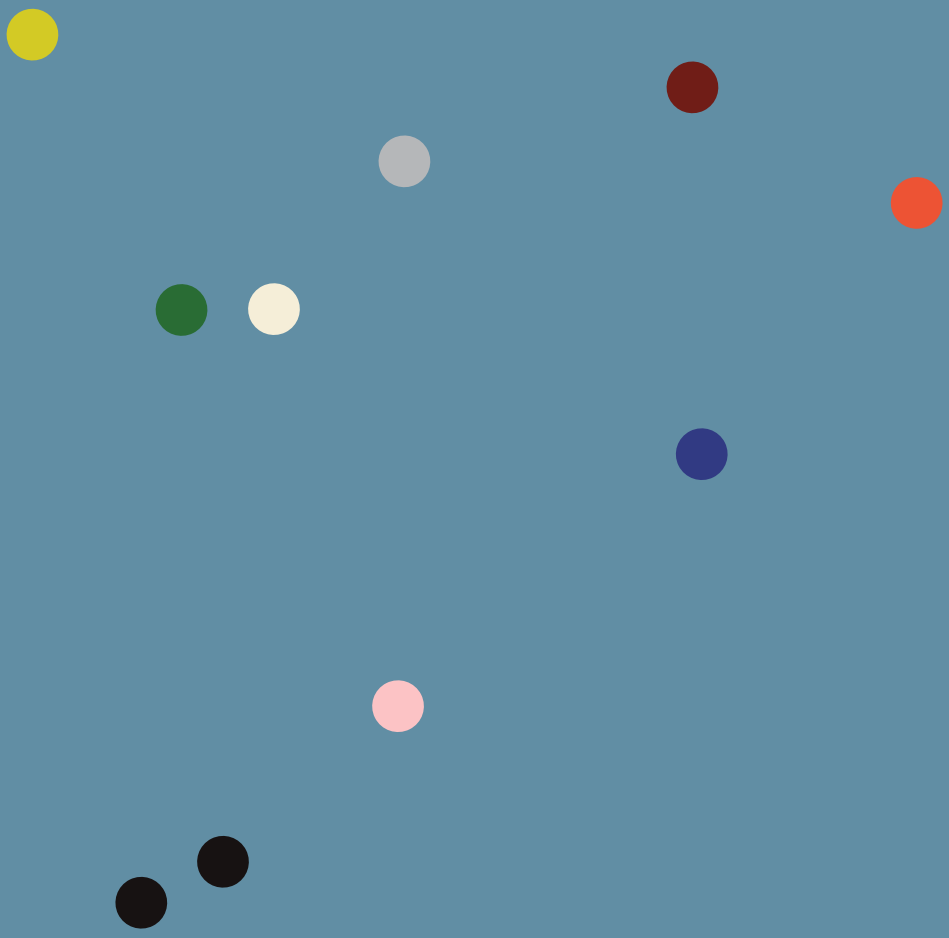
Spondyloarthritis

Accelerating the patient journey from first symptoms to adequate treatment



Henriëtte de Jong

SPONDYLOARTHRITIS: ACCELERATING THE PATIENT JOURNEY FROM FIRST SYMPTOMS TO ADEQUATE TREATMENT

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Colofon

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SPONDYLOARTHRITIS: ACCELERATING THE PATIENT JOURNEY FROM FIRST SYMPTOMS TO ADEQUATE TREATMENT

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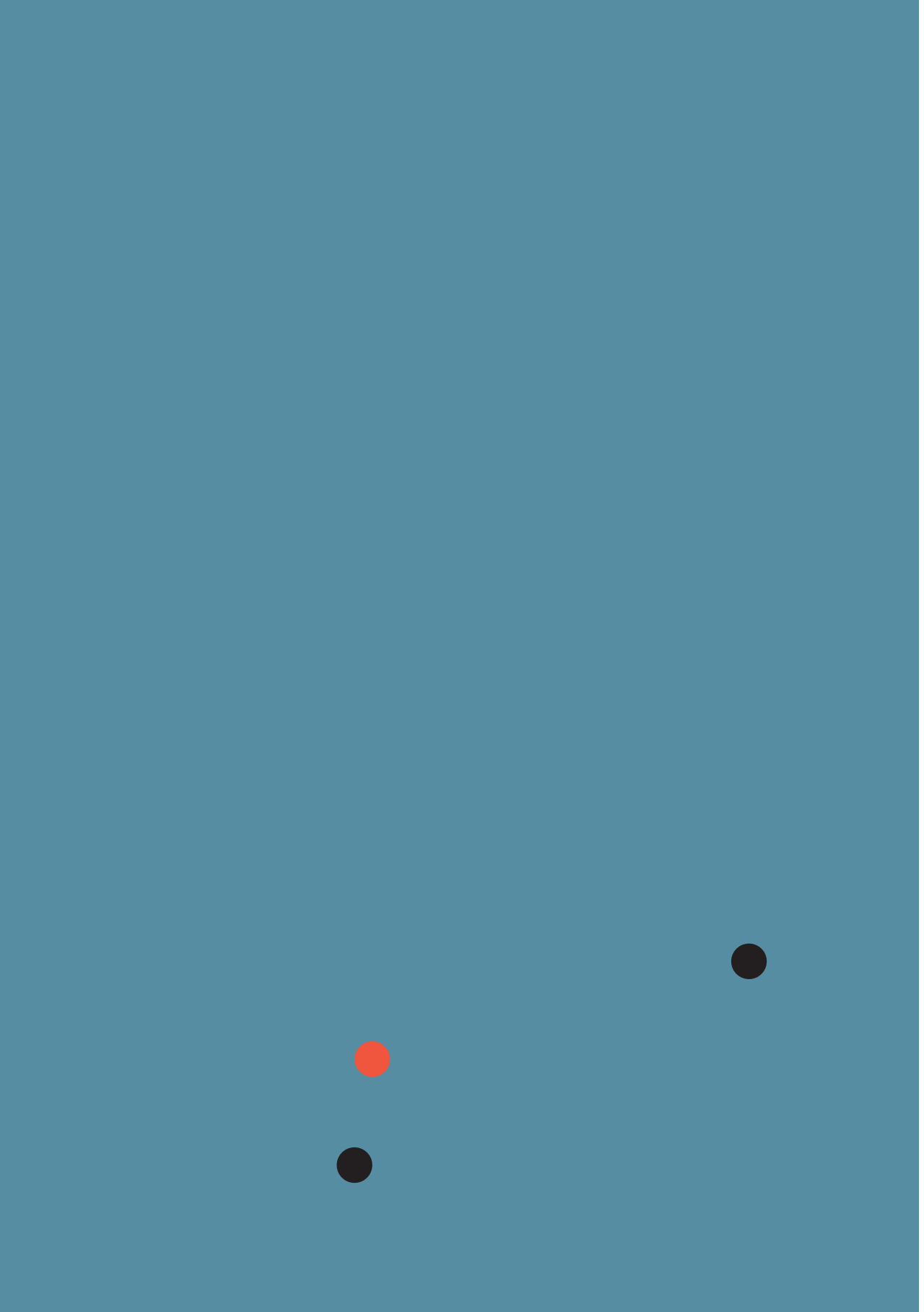

