline spinal radiographic damage and obesity, were independent predictors of spinal radiographic progression in both genders. Elevated baseline CRP was a significant predictor in men, but only a trend was observed in women. Smoking predicted progression in men, whereas high Bath Ankylosing Spondylitis Metrology Index (BASMI)

and exposure to bisphosphonates during follow up predicted progression in women (15). In contrast to our study, a minority of patients was under TNFi treatment (50/166,30%) and no correlation with time-averaged CRP was observed.

In the study of the Groningen Leeuwarden AS (GLAS) cohort, which included 176 patients under TNFi treatment, only a trend for the longitudinal association of CRP and ESR levels with radiographic progression was observed [23]. Additionally, the results from the GO-RAISE study indicated that elevated CRP levels after 2 years of golimumab treatment correlated with greater radiographic progression risk at 4 years (14).

Historical longitudinal observational cohort studies in AS patient described significant relationships between disease activity and radiographic progression and included patients with a high variability in disease activity status and treatment regimens (12), (20). In the Outcome in AS International Study (OASIS), patients with very high disease activity (ASDAS > 3.5) over time showed an additional increase of 2.3 mSASSS units per 2 years compared to patients with inactive disease (ASDAS < 1.3) (20). In another study of the same cohort, baseline ESR was significantly associated with the development of new syndesmophytes after 4 years of follow-up (OR 1.03, 95% CI: 1.00–1.07) in the univariate analysis (18).

In 210 early axial SpA patients from the German Spondyloarthritis Inception Cohort (GESPIC), elevated ESR levels at baseline (> 20 mm/hr) and time-averaged elevated CRP levels over 2 years (> 6 mg/L) were significantly associated with spinal radiographic progression during 2 years of follow-up (12). Moreover, another study from the same cohort, which included only a minority of patients under TNFi (2.2%), showed that time-averaged ASDAS-CRP was the strongest predictor for radiographic progression, after adjustment for baseline syndesmophytes (24). Similar results regarding the impact of time-averaged ASDAS on radiographic progression are derived from the Swiss Clinical Quality Management cohort with up to 10 years of follow-up (25).

Thus, previous studies assumed that the ASDAS-CRP, which includes both CRP and a patient-reported outcome, was a better predictor for radiographic progression (20), (24), (25). Although the multivariate analyses using the ASDAS showed a slightly better fit than the one with CRP level in those studies, it should be considered that the patient-reported outcome could be influenced by subjective symptoms such as pain and fatigue (26), (27).

Moreover, Machado et al showed that spinal inflammation, depicted by MRI, showed a stronger correlation with CRP levels compared to other measures of disease activity (28). Additionally, in the recent review of Aoua et. al, CRP has been proposed as a biomarker

of spinal radiographic change in AS (29). Therefore, we might assume that time-averaged CRP is a useful predictor of radiographic progression, especially if the time-averaged ASDAS is not always available, as is in our study, because it was not routinely measured in patients' medical records.

This study has some limitations. The lack of longitudinal mSASSS-scores with a 2-year interval in the majority of patients, does not allow us to make more accurate time-point estimations. Moreover, the relatively small percentage of female patients was insufficient for gender analyses.

A major disadvantage of the study is that there not sufficient longitudinal data on BASDAI and ASDAS-CRP, in order to estimate the time-averaged values and incorporate them in the analysis. Thus, it is not clear whether the patients with CRP < 5 mg/L have also low disease activity (i.e. 2.1 < ASDAS-CRP < 1.3). Additionally, CRP might be elevated in AS patients with obesity or other comorbidities. Also a proportion of our patients might have high CRP due to residual inflammation on bowel (IBD) or in peripheral joints.

Nevertheless, our long-term data suggest the positive effect of the inflammation resolution, as reflected by lowering of the CRP-levels due to TNFi treatment, on spinal changes in AS. An important observation arising from this study is that the symptoms relief during treatment with TNFi might not be an adequate parameter for prognosis of radiographic outcome. Thus, in case of sustained elevated CRP/ESR levels, during TNFi administration, a switch of treatment regime might be considered. The latter, in case that it is confirmed in other cohorts, could possibly influence/modify the therapeutic strategies in AS.