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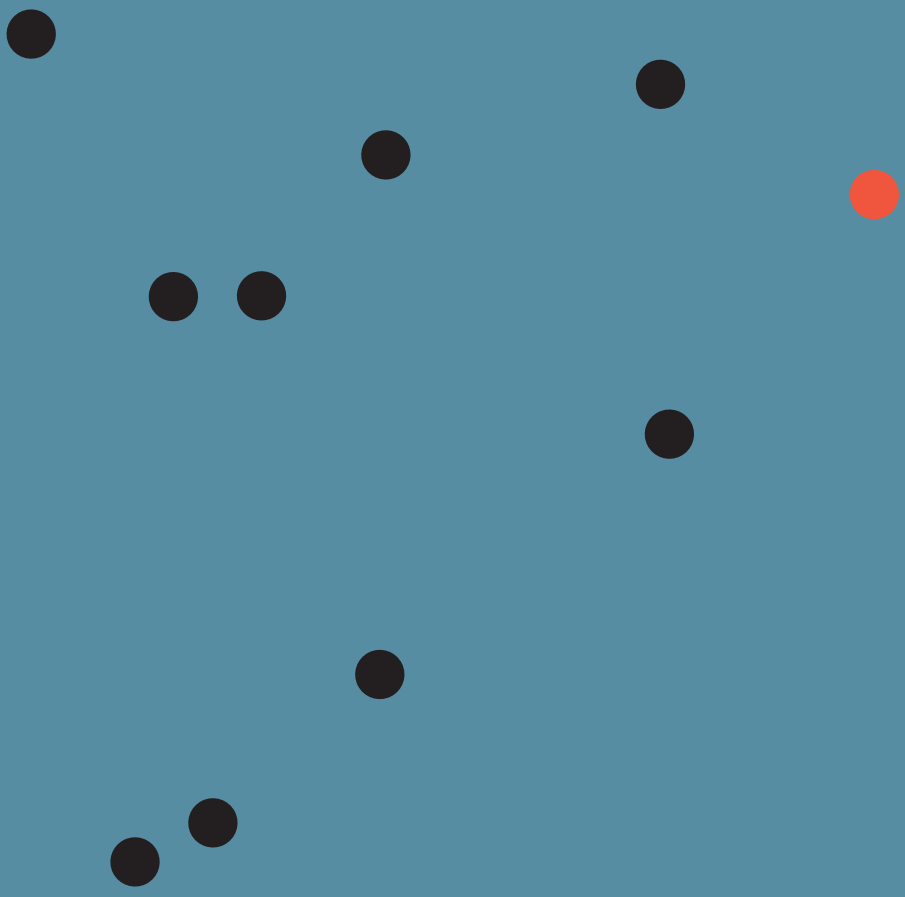
GENERAL INTRODUCTION AND OUTLINE



Spondyloarthritis (SpA) is one of the most common inflammatory rheumatic diseases, with a prevalence of 0.2-1.6% (1). Based on the main clinical symptom, we can distinguish two main subtypes of SpA with a shared genetic background (2): axial SpA (axSpA), characterized by inflammation of the spine and sacroiliac (SIJ) joints and peripheral SpA (perSpA), characterized by inflammation of (mainly large) peripheral joints. One of the key features of SpA, next to inflammation, is new bone formation, that can lead to ankylosis of the axial skeleton as well as the peripheral joints(3,4). AxSpA includes a radiographic and a non-radiographic subtype. Ankylosing spondylitis (AS), or radiographic axSpA, is the prototype of axSpA. Radiographic refers to the presence of high-grade sacroiliitis on plain radiography of the SIJ joints according to the modified New York criteria(5). Non-radiographic axSpA refers to the absence of sacroiliitis on plain radiography in the presence of either signs of inflammation on MRI of the SIJ or a very suggestive clinical picture in the presence of HLA-B27. The most common form of perSpA is psoriatic arthritis, which presents with psoriasis combined with arthritis, dactylitis or enthesitis. Other forms of perSpA are arthritis associated with inflammatory bowel disease, reactive arthritis and juvenile spondyloarthropathy. Despite this classification, the symptoms of axSpA and perSpA overlap and mixed phenotypes are very common amongst patients with SpA(6).

Features of spondyloarthritis

The main symptom of axSpA is back pain, usually presenting before the age of forty-five. Back pain associated with axSpA often has an inflammatory character. The ASAS working group defined inflammatory back pain as having at least four out of 5 of the following features: age at onset <40 years, insidious onset, improvement with exercise, no improvement with rest, pain at night (with improvement upon getting up)(7). Axial symptoms are also present in up to 19% of patients with perSpA(8).

The main symptoms of perSpA are arthritis, dactylitis and/or enthesitis. Arthritis presents with pain, stiffness and swelling of a joint, with usually an oligoarticular pattern in the early stages of disease that can evolve into an asymmetric polyarticular pattern. Dactylitis is characterized by swelling of the entire digit, also referred to as a sausage finger or toe. Enthesitis is inflammation of the insertion of a tendon to the bone, a typical site being the insertion of the Achilles tendon. Enthesitis is present in 35-50% of patients and can be a first sign of psoriatic arthritis(9). The arthritis in psoriatic arthritis can cause severe deformities to the joints in a short period of time, even despite treatment (10). Up to 50% of patients with predominantly axial disease also have peripheral symptoms with a significant impact on disease activity(11). The prevalence of peripheral symptoms is equal between patients with AS and non-radiographic axSpA(12).

Extra-articular manifestations such as psoriasis, inflammatory bowel disease and anterior uveitis can be present in both subtypes of SpA. In axSpA, the prevalence of the different extra-articular manifestations is approximately 25% for anterior uveitis, 10% for psoriasis and 6% for inflammatory bowel disease (12,13). The prevalence of anterior uveitis is higher in patients with AS than in patients with non-radiographic axSpA, for psoriasis and inflammatory bowel disease the prevalence is similar(12). Up to 50% of patients with psoriatic arthritis have extra-articular manifestations besides psoriasis, the most common ones being bowel and ocular involvement which are present in up to a third of psoriatic arthritis patients(14).

HLA-B27 was discovered in the 1970's as being highly associated with AS; 96% of patients with classical AS were found to be HLA-B27 positive(15). In contrast, 5-7% of the Caucasian population is estimated to be HLA-B27 positive (16) in whom the risk for development of disease is estimated about 5%, which increases if there a positive family history(17). Therefore, HLA-B27 can be of help to come to a diagnosis but cannot be used as a diagnostic marker for SpA. Although the association between HLA-B27 and psoriatic arthritis is not as strong as for AS, approximately 40% of psoriatic arthritis patients is HLA-B27 positive(18), and HLA-B27 has been shown to be associated with an earlier onset of psoriasis and arthritis(19). Another biologic feature of SpA is an elevation of the inflammatory markers CRP and ESR, although not present in all patients. An elevated CRP is a predictor of radiographic progression in early axSpA(20).

Signs of structural damage following inflammation in the SIJ are traditionally visualized using conventional radiographs, and vary from some blurring of the joint margins to complete ankylosis(21). In the spine, syndesmophytes can be present, that can eventually lead to complete ankylosis of the spine (also referred to as bamboo spine). Both sacroiliitis in the SIJ and syndesmophytes in the spine are usually a sign of longstanding disease and therefore lack specificity for diagnosing patients with early axSpA(22). Before syndesmophytes and sacroiliitis are visible on plain radiographs, MRI can visualize inflammatory lesions in the spine and SIJ(23,24), therefore MRI can help in making an earlier diagnosis. Imaging modalities that can aid in making a diagnosis of psoriatic arthritis are ultrasound, radiographs and MRI. With ultrasound, synovitis, tendinitis and erosions in joints can be visualized. With MRI, synovitis, tendinitis, enthesitis, bone marrow edema and structural changes can be visualized. On plain radiography, erosions and new bone formation in the peripheral joints can be seen (25).