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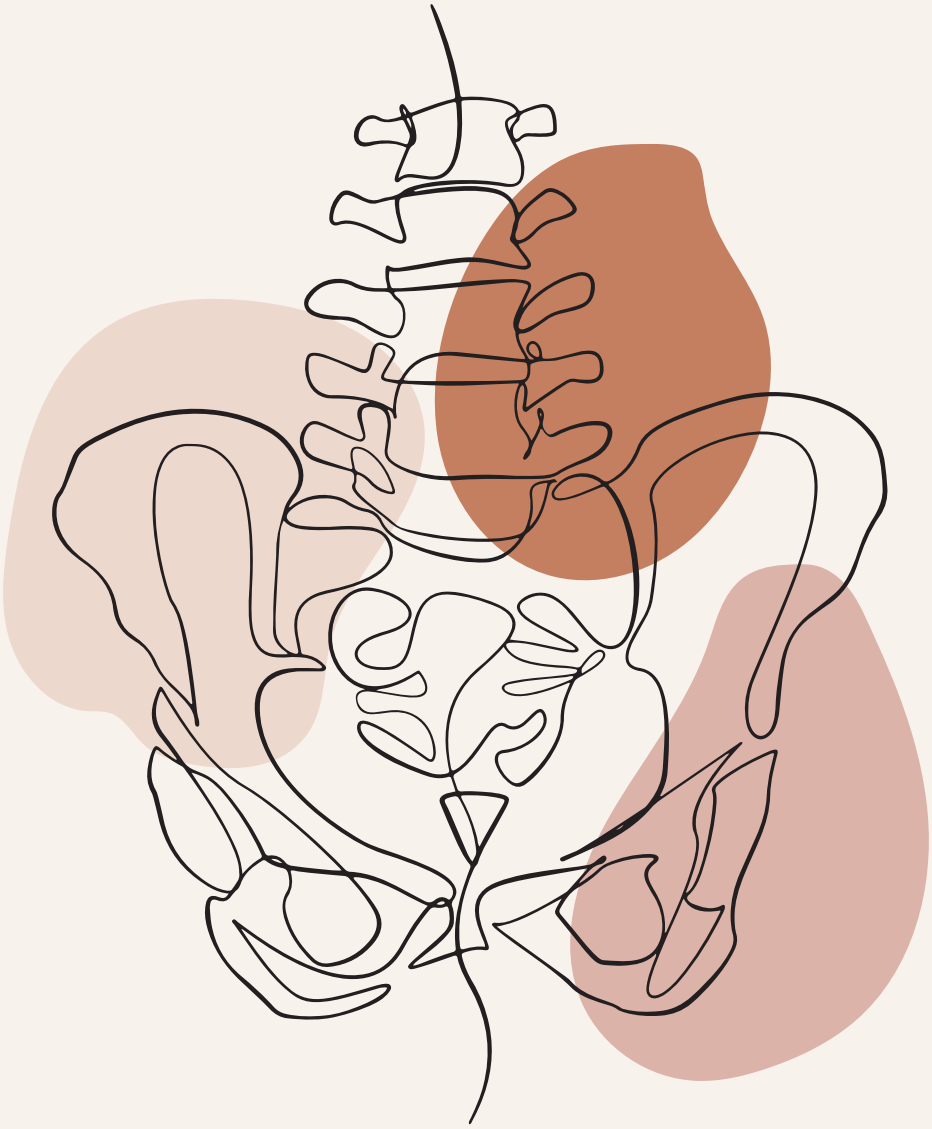


CHAPTER 11

SUMMARY

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that mainly affects the axial skeleton. The disease manifests itself at a young age (<40 years) and can be divided in a subtype with radiographic changes of the sacroiliac joints according to the Modified New York criteria, called ankylosing spondylitis (AS, or radiographic axSpA) and a subtype without radiographic changes, non-radiographic axSpA (nr-axSpA). For both, the radiographic and nr-axSpA, the main clinical symptom is chronic low back pain with an inflammatory character. In addition to the inflammatory back pain, articular (arthritis) and extra-articular manifestations (such as: uveitis, inflammatory bowel disease (IBD) and psoriasis) add to the disease burden of axSpA patients.

In **Chapter 1,** the general introduction, an overview of the epidemiology and disease characteristics of axSpA is given. Moreover, the main objectives of this thesis and the study populations used are briefly discussed. This thesis consists of two general subjects in axial spondyloarthritis on which, up to now, limited studies were conducted, namely 1) sex differences in clinical manifestations, treatment efficacy and drug survival and 2) early detection and treatment of the disease.

Part one: Sex differences in axial spondyloarthritis

In **Chapter 2** an extensive literature review on sex differences in axSpA is presented. The main aim was to increase awareness on sex differences by demonstrating that myths on sex differences in diagnosis, disease manifestation and drug effectiveness are still present despite data of the most recent literature. The main conclusions in axSpA are that sex differences play a role in biological processes, such as immune responses, pain mechanisms and disease manifestations including enthesitis and radiological progression, and in treatment efficacy. Although lower TNFi efficacy and drug survival were observed in women compared to men, sex differences in efficacy of other biologicals remain unsolved.

Gender differences in drug survival and occurrence of adverse events in ankylosing spondylitis (AS) patients treated with a TNFi in daily practice in a peripheral hospital are described in **Chapter 3**. Data of 122 AS patients (60.7% male) who fulfilled the modified New York criteria and who were TNFi naive were retrospectively collected in a period from January 2004 to January 2014. Patients had a mean treatment duration of 51 months (range 1;127 months), showing significant differences between men (44.9 months) and women (33.4 months). Overall, 21 patients (17.2%) stopped the TNFi, mainly due to inefficacy (52.4%). Women switched more often between TNF-inhibitors compared to men (26.9% vs. 16.3%).

Gender differences in long-term mean disease activity scores, short-term response and drug survival of TNFi were examined in **Chapter 4**. Overall, 356 patients (34% women) diagnosed with AS, who initiated a TNFi were recruited from the prospective Amsterdam Spondyloarthritis (AmSpA) cohort and followed until the last visit of the period on treatment with the first TNFi (drug survival). Patients were on average 46 years (SD 12) old and had a median disease duration of 12 years (inner quartiles 6;20). Longitudinal regression analyses for repeated measurements in disease activity scores showed that women had a 0.9 point higher Bath ankylosing spondylitis disease activity index (BASDAI)-score compared to men (mean difference β = 0.9, 95% Confidence Interval (CI) [0.4;1.4] p=0.001). Although no significant differences were observed for gender in ankylosing spondylitis disease activity score (ASDAS)- C-reactive protein (CRP) over time, there were significant gender differences observed in ASDAS-CRP response to TNFi. Women were less likely to achieve a clinically important response at six months than men 47% vs. 64% (Relative Risk (RR) 1.4, 95% CI 1.1;1.9, p=0.02). Moreover, numerically more women than men discontinued treatment over a period of 5 years (Hazard Ratio (HR): 1.5, 95% CI [0.9;2.5], p=0.15). In conclusion, the results from this cohort study demonstrate a higher burden of disease and lower response to TNFi in women.