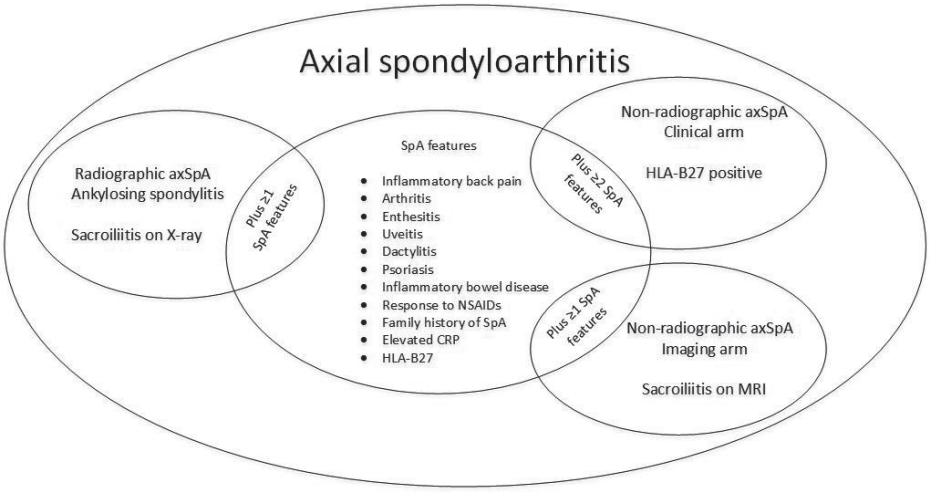
Spondyloarthritis has a broad impact on quality of life, influencing all aspects of life(26). The burden of SpA is high, even in the early stages of disease (27,28). Also in

established disease patients have a significantly lower quality of life compared to the general population, with one of the factors associated with a worse quality of life being the duration of symptoms (29). Disease activity and fatigue associated with SpA have a significant influence on work productivity(30–32).

Classification of SpA

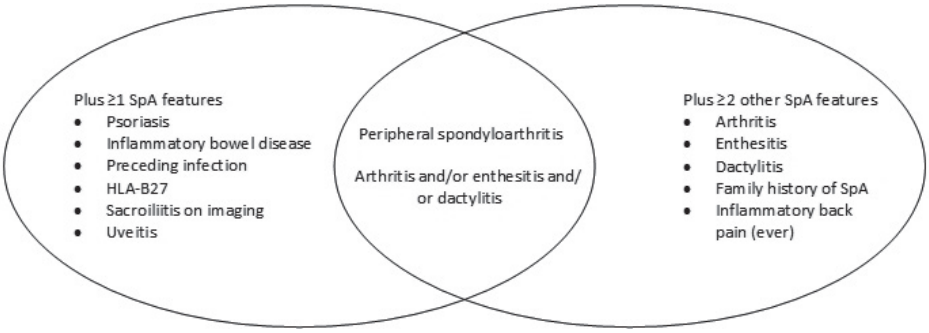
For the purpose of selecting homogeneous study populations for research, the Assessment of SpondyloArthritis international Society (ASAS) working group developed sets of classification criteria for axSpA in 2009 and for perSpA in 2011(33,34). The ASAS classification criteria for axSpA (Figure 1) define two arms of axSpA; the clinical and the imaging arm. To classify into the imaging arm of axSpA, one must have sacroiliitis on either MRI or plain radiography of the SIJ and at least one SpA feature. To classify in the clinical arm of axSpA, one must be HLA-B27 positive and have at least two SpA features. Note that the imaging arm of the classification criteria (sacroiliitis on either MRI or plain radiography) is different from the definition of radiographic axSpA or AS (sacroiliitis on plain radiography). To be classified as perSpA, patients must have either arthritis, dactylitis, or enthesitis and at least one or two other SpA features, dependent on which SpA features are present (Figure 2).

Figure 1. The ASAS classification criteria for axial spondyloarthritis



The ASAS classification criteria for axSpA. Radiographic axSpA refers to the presence of high-grade sacroiliitis on X-ray, patients must have one additional SpA feature. Non-radiographic axSpA can be subdivided in 1) the imaging arm, with sacroiliitis on MRI and at least one additional SpA feature, or 2) the clinical arm, with the presence of HLA-B27 and at least two additional SpA features.

Figure 2. The ASAS classification criteria for peripheral spondyloarthritis



The ASAS classification criteria for perSpA. The presenting symptom is arthritis, dactylitis and/ or enthesitis. Depending on the SpA features present, patients must additionally have at least one or two SpA features.

Diagnosis of SpA

The diagnosis of SpA is made on the clinical judgement of the treating rheumatologist and is based on pattern recognition. One difficulty with diagnosing axSpA is that the main presenting symptom, back pain, is highly prevalent in the general population and therefore lacks specificity. Even inflammatory back pain has a limited sensitivity and specificity(35). Another challenge is that HLA-B27 lacks specificity (16). Signs of axSpA on plain radiography can take years to develop, which makes plain radiography of the SIJ usually not applicable for making an early diagnosis. The use of the MRI as a diagnostic tool has enabled us to diagnose patients in the earlier stages of the disease, but recent studies showed that MRIs should be interpreted with caution since abnormalities suggestive of SpA can also be present in up to 23% of healthy volunteers(36). Despite the developments in the understanding, acknowledgement and diagnostic tools for axSpA, the diagnostic delay for axSpA is still 5-7 years(37–39).

Two of the main symptoms of perSpA, arthritis and dactylitis, are usually well recognized upon clinical examination. Enthesitis, which can be a first symptom of perSpA, can be more challenging to recognize with clinical examination(40). There is no gold standard to diagnose enthesitis with imaging modalities(41). It has been shown that a delay of diagnosis of as little as six months has a negative impact on long-term functioning in patients with perSpA (42).

Treatment of SpA

The treatment of spondyloarthritis consists of a step-up approach. The first step are non-steroidal anti-inflammatory drugs (NSAIDs). Next, for peripheral disease, treatment

with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) can be initiated: methotrexate, leflunomide or sulphasalazine. Methotrexate is the most prescribed csDMARD, although solid data on its efficacy is lacking(43). Conventional synthetic DMARDs have no effect on axial symptoms and are therefore not used for the treatment of axSpA(44). When a patient fails these treatments, treatment with biological DMARDs or targeted synthetic drugs can be initiated(45). TNFα inhibitors were the first available biologics and have shown clear efficacy in both axSpA and perSpA(46,47). Besides with TNFα inhibitors, AS can be treated with anti-IL17A treatment (48,49). For non-radiographic axSpA anti-IL17A treatment has not been approved yet but studies are ongoing. Psoriatic arthritis can, besides treatment with TNFα inhibitors, also be treated with anti-IL17A (50,51). Additionally, for treatment of perSpA, treatments with other mechanisms of action are approved: abatacept (cytotoxic T-lymphocyte associated protein-4-Fc contsruct(52)), ustekinumab (IL-12/IL-12 inhibitor (53)), apremilast (phosphor-diesterase inhibition (54)) and tofacitinib (JAK inhibition (55)). Because not all patients respond to these treatments, and a proportion of patients only respond partially, the search for new therapeutic options that can induce remission in higher numbers of patients for both axSpA and perSpA continues to improve outcome for all SpA patients. A delay in treatment has shown to be associated with worse outcomes and poor treatment responses in patients with SpA(42,56).

General aim

Despite the major improvements in the recognition of spondyloarthritis and available treatment options, there are still unmet needs in both the recognition and treatment of SpA. First, the diagnostic delay for patients with early disease and females is still significant and underlines the need for better tools/markers to diagnose disease even earlier. Secondly, there is a need for novel treatments inducing remission in all patients as not all patients respond to the available treatments or respond only partially, with residual disease activity despite treatment. Another unmet need is the availability of highly effective treatment options for patients without moderate to high disease activity that can bring patients with low disease activity in complete remission (and thereby improve their quality of life and functioning).