In **Chapter 5,** the long-term effects of TNFi on bone mineral density (BMD) and the incidence of vertebral fractures (VF) were evaluated. Overall, 135 AS patients (70.4% men, mean age 34 (SD 8.6) years, mean disease duration 11.9 years (SD 9.5)) with active AS (BASDAI ≥4), treated with TNFi and with available DEXA scans and X-rays, were included. At baseline, 40.1% of the patients had a low BMD of the hip and 40.2% of the lumbar spine (according to the WHO criteria for osteoporosis). After four years of TNFi treatment there was a significant decrease in patients with a low hip BMD (38.1%, p=0.03) and low BMD of the lumbar spine (25.3%, p<0.001). VF (classified as a Genant score >1/≥20% height loss) were present at baseline in 11.1% of the population and in 19.6% after four years of TNFi treatment. A Genant score ≥2, was observed at baseline in 3 out of 14 VF (21.4%), with a slight increase over four years to 7 out of 27 VF (25.9%). Unfortunately, despite significant improvement of disease activity and BMD after four years of TNFi treatment, the number and severity of VF increased. In addition, the radiological progression, measured by the modified Stoke Ankylosing Spondylitis Spinal score (mSASSS), significantly increased as well, from a median mSASSS of 4.0 (1.5;16.0) at baseline to 6.5 (2.1;22.9) after four years of treatment.

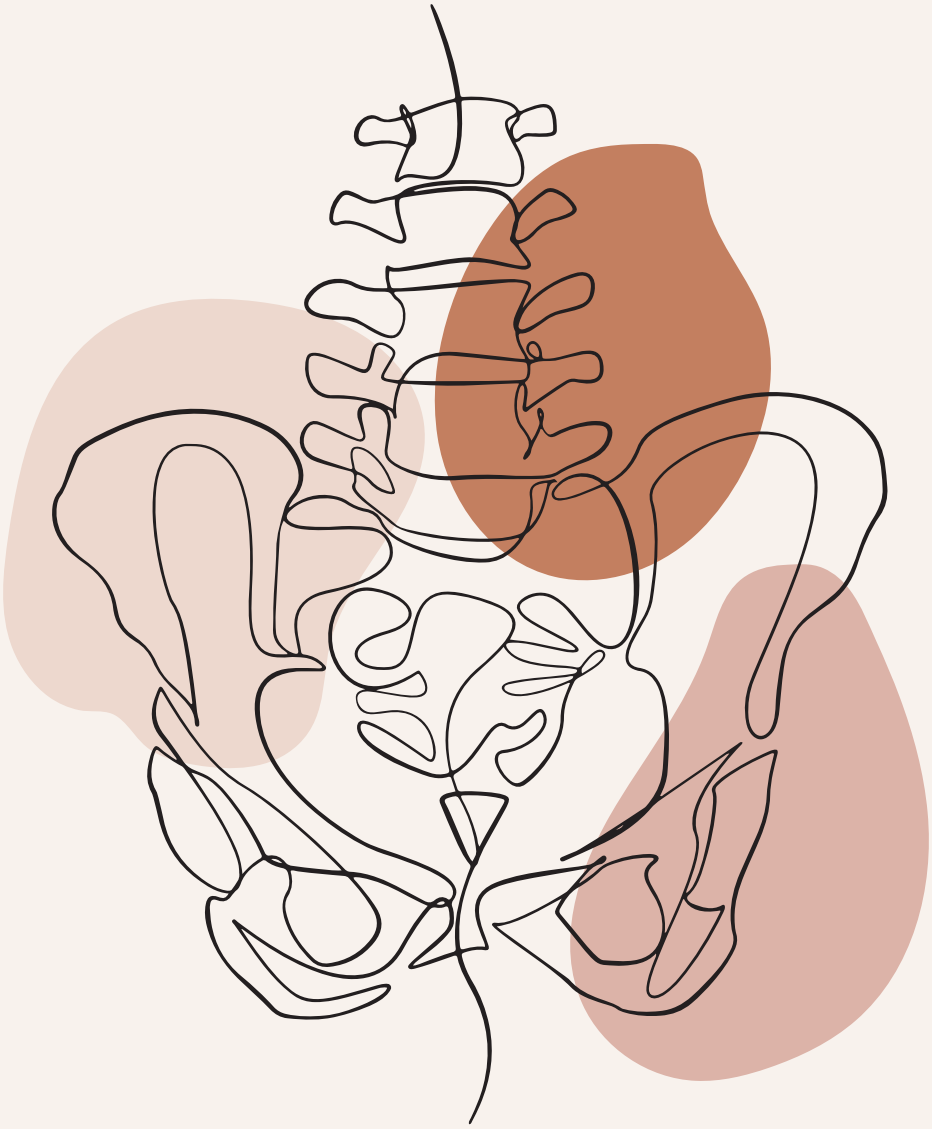
Part two: Early detection and treatment in axial spondyloarthritis

Signs of inflammation on MRI of the SIJ and spine in patients with inflammatory back pain (IBP) who were suspected of having nr-axSpA, with high disease activity (BASDAI ≥4) were studied in **Chapter 6**. In addition, the onset of new inflammatory lesions at the MRI after six months in patients without any lesions at baseline and gender differences in the presence of inflammation were evaluated. The main conclusion was that forty percent of the included patients showed inflammatory lesions on MRI of the SIJ and/or spine, which was observed most in MRI-SIJ and occurred more often in males compared to females. If patients had an MRI without inflammatory lesions, the majority (95.3%) of the MRI's remained negative after six months, despite high disease activity.