The general aim of this thesis is to tailor the diagnostic process and treatment for patients with SpA and hereby to improve the journey of patients from first symptoms to induction of remission with adequate treatment.

The aim of **chapter** 2 was to investigate whether there are differences between females and males in disease presentation in a real-life cohort of patients with SpA, that could

explain the longer diagnostic delay for females with axSpA. Historically, AS has long been believed to be a predominantly male disease. This can mainly be explained by the fact that males more often develop signs of sacroiliitis on X-ray compared to females. Since the recognition of non-radiographic axSpA as a disease entity, the estimated prevalence of spondyloarthritis is nearly equal between males and females. However, females still have a longer diagnostic delay compared to males and there is a major risk of underdiagnosis. Increased knowledge on disease presentation in both males and females could aid in better recognizing SpA in both sexes.

In **chapter 3** we describe the baseline characteristics and data after one year of follow-up of the Pre-SpA cohort, a cohort of individuals at increased risk to develop axSpA. Studying an at-risk population such as the Pre-SpA cohort could help to identify clinical signs, imaging abnormalities and biomarkers that are predictive for the development of axSpA. Additionally, we assessed the progression towards clinical disease over one year of follow-up.

Initiatives such as the Pre-SpA cohort, described in chapter 3, might lead to preventive treatment strategies. In rheumatoid arthritis, studies are being done with preventive treatment in individuals at risk to develop disease, but without established clinical disease (yet). It has not been investigated whether individuals at risk to develop SpA would be willing to use preventive medication and under what circumstances. To that purpose, we investigated the willingness of individuals at risk to develop SpA to use preventive medication in **chapter 4**.

With the current step-up approach in the treatment of SpA, only patients with severe disease or high disease activity are treated with biologics. Additionally, only 60-70% of patients respond to treatment, of whom 30% only respond partially. This indicates that there is still an unmet need in the treatment of spondyloarthritis for both patients with early disease and patients with residual disease activity. Furthermore, there is an increasing interest in complementary therapies, and patients want to be more in control of their own disease and treatment.

In **chapter 5**, we investigated whether TNFα inhibitors initiated as first line treatment in the early stages of psoriatic arthritis are superior to methotrexate when aiming at remission. To explore this aim, we performed a randomized double-blind controlled trial in which we compared golimumab (a TNFα inhibitor) and methotrexate to placebo and methotrexate for 22 weeks in methotrexate-naïve patients with early disease.

The so called 'window of opportunity' hypothesis states that if patients are treated in the early stages of disease, this could modulate the chronic inflammatory disease state disease and therefore enable physicians to withdraw treatment while patients remain in remission. In **chapter 6,** we investigated whether remission is sustained after discontinuation of anti-TNFα treatment in patients with early psoriatic arthritis.

Treatment with biologics is reserved for patients with moderate to severe disease. Additionally, a substantial proportion of patients who do use biologics respond only partially. This raises the question whether we should prescribe biologics to patients with mild to moderate disease as well, or whether we should investigate other pharmacological treatments for patients with SpA. Another approach could be to investigate non-pharmaceutical treatments as an add-on treatment. One of these non-pharmaceutical treatments consists of cold exposure, meditation and breathing exercises. In **chapter 7**, we investigated an add-on treatment consisting of cold exposure, meditation and breathing techniques in patients with axSpA and residual disease, irrespective of the treatment they received from their treating rheumatologist.

Finally, **chapter 8** gives a summary of the studies in this thesis and discusses the findings.

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2

DIFFERENCES BETWEEN FEMALES AND MALES IN AXIAL SPONDYLOARTHRITIS: DATA FROM A REAL-LIFE CROSS-SECTIONAL COHORT

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ABSTRACT

Objectives

Axial spondyloarthritis (axSpA) is a chronic inflammatory joint disease that usually presents with axial symptoms, but can also present with peripheral and extra-articular manifestations. AxSpA occurs equally in both females and males. The diagnostic delay for axSpA is 5-7 years, and is significantly longer in females compared to males. The aim of this study is to investigate the difference in disease characteristics between females and males with axSpA and stratify this difference to HLA-B27 status.

Methods

Clinical characteristics, spondyloarthritis (SpA) features, disease activity parameters, X-rays of sacroiliac joints and laboratory results were assessed in a real-life cross-sectional cohort of 389 patients with a clinical diagnosis of axial or peripheral SpA and were compared between females and males.

Results

Of 389 patients included, 313 had a clinical diagnosis of axSpA (females vs. males, 131(42%) vs. 182 (58%), respectively). Females had less radiographic axSpA according to the modified New York (mNY) criteria (38.9% vs. 63.7%, respectively), had a higher ESR ((median(IQR) 11(5-23) vs. 8(3-16)mm/hr, resp.) and reported higher disease activity by BASDAI (mean(SD) 5.2(2.1) vs. 4.6(2.2)). We found no differences in clinical characteristics or SpA features. When stratifying for HLA-B27 status, no differences were found.

Conclusions

In this real-life cohort of patients we showed that in axSpA, although males more often have structural damage on X-rays, females have quite similar disease with regard to SpA features and have at least equal disease activity parameters compared to males.

INTRODUCTION

It is increasingly being acknowledged in many diseases that females differ from males with regard to disease presentation(1), clinical symptoms, disease burden(2), pain perception(3) and response to medication(4,5). Until recently, axial spondyloarthritis (axSpA) was considered a predominantly male disease(6). The recognition of non-radiographic axSpA as a disease entity and the use of MRI as a diagnostic tool showed that axSpA prevalence is nearly equal between females and males(7). Nevertheless axSpA recognition is still worse in females resulting in underdiagnosis and a prolonged time until diagnosis(8). One proposed explanation is that females and males differ with regard to disease characteristics.

One major issue is that most studies on sex differences in axSpA used either the modified New York(mNY)-criteria for ankylosing spondylitis (AS) or the newer Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA(2,9,10). Whereas the use of these criteria allows to select more homogenous populations, they heavily rely on the presence of sacroiliitis on imaging and may therefore select a subgroup of female patients that is not completely representative of the patients presenting in daily clinical practice.

To overcome these potential biases complicating the evaluation of sex differences in axSpA, we included a real-life cross-sectional cohort of patients with a clinical diagnosis of axial and/or peripheral SpA. We evaluated differences between females and males in the prevalence of extra-articular and peripheral disease manifestations and disease activity parameters. Furthermore, we evaluated the influence of HLA-B27 status on disease presentation.

METHODS

Study population

Patients (≥ 18 years old) with a clinical diagnosis of axial, peripheral, or combined spondyloarthritis (SpA) according to the expert opinion of their treating physician who visited the specialized SpA outpatient clinics of the Academic Medical Center Amsterdam (n=272) and the University Medical Center Utrecht (n=42) between June 2007 and August 2012 were included in this real-life cross-sectional observational study, as approved by the local medical ethics committees with approval number WII-032#11.17.0419. Informed consent was waived since no additional procedures were

performed for this observational study and all data was available from standard patient care.

Demographic and disease characteristics, presence (past or present) of extra-articular manifestations (dactylitis, enthesitis, anterior uveitis (AU), inflammatory bowel disease (IBD), psoriasis) and family history (defined as ≥1 first or second degree relative with ankylosing spondylitis (AS), AU, reactive arthritis (ReA), IBD or psoriasis) were recorded. HLA-B27 status, CRP (mg/L) and ESR (mm/hr) were collected. X-rays of the sacroiliac joints were collected if available and scored locally according to the modified New York (mNY) criteria(11). Current and previous medication use (non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease modifying anti-rheumatic drugs (cDMARDs) and biologics) were recorded. Clinical assessment consisted of 66 swollen and 68 tender joint count, Schober index and chest expansion. Enthesitis and dactylitis were scored as positive if clinically apparent. Active inflammatory back pain was defined as pain at night at least 1 time a week and/or an average morning stiffness of at least 30 minutes in the past week.

Disease activity was evaluated by patient and physician global disease activity (scored on a 100mm Visual Analogue Scale (VAS)), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)(12) and Ankylosing Spondylitis Disease Activity Score (ASDAS)(13). Patients were classified as AS if they fulfilled the mNY criteria(11).

Statistics

First, we compared females and males with axial spondyloarthritis (axSpA). Second, to investigate whether the reported differences are consistent in AS versus non-radiographic axSpA, we compared disease parameters between females and males in both subgroups. Third, to validate these results, we compared females and males with perSpA. Fourth, we compared disease parameters between HLA-B27 positive females and males and HLA-B27 negative females and males. Categorical data are presented as numbers(%), continuous data as mean(standard deviation) or as median(interquartile range). Categorical data were analyzed using Chi square tests, continuous data using Mann-Whitney U tests or unpaired T tests. Statistical tests were 2-sided, and p-values less than 0.05 were considered significant.

RESULTS

Study population

Three hundred eighty-nine spondyloarthritis (SpA) patients were included. One hundred eighty-two (46.7%) patients were diagnosed with axial spondyloarthritis (axSpA), 76(19.5%) with peripheral spondyloarthritis (perSpA) and 131(33.7%) with combined SpA. Patients with combined SpA were included in the analysis of axSpA (n=313). In total, 230(73%) patients with a clinical diagnosis of axSpA fulfilled the ASAS criteria for axSpA and 83(27%) patients did not (Table 1).

Table 1. Axial spondyloarthritis: comparison between males and females

	Total (n=313)	Male (n=182)	Female (n=131)	p
Age, mean (SD)	42.9 (12.7)	43.3 (12.4)	42.3 (13.2)	0.471
Disease duration, years	3.5(0.6-10.3)	3.8(0.6-11.7)	2.8(0.9-7.9)	0.420
Age at disease onset, years, mean (SD)	34.9 (13.1)	34.4 (12.5)	35.5 (13.8)	0.464
Active IBP#, n(%)	286 (91.4)	166 (91.2)	120 (91.6)	0.902
Arthritis ever, n(%)	131 (41.9)	74 (40.7)	57 (43.5)	0.614
Dactylitis ever, n(%)	14/293 (4.8)	8/172 (4.7)	6/121 (5.0)	0.903
Enthesitis ever, n(%)	124 (39.6)	71 (39)	53 (40.5)	0.796
Uveitis ever, n(%)	69 (22)	41 (22.5)	28 (21.4)	0.808
IBD ever, n(%)	36 (11.5)	17 (9.3)	19 (14.5)	0.158
Psoriasis ever, n(%)	38 (12.1)	22 (12.1)	16 (12.2)	0.973
Family history, n(%)	112 (35.8)	57 (31.3)	55 (42)	0.052
HLA-B27 positivity, n(%)	173/297 (58.2)	105/172 (61.0)	68/125 (54.4)	0.251
Fulfill mNY criteria for sacroiliitis, n(%)	167 (53.7)	116 (63.7)	51 (38.9)	<0.001
Fulfill ASAS criteria for axSpA, n(%)	230(73%)	145(79.7)	85(64.9)	0.003
BASDAI, mean(SD)	4.8 (2.2)	4.6 (2.2)	5.2 (2.1)	0.008
ESR mm/hr	9 (5-18.8)	8 (3-16)	11 (5-23)	0.008
CRP mg/L	3.3 (1-10.1)	3.2 (1.3-9.7)	3.3 (1-10.9)	0.331
ASDAS-CRP, mean(SD)	2.7 (1.0)	2.7 (1.0)	2.8 (1.1)	0.212
SJC68 >0, n(%)	69(22)	40(22)	29(22)	0.973
TJC68 >0, n(%)	143(45.7)	75(41.2)	67(51.1)	0.082
Schober <4cm, n(%)	147/305(48.2)	91/178(51.1)	56/127(44.1)	0.226
Chest expansion <2.5cm, n(%)	23/273(8.4)	15/159(9.4)	8/114(7.0)	0.478

	Total (n=313)	Male (n=182)	Female (n=131)	p
Physician VAS disease activity, mean(SD)	46 (27-60)	45 (25-58)	47 (28-62)	0.265
Patient VAS disease activity, mean(SD)	52.3 (25.4)	49.7 (24.9)	56.0 (25.8)	0.032
Use of bDMARD ever, n(%)	71 (22.7)	39 (21.4)	32 (24.4)	0.532
Use of cDMARD ever, n(%)	112 (35.8)	58 (31.9)	54 (41.2)	0.089
Use of NSAID, ever, n(%)	288 (92)	168 (92.3)	120 (91.6)	0.821

All data are presented as median (IQR) unless indicated otherwise
IBP; inflammatory back pain, NSAID; non-steroidal anti-inflammatory drug, IBD; inflammatory bowel disease, BASDAI; Bath Ankylosing Spondylitis Disease Activity Index, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, SJC; swollen joint count, TJC; tender joint count, VAS; visual analogue scale, bDMARD; biological disease modifying anti-rheumatic drug, cDMARD; conventional disease modifying anti-rheumatic drug
[#] active IBP during study visit

Differences between females and males in axSpA

Of the 313 patients with axSpA, 131(42%) were female and 182(58%) were male. Females less often fulfilled the modified New York (mNY) criteria for radiographic sacroiliitis (38.9% vs. 64.4%, p<0.001) and the ASAS classification criteria for axSpA (64.9 vs. 79.7%, p=0.003). Females had a higher median ESR (median(IQR) 11(5-23) vs. 8(3-13)mm/hr, p=0.008) and reported a slightly higher mean patient VAS disease activity (mean(SD) 56.0(25.8) vs. 49.7(24.9)mm, p=0.032) and BASDAI (mean(SD) 5.2(2.1) vs. 4.6(2.2), p=0.008)(Table 1).

Differences between females and males in ankylosing spondylitis (AS) versus non-AS axSpA

One hundred sixty-seven patients were diagnosed with AS (males (n=116) and females (n=51)). Females had a higher median ESR (16(6.5-30)mm/hr vs. 9(5-20)mm/hr, p=0.018, females versus males respectively). Females with AS reported more anterior uveitis (AU) (37.3% vs. 21.6%, p=0.034).

One hundred forty-four patients had non-AS axSpA(not fulfilling the mNY criteria) (males (n=64) and females (n=80)). Females had a higher ESR (median(IQR) 9(5-17) vs. 5 (2-14)mm/hr, p=0.009), reported a higher VAS disease activity (mean(SD) 61.6(23.3) vs. 51.3(24.4)mm, p=0.009) and BASDAI (mean(SD) 5.6(1.8) vs. 4.8(2.3), p=0.039). AU prevalence was lower in females when compared to males with non-AS axSpA (11.3 vs. 25.0%, p=0.030). Other parameters showed no statistically significant differences (data not shown).

Differences between females and males in peripheral spondyloarthritis

In total, 76 patients had a clinical diagnosis of peripheral SpA of whom 39(51.3%) males and 37(48.7%) females. Females reported a higher mean BASDAI (mean(SD) 4.3(2.1) vs. 3.3(2.2), p=0.041). Other parameters showed no statistically significant differences (data not shown).