In **Chapter 7,** the six month results of the Prevention of the progression of very early symptoms in Ankylosing Spondylitis (PrevAS) study are described. With this placebo-controlled, double blind randomized clinical trial (RCT) the efficacy of 16 weeks treatment with etanercept (ETN) in patients suspected of non-radiographic axial spondyloarthritis (nr-axSpA) was compared to placebo. Patients with, inflammatory back pain (IBP) with at least two SpA-features, high disease activity (BASDSAI ≥ 4) and who were TNFi naive were included, without the requirement of having a positive MRI and/or elevated C-Reactive Protein (CRP). They were randomized (1:1) to ETN (n=40) or placebo (PBO) (n=40) for 16 weeks and followed thereafter without study medication up to 24 weeks. Patients characteristics at baseline were comparable between ETN and PBO. This study showed that in patients suspected of nr-axSpA with high disease activity but without the requirement of positive MRI and/or elevated CRP, treatment with etanercept was not effective. As a response to a reaction on the first PrevAS results, we have written a letter, focused on the lack of good diagnostic and monitor tools for disease activity in axSpA (**Chapter 8**).

The three year results of the PrevAS study (**Chapter 9**) include the course of clinical symptoms and radiological changes after a short period biological treatment in patients suspected of nr-axSpA at three years follow up. The main conclusion was that early treatment with etanercept in this group of patients apparently was not effective since high disease activity remained to be present during three years of follow-up without significant changes in radiological progression between both groups.

In **chapter 10** we have investigated whether the impact of long-term treatment (>3 years) with TNFi on radiographic progression in established AS is associated with the level of acute phase reactants during therapy. The main conclusion was that in AS patients with long standing disease increased levels of time-averaged CRP (>5mg/L) were significantly associated with radiographic progression during TNFi treatment.



CHAPTER 12

GENERAL DISCUSSION

SEX DIFFERENCES IN AXIAL SPONDYLOARTHRITIS

Clear sex differences in several aspects within the axSpA spectrum are demonstrated in part one of this thesis. These sex differences not only influence the onset and progression of axSpA, but also affect the efficacy of TNFi treatment. Women remained a higher level of disease activity during TNFi treatment and had a shorter time on drug compared to men. These findings raise the question if TNFi treatment in general is the right treatment strategy for women diagnosed with axSpA and, if so, what causes these differences.

One hypothesis is that treatment with biologicals in axSpA is effective in the reduction of inflammation but might be less beneficial in reducing pain response in women. Recent studies revealed higher pain scores in women diagnosed with axSpA compared to men measured with visual analogue scales (1-5). These higher pain ratings in women could partly be explained by higher pain sensitivity described in women in general and not only in rheumatic diseases (6), which might be related to the influence of sex steroids like estrogen (7, 8). Sub-optimal treatment of pain might be an explanation for the high disease activity scores in women under TNFi treatment.

Another hypotheses for the suboptimal improvement of disease activity scores under TNFi treatment in women could be sex differences in body composition. Women in general have a 10% higher body fat percentage (BF%) compared to men (9). Previous studies revealed that a higher Body Mass Index (BMI) is associated with a lower response rate to TNFi, which might be due to a higher BF%. Women with AS and a high BF% or fat mass index (FMI) showed a significant relationship with high disease activity (ASDAS and BASDAI), which is contradicting since male patients with high disease activity scores had a low BF% and FMI (10). The underlying physiological mechanism could be that adipose tissue acts as an endocrine organ and secretes, in addition to the anti-inflammatory adiponectin and the pro-inflammatory leptin, also other pro-inflammaory cytokines such as tumor necrosis factor. One study showed a correlation between BMI and the inflammation marker C-reactive protein in women diagnosed with axSpA (11-13).

Aside from hormones and body composition, sex differences were also observed in immunological responses. Studies on sex differences in immune response showed that male AS patients had significantly higher levels of TNFi and IL-17A compared to female patients (14, 15). This might explain the higher response rates to TNFi in men compared to women. However, preliminary results on sex differences in treatment with IL-17 inhibitors show much smaller sex differences in drug efficacy after twelve months, in contrast to TNFi (16). As the current guidelines advise to decide on treatment efficacy after three months, it could be discussed if this decision might be taken too early as the benefits

of this treatment in women improve during one year. The results on secukinumab and ixekizumab revealed significant sex differences up to sixteen weeks of treatment, but thereafter the efficacy outcomes were comparable, with no sex differences in dropout rates (16, 17). These differences in response rates between men and women over time with different types of biologicals should be studied more consequently in future research.

Apart from sex differences in treatment efficacy, the prevalence of comorbidities like osteoporosis, is also related to age and sex. Osteoporosis, a common comorbidity within the axSpA disease, is considered to be a typical postmenopausal women's disease (Chapter 2). However, young male axSpA patients also revealed an increased risk for osteoporosis, including the onset of vertebral fractures (18-21). Recognition of these different manifestations and symptoms within subgroups of patients is not always obvious. Physicians are trained to recognize patterns of complaints which correspond with a specific disease, based on recent scientific literature and experiences of the previous generation of physicians. Thinking in patterns, in general, results in efficient diagnosis in a group of patients. However, if a patient does not correspond with the known, standardized patterns, this might influence the correct diagnosis, which also influences treatment strategies (22).

EARLY DETECTION AND TREATMENT IN AXIAL SPONDYLOARTHRITIS

In AS, men are two to three times more likely to get the diagnosis than women (Chapter 2). A probable cause of underdiagnosis of AS in women could be that they suffer more from peripheral complaints such as enthesitis instead of the merely axial complaints as inflammatory back pain (23). Moreover, radiological progression is less evident in an early disease stage in women compared to men, because of a slower radiological progression.

Early diagnosis of axSpA is based on the history of chronic back pain, morning stiffness, a positive family history of SpA, extra-articular manifestations and physical examination. Objective signs of inflammation however are easier to asses in case of peripheral arthritis (as in rheumatoid arthritis), compared to the examination of the lumbar spine. The modified Schober's test can be useful for diagnosis but is not sensitive to change after treatment.