Differences between females and males in axSpA and relation to HLA-B27 status

HLA-B27 status is missing in 16 patients, therefore 297 patients were included in the analysis. When comparing HLA-B27 positive females and males, females significantly less often fulfillled the mNY criteria for radiographic sacroiliitis (52.9 vs. 74.3%, p=0.008). More HLA-B27 positive males had a limited Schober index compared to HLA-B27 positive females (32.8 vs. 52.9%, p=0.010). The comparison between HLA-B27 negative females and males showed no statistically significant differences(Table 2).

Table 2. Comparison between HLA-B27 positive males and females and between HLA-B27 negative males and females with a clinical diagnosis of axSpA

	HLA-B27 positive			HLA-B27 negative		
	Male (n=105)	**Female (n=68)**	**p**	**Male (n=67)**	**Female (n=57)**	**p**
Age, mean(SD)	41.4 (12.5)	38.9 (12.6)	0.254	45.4 (11.3)	45.1 (12.9)	0.604
Age at disease onset, years, mean(SD)	30.7 (10.6)	31.5 (11.6)	0.634	40.2 (12.9)	38.8 (14.7)	0.559
Disease duration, years	6.1(1.1-17.9)	3 (1.1-9.3)	0.111	1.5 (0.3-5.8)	2.8 (0.5-7.5)	0.235
Response NSAID, n(%)	73/80 (91.3)	46/58 (79.3)	0.045	36/42 (85.7)	36/42 (85.7)	1.000
Active IBP, n(%)	103 (98.1)	67 (98.5)	0.831	56 (83.5)	50 (87.7)	0.515
Arthritis ever, n(%)	36 (34.3)	26 (38.2)	0.597	35 (52.2)	26 (45.6)	0.462
Dactylitis ever, n(%)	2/102 (2.0)	5/66 (7.6)	0.075	5/60 (8.3)	1/50 (2.0)	0.145
Enthesitis ever, n(%)	34 (32.4)	20 (29.4)	0.681	35 (52.2)	30 (52.6)	0.965
Uveitis ever, n(%)	34 (32.4)	22 (32.4)	0.997	7 (10.4)	6 (10.5)	0.989
IBD ever, n(%)	6 (5.7)	4 (5.9)	0.963	9 (13.4)	13 (22.8)	0.173
Psoriasis ever, n(%)	6 (5.7)	4 (5.9)	0.963	12 (17.9)	8 (14)	0.559
Family history, n(%)	39 (37.1)	34 (50)	0.094	16 (23.9)	19 (33.3)	0.244
Fulfill mNY criteria for sacroiliitis, n(%)	78/104 (75.0)	36/68 (52.9)	0.008	30/66 (45.5)	15/57 (26.3)	0.058
BASDAI, mean(SD)	4.5 (2.1)	5.0 (2.1)	0.114	5.0 (2.0)	5.5 (2.0)	0.199

	HLA-B27 positive			HLA-B27 negative		
	Male (n=105)	**Female (n=68)**	**p**	**Male (n=67)**	**Female (n=57)**	**p**
Physician VAS disease activity, mean(SD)	46 (25-59.8)	49 (26.5-65)	0.507	45.5 (30.3-58)	47 (33-61)	0.592
Patient VAS disease activity, mean(SD)	50.7 (25.5)	53.4 (26.7)	0.512	51.2 (21.9)	59.2 (24.2)	0.061
ESR, mm/hr	8 (2-16)	11 (5-21.3)	0.068	7.5 (3.8-19.3)	11 (5-23.5)	0.116
CRP, mg/L	3.7 (1-12)	4 (1-11.6)	0.784	2.4 (1.5-9.5)	1.5 (1-10.5)	0.131
ASDAS-CRP, mean(SD)	2.7 (1.1)	2.8 (1.0)	0.518	2.8 (0.9)	2.9 (1.2)	0.661
SJC68 >0, n(%)	16 (15.2)	15 (22.1)	0.253	22 (32.9)	12 (21.1)	0.143
TJC68>0, n(%)	39 (37.1)	30 (44.1)	0.360	32 (47.8)	33 (57.9)	0.260
Schober <4cm, n(%)	55/104 (52.9)	22/67(32.8)	0.010	31/65(47.7)	30/54(55.6)	0.393
Chest expansion <2.5cm, n(%)	9/96(9.4)	4/60(6.7)	0.552	3/55(5.5)	3/49(6.1)	0.884
Use of biologicals ever, n(%)	21 (20)	13 (19.1)	0.887	13 (19.4)	15 (26.3)	0.359
Use of cDMARDs ever, n(%)	30 (28.6)	23 (33.8)	0.464	23 (34.3)	27 (47.4)	0.140
Use of NSAIDs ever, n(%)	98 (93.3)	63 (92.6)	0.862	63 (94)	51 (89.5)	0.353

All data are presented as median (IQR) unless indicated otherwise
NSAID; non-steroidal anti-inflammatory drug, IBD; inflammatory bowel disease, BASDAI; Bath Ankylosing Spondylitis Disease Activity Index, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein, SJC; swollen joint count, TJC; tender joint count, VAS; visual analogue scale, bDMARD; biological disease modifying anti-rheumatic drug, cDMARD; conventional disease modifying anti-rheumatic drug

DISCUSSION

In this real-life cross-sectional cohort of patients with a clinical diagnosis of axial spondyloarthritis (axSpA) we showed that 1) radiographic sacroiliitis according to mNY criteria prevalence is higher in males, 2) the prevalence of extra-articular and peripheral disease manifestations is equal between males and females and 3) females report higher disease activity (BASDAI and patient VAS global disease activity) and have higher ESR values. These differences between male and female axSpA patients were consistent

in the non-AS patient subgroup, while in the AS subgroup only ESR was increased. When subdividing axSpA patients according to HLA-B27 status, HLA-B27 positive females less often fulfilled the mNY for sacroiliitis, and males more often had a limited Schober index.

Besides the subjective disease activity parameters, we observed increased ESR levels in females in the whole axSpA population as well as in the AS and non-AS subgroup, although all below the upper limit of normal (20mm/hr). This is in line with previous data on blood inflammatory markers showing conflicting results(8,9). Based on our findings we can conclude that disease activity is at least as severe in males and females and that they show similar disease characteristics supporting the suggestion by a recent study by Ortolan *et al*(2018)(14) that there should be no gender-specific diagnostic strategies for early axSpA patients.

To our knowledge, this is the first study to compare sex differences in a real-life cohort of patients with a clinical diagnosis of axSpA and not classified according to classification criteria. But although we included patients with a clinical diagnosis instead of patients classified as axSpA according to classification criteria, our findings were similar to findings in the ASAS criteria based cohorts(7,15).

This study has some limitations to consider: 1) patients were included in this cohort when first visiting the dedicated SpA outpatient clinic, thus not at first presentation in a rheumatology outpatient clinic. This hinders us to state anything about differences in first presentation of disease between females and males. 2) MRI of the sacroiliac joints was available of very few patients, therefore this data are not included nor shown in the present study. And 3) We do not have data on comorbidities of the patients included. Therefore we cannot make a statement on the presence or absence of comorbidities such as fibromyalgia as an explanation for the higher VAS pain and disease activity as scored in this cohort.

In conclusion, our and previous studies show that axSpA is, except for presence of structural damage, at least as severe in females compared to males, and this should be recognized when treating patients with axSpA. Because it was long thought that axSpA is mainly a male disease, it could be of importance to also focus on the physicians' perspectives on sex differences in axSpA.