As radiographic changes are usually not yet present in the early phase of the disease, detection of inflammatory lesions on MR-imaging (MRI) of the sacroiliac joints (SIJ) can be useful (24) and Chapter 8. MRI has a prominent place for diagnosis in clinical practice and within the ASAS classification criteria (24). However, MRI-imaging might also show

controversial results as bone marrow edema (BME) in the SIJ also occurs in healthy individuals who perform intensive sporting activities and in postpartum women (25, 26). In addition, as we have demonstrated, MRI is often negative, even in patients with high disease activity scores (BASDAI ≥4 , Chapter 7). MRI changes seems therefore not exclusive for the axSpA disease spectrum.

Apart from observing inflammation with MRI-techniques, increased blood levels of phase reactants like CRP might also contribute to an early diagnosis. High CRP-levels were significantly associated with radiological progression (Chapter 10). However only 30% of the axSpA patients have raised CRP-levels, even in case of severe manifestations of r-axSpA (27). Men present themselves more often with raised CRP-levels compared to women. Therefore, CRP-levels were not the most representative tool to measure disease activity in axSpA. Because axSpA had, up to now, insufficient objective diagnostic tools, the golden standard to diagnose axSpA is still based on clinical evaluation, laboratory values and conventional radiographs.

Additional to axial complaints, many early axSpA patients, and especially women, present themselves with peripheral complaints such as enthesitis (23). Currently, reliable imaging tools to measure objective signs of enthesitis are limited in clinical practice. MRI is limited to the selected body part of view, while whole-body MRI is not sensitive enough, because of low reproducibility and higher slice thickness influencing the judgement of enthesitis (28-30). New imaging techniques, such as ultrasound, low dose CT and PET-CT scan seem to be very promising in diagnosing axSpA at an early stage and to monitor disease progression, but have their limitations. Ultrasound, although noninvasive, is very time consuming and not well standardized. Ultrasound techniques could also be influenced by bodyweight and repetitive physical activity and give an overestimation of the observed enthesitis (31, 32). Low dose CT scans are helpful in determining structural and chronic changes, but limited evidence is available for the detection of enthesitis. Positron Emission Tomography (PET), however, could be a promising alternative for the aforementioned methods, since it could detect inflammation in the whole body, in an early disease stage and is sensitive for changes over time (33).

The recognition of axSpA symptoms in an early disease stage is important, because early treatment could delay radiological progression (34-36). However, clear recommendations on the correct timing to attribute certain symptoms to axSpA and initiate appropriate treatments is still not clear.

Especially in nr-axSpA patients without a positive MRI of the SIJ and/or raised CRP-level, there is limited evidence to support certain treatment interventions. Several studies in

nr-axSpA have demonstrated a high efficacy of biologicals in patients with a positive MRI of the SIJ and raised CRP-levels. In contrast, the PrevAS study (Chapter 7) was performed in a group of patients who were highly suspicious of having nr-axSpA (37) and had a high disease activity (BASDAI ≥4), without these features. This study, showed that TNFi treatment was not effective in lowering the disease activity nor in preventing symptom progression in this particular group of patients (Chapter 7 and 9).

Current practice is mainly focused at medical interventions, including treatment with biologicals. The threshold for prescribing biologicals in many countries is low in order to improve the accessibility to this medication. However, discussions are raised on overtreatment with biologicals in this group of patients, as the response rates are lower compared to clinical trials (38, 39).

Historically, encouraging exercise therapy and sporting activities were, in combination with the use of Non-steroidal anti-inflammatory drugs (NSAIDs), an important corner stone of the treatment strategy in axial SpA. Unfortunately, nowadays exercise therapy has a less prominent place in the current treatment guidelines. As also mentioned above in the evaluation of treatment efficacy in biologicals, the time described in the international guidelines to evaluate the efficacy of NSAIDs (with at least two different NSAIDs) and exercise therapy of three months might be too short and should be prolonged to six months up to one year. This evaluation period could be used to monitor and evaluate the efficacy of this treatment strategy in patients without a positive MRI-SIJ and raised CRP-level.

Although NSAIDs substantially lower symptoms by 70-80% in axSpA patients, the efficacy of NSAIDs on radiological progression is still uncertain and conflicting results are presented(40, 41). Full dose of NSAID's in AS patients might delay the radiological progression in contrast with a low dose in comparison with treatment on demand. However, for nr-axSpA, no association was found between a high and low dose NSAIDs and radiological progression (42). NSAIDs seems to enhance exercise therapy, because they reduce pain and stiffness(41). Exercise therapy studies are challenging, but recently a new study has started to evaluate the effect of long-term, ongoing exercise therapy in axSpA patients who experience severe disabilities in their daily lives. To observe the effect of the treatment strategy of NSAIDs and exercise therapy, objective measurement tools are preferred, alongside the already used and integrated response measurements such as the ASAS20/40 and ASDAS.

Nowadays, there is an unmet need for reliable objective measurements to evaluate and monitor disease progression and treatment response (39). Recently, a new tool was

developed for evaluating and monitoring disease progression and treatment response. The Ankylosing Spondylitis Physical Performance-based Index (ASPI) is based on physical performance measurements, which is reliable, feasible for daily practice and sensitive to change by treatment in patients with r-axSpA. These findings in r-axSpA are currently being validated in a nr-axSpA population and must be studied more extensively. ASPI seems to be a feasible tool for monitoring treatment efficacy in axSpA patients and might be useful to detect sex differences in longitudinal treatment response as well. Moreover, it would be interesting to assess if the same response rates were observed over the different types of biologicals and during tapering of medication in men and women while monitored with the ASPI.

So far, evidence on sex differences in physiological processes and treatment responses are sufficiently reported in reviews and clinical studies in many rheumatic diseases. However, translation of these data towards clear treatment recommendations for daily clinical practice are lacking. In additional research, more attention should be paid for sex differences within study designs and analyses. Other recommendation for future research could be with, for instance, prediction models including among others sex, age, comorbidities, life events (such as having a pregnancy wish) are needed to develop recommendations for clinical practice in which biological would be the best option for a patient.

Additional recommendations for clinical practice are to pay more attention for sex difference within comorbidities, including osteoporosis in males diagnosed with axSpA and cardiovascular diseases in women. Moreover, to reconsider a longer evaluation period for treatment up to six or twelve months instead of three months. Lastly, it is important to be aware of the limitations of the current used outcome measurement tools and to consider the use of the reliable and objective ASPI test.

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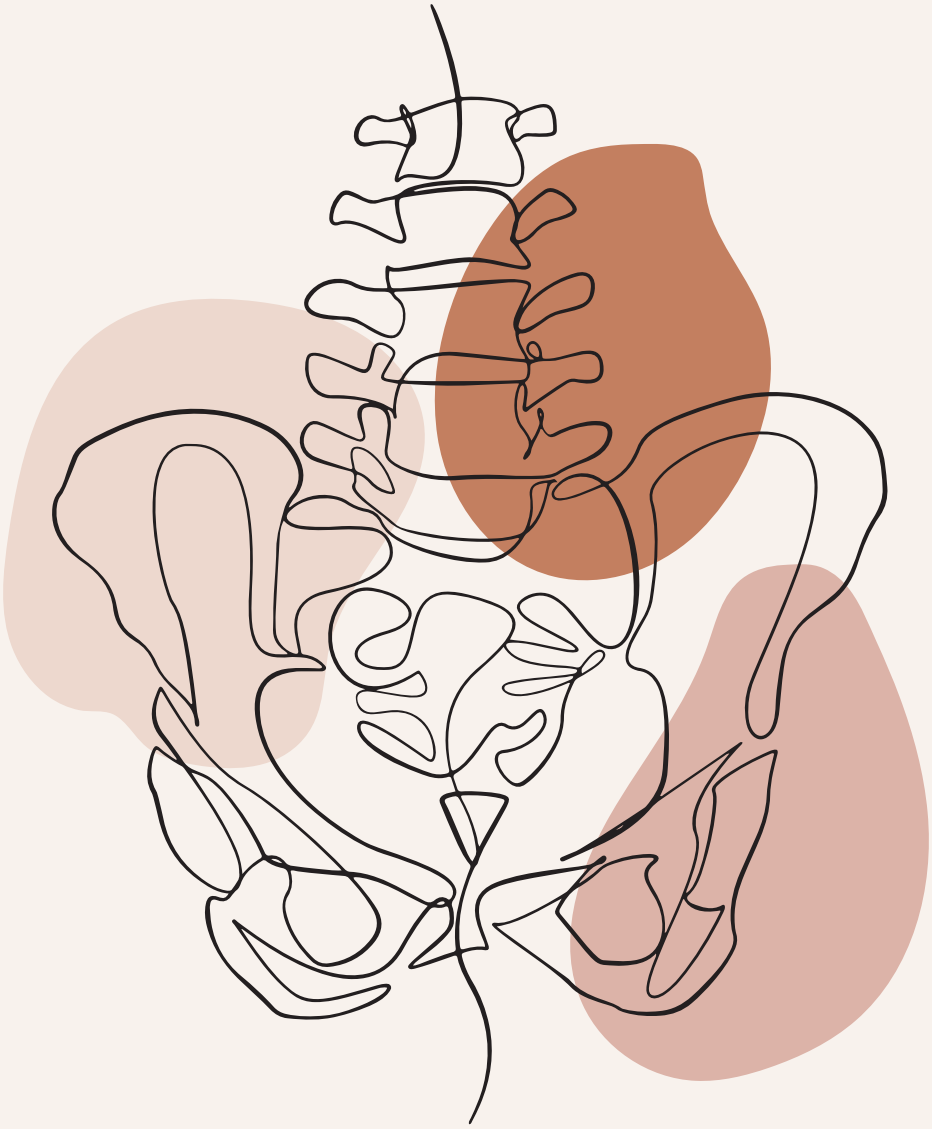

APPENDICES

NEDERLANDSE SAMENVATTING

LIST OF PUBLICATIONS

CURRICULUM VITAE

DANKWOORD

NEDERLANDSE SAMENVATTING

Axiale spondyloartritis: sekseverschillen, ziekteverloop en vroege behandelstrategieën

Introductie

Axiale spondyloartritis (axSpA) is een reumatische ontstekingsziekte die onderdeel is van een verzameling ontstekingsziekten, spondyloarthritis (SpA). De eerste symptomen van axiale SpA ontstaan op relatief jonge leeftijd, voor het 45ste levensjaar. Bij AxSpA staan vooral de rugklachten op de voorgrond door chronische ontstekingen van de wervelkolom en het bekken (de heiligbeengewrichten (SI)). Tevens kunnen er gewrichtsklachten ontstaan, waaronder gewrichtsontstekingen in de handen en knieën en peesontstekingen (enthesitis). Daarnaast kunnen oogontstekingen optreden (regenboogvliesontsteking) en aandoeningen van de huid (psoriasis) en/of darmontstekingen (ziekte van Crohn en colitis ulcerosa). Wanneer er vooral gewrichtsontstekingen aanwezig zijn dan wordt deze vorm "perifere SpA" genoemd. Verder kan AxSpA onderverdeelt worden in twee groepen, namelijk radiografische AxSpA met aantoonbare radiografische veranderingen in de SI-gewrichten op de röntgenfoto's (spondylitis ankylopoetica, SA) en de non-radiografische AxSpA (nr-AxSpA) waar deze veranderingen (nog) niet zichtbaar zijn.