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3

HLA-B27 IS ASSOCIATED WITH PROGRESSION FROM SUBCLINICAL INFLAMMATION TO OVERT SPONDYLOARTHRITIS RATHER THAN THE PRESENCE OF SUBCLINICAL INFLAMMATION PER SE IN SEEMINGLY HEALTHY FIRST DEGREE RELATIVES OF SPONDYLOARTHRITIS PATIENTS: DATA FROM THE PRE-SPA COHORT

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ABSTRACT

Objectives

As first-degree relatives (FDRs) of HLA-B27-positive axial spondyloarthritis (axSpA) patients have an increased risk of developing axSpA, the objectives were 1)to evaluate presence of highly specific imaging features as well as clinical signs of SpA at baseline and after one year of follow-up, and 2) describe the evolution towards clinical disease within one year of follow-up in a cohort of seemingly healthy FDRs of HLA-B27 positive axSpA patients.

Methods

The Pre-SpA cohort is a 5-year prospective inception cohort of seemingly healthy FDRs of HLA-B27 positive axSpA patients, aged 18-40 years. Clinical and imaging features were collected and recorded.

Results

At baseline 19% of the FDRs reported inflammatory back pain. Thirty-two percent reported current arthralgia, 3% arthritis (ever), 5% enthesitis (ever) and 1% dactylitis (ever). Three percent had an extra-articular manifestation. CRP was elevated in 16%, ESR in 7%. On MRI-SIJ, 10% had a SPARCC score ≥2, 4% ≥5, and 4% deep lesions. One percent fulfilled the mNY criteria for high-grade radiographic sacroiliitis (grade ≥2 bilateral or ≥3 unilateral). Clinical, MRI and acute phase findings were equally distributed between HLA-B27 positive and negative FDRs. After 1 year of follow-up, clinical parameters did not change on the group level but 6% of the FDRs were clinically diagnosed with axSpA, of whom 86% was HLA-B27 positive.

Conclusion

Spondyloarthritis features such as inflammatory back pain, arthralgia, an elevated CRP, or imaging abnormalities were found in up to 32% of seemingly healthy FDRs, with an equal distribution between HLA-B27 positive and negative FDRs. Progression to clinical axSpA within 1 year of follow-up was mainly observed in HLA-B27 positive FDRs.

INTRODUCTION

Axial spondyloarthritis (axSpA) usually presents between 18 and 40 years of age and is characterized by inflammation and structural damage of the spine. Also, peripheral manifestations including arthritis, dactylitis and enthesitis, and exta-articular manifestations including psoriasis, inflammatory bowel disease (IBD) and uveitis can be present(1). Diagnosis is challenging and often delayed by several years, resulting in a delay of treatment. This can be explained by an insidious disease onset, limited specificity of signs and symptoms, and the lack of diagnostic biomarkers with sufficient positive predictive value. Carriership of HLA-B27 is broadly considered a predisposing factor for axSpA. It is known that first-degree relatives (FDRs) of HLA-B27 positive axSpA patients have an increased risk of developing SpA(2–5), and studying them could help to identify clinical signs, imaging abnormalities and biomarkers that are predictive of development of axSpA.

Previously we have reported the data of the first 51 participants of the Pre-SpA cohort, an ongoing prospective inception cohort study in which FDRs of HLA-B27 positive axSpA patients are included and prospectively followed for a period of 5 years(6). Although the FDRs did not have a clinical diagnosis of SpA, we observed clinical features associated with SpA in up to 33% of FDRs. Additionally, there was a high prevalence (20%) of bone marrow edema suggestive of (subclinical) sacroiliitis on MRI. Meanwhile, recent studies reported that up to 23% of MRIs of healthy volunteers, athletes and women postpartum are scored positive for sacroiliitis according to the ASAS definition(7–9) suggesting that BME itself is not very specific for SpA but rather omnipresent and related to mechanical stress. In contrast, deep (extensive) lesions on MRI of the sacroiliac joints were not seen in healthy volunteers and were far more specific for axSpA patients(10). Scoring of MRI-SIJ by the Spondyloarthritis Research Consortium of Canada (SPARCC) score rather than by a binomial score was reported to be more specific for axSpA(10,11). So far, it is not known if these extensive and deep lesions are also present in the at risk cohort of FDRs of HLA-B27 positive axSpA patients. More importantly, it is not known if FDRs with clinical or imaging features highly suggestive of SpA but without a clinical diagnosis of SpA, will develop clinically manifest disease over time.

The objectives of this study were 1) to evaluate presence of highly specific imaging features as well as clinical signs of SpA suggestive of subclinical disease at baseline and after one year of follow-up, and 2) describe the evolution towards clinical disease within one year of follow-up in a cohort of seemingly healthy FDRs of HLA-B27 positive axSpA patients.

METHODS

Study design and FDRs

The Pre-SpA cohort is an ongoing, multicenter, prospective 5-year inception cohort study(6). First-degree relatives (FDRs) of HLA-B27 positive axial spondyloarthritis (axSpA) patients were included; all were between 18-40 years of age at the time of inclusion and were able and willing to give written informed consent. Main exclusion criteria were a clinical diagnosis of SpA, or back pain with a previously confirmed non-rheumatic diagnosis, such as spinal disc herniation. First-degree relatives who were diagnosed with axSpA at or directly after the baseline visit were judged as 'missed diagnosis' and therefore excluded from the analyses in this report, since the aim was to investigate whether FDRs who are at risk to develop SpA have clinical or imaging signs of (subclinical) SpA, and not to describe features of FDRs with clinically manifest disease at baseline.

To confirm our preliminary findings in the original cohort of 51 FDRs, which showed that a high number of FDRs had clinical and imaging findings suggestive of SpA (2), we analyzed the data of 156 additionally and consecutively included FDRs whose baseline data were not reported in the previous manuscript on the Pre-SpA cohort.

The study was approved by the medical ethics committee of the Academic Medical Center/University of Amsterdam, The Netherlands. All FDRs gave written informed consent to participate in the study. Participating sites across the Netherlands were the Amsterdam University Medical Center, location AMC and VUmc, Leiden University Medical Center, Maastricht University Medical Center, Maasstad hospital in Rotterdam, and Reade in Amsterdam.

Assessments

Baseline demographics included year of birth, gender, ethnicity and smoking status. A complete medical history and family history of SpA (first and second degree relatives with axSpA, reactive arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease (IBD), uveitis or peripheral spondyloarthritis) were recorded.

Yearly the FDRs were asked about the presence or absence of back pain. If back pain was present, specific features of inflammatory back pain according to the ASAS definition(12) were recorded: age at onset below 40 years, insidious onset, improvement with exercise, no improvement with rest and pain at night (with improvement upon getting up). Also buttock pain and a good response to NSAIDs were recorded. First-degree relatives were

asked yearly about the presence or absence of the following SpA features, as diagnosed by a physician in the previous year: dactylitis, enthesitis, uveitis, IBD and psoriasis.

Physical examination was repeated yearly: swollen and tender joint count (66/68 joints), spinal mobility measures (Bath Ankylosing Spondylitis Metrology Index (BASMI), chest expansion, occiput to wall distance), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and evaluation of the presence of dactylitis (recorded as present/absent). The normal reference values used for the Schober and chest expansion were >4.5cm and >3.6cm, respectively(13).

Although the FDRs of the Pre-SpA cohort do not have a clinical diagnosis at baseline, at every visit patient reported outcomes (PROMs) relevant to axSpA were collected: global disease activity on a Visual Analogue Scale (VAS, 0-100mm), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), VAS total back pain (0-100mm) and VAS nocturnal back pain (0-100mm). A VAS physician global disease activity was filled out at every visit. ASDAS-CRP was calculated for each FDR at every visit(14).