In **Hoofdstuk 1 (de Introductie)** worden het voorkomen en ziektekenmerken van AxSpA uiteengezet en de behandelmethoden beschreven, waaronder het gebruik van biologicals, zoals tumor necrosis factor alfa remmers (TNFi). Daarnaast worden de doelstellingen beschreven en de studiepopulaties van dit proefschrift nader omschreven. Dit proefschrift bevat twee hoofdthema's waar tot op heden weinig studies over zijn uitgevoerd, namelijk 1) man-vrouw verschillen in ziektekenmerken, ziektebeloop, effectiviteit en duur van behandeling en 2) vroege opsporing en behandeling bij patiënten die kenmerken hebben van nr-AxSpA. Tevens wordt er een hoofdstuk gewijd aan de afwijkingen op de röntgenfoto's die kunnen ontstaan bij deze groep patiënten.

Deel 1: Man-vrouw verschillen binnen axiale spondyloartritis

Hoofdstuk 2 bevat een uitgebreid literatuuroverzicht met als primaire doelstelling de bewustwording over man-vrouw verschillen in ziektekenmerken, ziektebeloop en de effectiviteit van behandelingen te vergroten. De review is opgebouwd uit verschillende mythes die heersen over man-vrouw verschillen binnen de AxSpA, ondanks de beschikbare literatuur. De belangrijkste conclusies uit dit overzicht zijn dat man-vrouw verschillen een rol spelen in biologische en fysiologische processen zoals in de afweer (immuunreacties), pijnmechanisme en ziektepresentatie waaronder peesontstekingen (enthesitis), beloop van radiologische veranderingen en behandeleffectiviteit. Binnen de literatuur zijn duidelijke man-vrouw verschillen beschreven waarbij vrouwen

minder goed op TNFi reageren en een kortere behandelduur laten zien dan mannen. Deze waarnemingen zijn echter nog nauwelijks beschreven voor andere biological behandelingen.

De man-vrouw verschillen in behandelduur en bijwerkingen bij TNFi behandelingen in patiënten gediagnosticeerd met SA worden beschreven in **Hoofdstuk 3**. Retrospectieve data van 122 SA patiënten (39% vrouw), behandeld met hun eerste TNFi binnen een perifeer ziekenhuis werden verzameld van januari 2004 tot januari 2014. De gemiddelde behandelduur was 51 maanden (range 1 tot 127 maanden), waar mannen bijna een jaar langer het middel gebruikten dan vrouwen (44,9 vs. 33,4 maanden). In totaal stopte 21 patiënten (17,2%) met hun eerste TNFi met als belangrijkste reden ineffectiviteit (52,4%). Tevens wisselden vrouwen vaker tussen verschillende TNF-remmers dan mannen (26,9% vs. 16,3%).

In **Hoofdstuk 4** worden de onderzoeksresultaten gepresenteerd van man-vrouw verschillen in gemiddelde ziekteactiviteitscores en behandelduur na korte termijn en na vijf jaar follow-up. De studiepopulatie bestond uit 356 SA patiënten (34% vrouwen) uit het Amsterdam Spondyloarthritis (AmSpA) cohort, die in de tijd gevolgd zijn gedurende de behandeling met hun eerste TNFi behandeling. Vrouwen laten gemiddeld een hogere ziekteactiviteitscore zien, gemeten met de Bath ankylosing spondylitis disease activity index (BASDAI) score, dan mannen. Tevens toonden vrouwen onder TNFi behandeling een kleinere kans op een goede behandeleffectiviteit na 6 maanden ten opzichte van mannen (47% vs. 64%). Daarbij stopten meer vrouwen dan mannen met de TNFi behandeling in een periode van vijf jaar. Concluderend, de resultaten uit deze cohortstudie laten een hogere ziektelast en lagere behandeleffectiviteit op TNFi zien bij vrouwen in vergelijking tot mannen.

De lange termijn effecten van TNFi behandeling op de botdichtheid en het ontstaan van wervelfracturen worden geëvalueerd in **Hoofdstuk 5**. De studiepopulatie bestond uit 135 jonge SA patiënten (70,4% man, gemiddeld 34 jaar oud) met hoge ziekteactiviteit (BASDAI≥4) die behandeld werden met een TNFi. Gedurende de vier jaar TNFi behandeling was er een grote vermindering te zien in patiënten met een lage botdichtheid van de heupen (40% vs. 38%) en de rug (lumbale wervelkolom) (40% vs. 25%). Het aantal wervelfracturen (11% vs. 20%) en de ernst van fracturen namen echter toe tijdens vier jaar TNFi behandeling. Tevens was er een stijging te zien in de radiologische veranderingen op de röntgenfoto's na vier jaar TNFi behandeling.

Deel 2: Vroege herkenning en ziekteverloop in axiale spondyloartritis

In **Hoofdstuk 6** worden patiënten met chronische ontsteking aan de rug, hoge ziekteactiviteit (BASDAI≥4) en verdenking op nr-AxSpA, onderzocht op tekenen van ontsteking op de MRI-scan van de SI-gewrichten en de wervelkolom. Bij patiënten zonder ontstekingshaarden op de eerste MRI-scan werd de scan herhaald na 6 maanden om nieuwe ontstekingen op te sporen. Deze gegevens zijn ook onderzocht op man-vrouw verschillen. De hoofdconclusie van deze studie was dat bij 40% van de geïncludeerde patiënten ontstekingshaarden werden gevonden, vooral in de SI-gewrichten en minder in de wervelkolom, en dat deze afwijkingen vaker bij mannen dan vrouwen voorkwamen. Bij de meest patiënten zonder ontstekingshaarden bleven de MRI-scans na 6 maanden in 95% van de gevallen negatief, ondanks de hoge ziekteactiviteit.

Hoofdstuk 7 bevat de resultaten van het eerste artikel over de "Prevention of very early symptoms in Ankylosing Spondylitis (PrevAS)" studie. In deze studie werd het effect van een TNFi, etanercept, op het verlagen van de ziekteactiviteit en ontstekingen op MRI-scans in patiënten die verdacht waren voor nr-AxSpA vergeleken met een placebo. Patiënten hoefden bij de inclusie niet te voldoen aan het hebben van ontstekingen op MRI en/of een verhoogd ontstekingseiwit in het bloed (C-Reactief Proteïne (CRP)). De conclusie van deze studie was dat 16 weken met etanercept behandeling niet effectief was in het verlagen van de ziekteactiviteit. In reactie op het eerste PrevAS artikel is er een korte brief geschreven waarin het focus lag op het ontbreken van goede diagnostische en evaluatie instrumenten om de ziekteactiviteit in AxSpA patiënten te meten (**Hoofdstuk 8**).

Hoofdstuk 9 beschrijft de drie jaar follow-up resultaten van de PrevAS studie over het beloop van de ziekteactiviteit en radiologische veranderingen na een korte behandeling met etanercept. De hoofdconclusie is dat een vroege behandeling met etanercept in patiënten die verdacht worden van nr-AxSpA niet effectief blijken te zijn, omdat de ziekteactiviteit hoog blijft. Verder zijn er geen verschillen geobserveerd in beloop van radiologische veranderingen tussen de patiënten die wel een vroege, kortdurende behandeling met etanercept hebben gehad en patiënten die een placebo hebben gekregen tijdens deze periode.

In **Hoofdstuk 10** is beschreven of de mate van het ontstekingseiwit CRP in het bloed geassocieerd is met de invloed van langdurige TNFi behandeling op het beloop van radiologische veranderingen in patiënten gediagnosticeerd met SA. Concluderend is een verhoogd (tijdgemiddeld) CRP in het bloed (>5mg/L) geassocieerd zijn met radiologische veranderingen tijdens de behandeling met TNFi.

LIST OF PUBLICATIONS

In this thesis (in order)

1. Rusman T, van Bentum RE, van der Horst-Bruinsma IE, Sex and gender differences in axial spondyloarthritis: myths and truths, *Rheumatology*, Volume 59, Issue Supplement_4, October 2020, Pages iv38–iv46, https://doi.org/10.1093/rheumatology/keaa543

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1. Rusman, T., van Vollenhoven, R.F. & van der Horst-Bruinsma, I.E. Gender Differences in Axial Spondyloarthritis: Women Are Not So Lucky. *Curr Rheumatol Rep* **20,** 35 (2018). https://doi.org/10.1007/s11926-018-0744-2

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CURRICULUM VITAE

Tamara Rusman werd geboren op 19 maart 1992 in Sassenheim, waarna zij opgroeide in Hillegom. In 2011 behaalde zij haar atheneum diploma (ROC Leiden), waarna zij startte met de studie Gezondheid en Leven aan de Vrije Universiteit te Amsterdam. In 2014 verrichtte zij haar wetenschappelijke bachelor stage op de afdeling Reumatologie in het voormalige Kennemer Gasthuis onder supervisie van dr. S. ten Wolde en prof. I.E. van der Horst-Bruinsma. In 2015 startte zij haar masteropleiding Health Sciences, waarvoor zij in datzelfde jaar haar master stage verrichtte op de afdeling Reumatologie van de Vrije Universiteit medisch centrum (VUmc) onder supervisie van prof. I.E. van der Horst-Bruinsma. Aansluitend kreeg zij de kans om in 2015 een promotietraject te starten in het VUmc bij de vakgroep Reumatologie onder leiding van prof. I.E. van der Horst-Bruinsma en prof. R.F. Vollenhoven. Naast haar onderzoekstaken volgde zij tijdens deze periode de masteropleiding Epidemiologie aan het EMGO instituut, die zij in 2022 succesvol afrondde. Na haar werkzaamheden in het VUmc in 2020 is zij voor een jaar werkzaam geweest bij het Nederlands Instituut voor Onderzoek van de Gezondheidszorg (NIVEL) waar zij haar onderzoek naar gender- en sekseverschillen binnen de reumatologie heeft voortgezet. Momenteel is zij werkzaam als programmamanager bij de Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie ZonMw voor het programma DoelmatigheidsOnderzoek.

Tamara Rusman was born on March 19, 1992 in Sassenheim, the Netherlands. She grew up in Hillegom and graduated from high school in 2011 (ROC Leiden). After that, she started the bachelor study Health and Life sciences at the VU University of Amsterdam. In 2014 she performed her scientific research internship at the former Kennemer Gasthuis supervised by dr. S. ten Wolde and prof. I.E. van der Horst-Bruinsma. In 2015, she started her master study Health Sciences at the VU University of Amsterdam. In the same year she performed her scientific research internship at the Rheumatology department of the VU University medical center (VUmc) supervised by prof. I.E. van der Horst-Bruinsma. Subsequent she was granted the opportunity to initiate a PhD project at the same department supervised by prof. I.E. van der Horst-Bruinsma and prof. R.F. Vollenhoven. During this period she also studied clinical epidemiology at the EMGO institute, which she successfully completed in 2022. After her research work at the VUmc in 2020, she worked for over one year at the Dutch institute for healthcare research (NIVEL), in which she continued her research on gender and sex differences in rheumatology. Currently, she works at the Dutch organisation for health research and care innovation ZonMw, for the program DoelmatigheidsOnderzoek.

DANKWOORD

Het heeft even geduurd, maar daar is het proefschrift dan eindelijk!

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