Peripheral blood samples were collected at every visit to measure CRP (mg/L) and ESR (mm/hr). At baseline, HLA-B27 genotyping was performed.

First-degree relatives with symptoms suspicious of (ax)SpA were discussed by the study team and with an experienced rheumatologist. If the suspicion of clinical disease was high or in case of doubt, the FDRs was referred to a rheumatologist for confirmation of a possible clinical diagnosis. In case of a new clinical diagnosis (confirmed by a rheumatologist), date of diagnosis and subtype of diagnosis were recorded. All FDRs (both with and without a clinical diagnosis over time) were followed over time in the Pre-SpA cohort.

Imaging

Plain radiographs of the sacroiliac joints (SIJ), lumbar spine and cervical spine were obtained at baseline. Radiographs of the SIJ were scored according to the modified New York (mNY) criteria (15) by two experienced readers (HdJ and RL). High-grade sacroiliitis was defined as ≥ grade 2 bilateral, or ≥ grade 3 unilateral. Only X-rays that were scored as high-grade sacroiliitis by both readers were considered as such. Lateral X-rays of the lumbar and cervical spine were scored according to the modified Stoke Ankylosing Spondylitis Score (mSASSS)(16) by one experienced reader (RL).

MRI of the SIJ was performed on a 3 Tesla MRI scanner, semicoronal with T1 and STIR sequences and a slice thickness of 4 millimeters. MRIs were scored according to the SPARCC scoring system(17) by two experienced readers (JdW and RL). The SPARCC scoring system divides each SIJ in 4 quadrants (upper iliac, lower iliac, upper sacral, lower sacral). The presence of increased signal on STIR images in each of these quadrants was scored dichotomous (0=normal, 1=increased signal). Joints with a lesion with an increased signal were additionally scored when this signal was intense (+1) or deep, defined as a homogeneous, unequivocal increase in signal extending >1cm from the articular surface. This scoring was repeated in six consecutive slices, the maximum score being 72. The mean of the scores of both readers was used for the analyses. Previously we reported abnormalities on MRI suggestive of SpA in up to 20% of the initial cohort (n=51). The scoring method that was used in the previous report was the ASAS scoring system(18). We extended the evaluation of imaging findings on MRI in the previous cohort by using the SPARCC scoring method with 2 and 5 as cutoff values as well as a score for deep lesions (10,17).

Statistical analyses

Clinical features and imaging data were reported descriptively. All data are presented as median (IQR) unless stated otherwise. We compared the baseline features of HLA-B27 positive and negative FDRs. Binary data were analyzed using a chi-square test, nominal data were analyzed using a Students' T-test or Mann-Whitney U test, as appropriate. Interreader agreement on a SPARCC ≥2 was investigated using Cohen's kappa coefficient and interpreted according to the standards of Landis and Koch(19). Interreader agreement on absolute SPARCC scores was evaluated using intra-class correlation coefficients (ICCs). Statistical tests were 2-sided and p values <0.05 were considered significant.

All data are presented as median (IQR) unless stated otherwise. The baseline data of the first 51 participants have been reported before(6).

To investigate whether clinical signs of SpA or inflammatory markers changed over 1 year of follow-up, we compared baseline and one year follow-up clinical signs of SpA and inflammatory markers of the FDRs who had completed the one year follow-up visit (n=123). Finally, we compared the baseline features of the FDRs who were clinically diagnosed with axSpA within the first year of follow-up to the baseline features of the FDRs without a clinical diagnosis after one year. The data are reported descriptively as median (IQR) unless stated otherwise. Chi-square tests were used to analyze binomial data and Mann-Whitney U tests or Students' T-test, as appropriate, for continuous data.

RESULTS

First-degree relatives

In total, 207 first-degree relatives (FDRs) had been included at the time of analyses. The baseline data of 51 FDRs had been reported before(6). An additional 156 FDRs were consecutively included in the Pre-SpA cohort. Of those 156, 5 FDRs were immediately referred to a rheumatologist because of signs and symptoms suggestive of clinical axSpA. Since the clinical diagnosis was confirmed, these FDRs were considered 'previously missed diagnosis' rather than healthy FDRs 'at risk of SpA' and were therefore excluded from further analysis. Therefore, the baseline characteristics of 151 FDRs were analyzed in the current report. In total, 123 participants had completed the one-year follow-up visit at the time of the analyses. None were lost to follow-up during the first year of follow-up.

Confirmation of preclinical signs in an independent cohort of FDRs

Demographics and baseline characteristics of the confirmation cohort (n=151) are shown in Table 1. HLA-B27 status was missing in 7 FDRs, imaging data in 12 FDRs. Ninety-eight (65%) FDRs reported back pain at baseline, and 29 (19%) fulfilled the criteria for inflammatory back pain. However, severity of back pain was low as the FDRs who reported back pain (n=98) had a median (IQR) VAS total back pain (0-100mm) of 22 (11.8-48.5). Forty-eight (32%) FDRs reported the current presence of arthralgia and in 16 (11%) FDRs at least 1 tender joint was found at clinical examination. No active arthritis was observed. Five (3%) FDRs had a past diagnosis of arthritis confirmed by a physician, 8 (5%) of enthesitis and 1 (1%) of dactylitis diagnosed in the past. In none of these FDRs a previous diagnosis of spondyloarthritis was made. Two (1%) FDRs reported the presence of psoriasis, none reported inflammatory bowel disease (IBD) and one (1%) reported a history of uveitis.

Median disease activity measures were low in the total study population, both the patient-reported parameters as well as the serum inflammatory markers. CRP was elevated (>5mg/L) in 24 (16%) participants (median (IQR) 8.8(6.8-12.8)mg/L) and ESR (>20mm/hr) in 11 (7.3%) (median (IQR) 27 (24-34) mm/hr). Very few showed decreased spinal mobility: the Schober test was decreased (<4.5cm) in 5 (3%) FDRs and chest expansion was decreased (<3.6cm) in 3 (2%).

Imaging data were available for 139/151 FDRs. Two (1%) FDRs formally fulfilled the modified New York (mNY) criteria for high-grade radiographic sacroiliitis on conventional imaging with grade 2 sacroiliitis bilateral, according to the scoring of both readers. One

hundred seventeen (84%) X-rays were scored as grade 0 bilateral by both readers. None of the FDRs had abnormalities on the X-rays of the lumbar and cervical spine according to the mSASSS. On MRI of the SI joints, 14 (10%) FDRs had a SPARCC score of ≥2 and 5 (4%) a SPARCC score ≥5. 'Deep lesions' were present in 5 (4%) FDRs. The inter-reader agreement for the absolute SPARCC score was high (intra-class coefficient 0.94), the kappa for SPARCC scores ≥2 was substantial (0.68).

When comparing HLA-B27 positive and negative FDRs, no statistically significant differences were found for demographic, clinical, or imaging findings (Table 1).

Table 1. Demographic and clinical characteristics, laboratory test results and imaging signs of spondyloarthritis at baseline and stratified by HLA-B27 positive and HLA-B27 negative first-degree relatives

		HLA-B27 status*	
	Baseline (n=151)	**Positive (n=80)**	**Negative (n=64)**
Male sex, no. (%)	90 (60)	48 (60)	40 (63)
Caucasian, no. (%)	134 (89)	73 (91)	55 (86)
Age, years, mean ± SD	27.1 ± 6.7	27.5 ± 6.7	27.2 ± 5.6
HLA-B27 positive, no. (%)*	80 (53)	80 (100)	0 (0)
Current smoker, no. (%)	28 (19)	13 (16)	13 (20)
Axial disease, no. (%)			
Back pain (current)	98 (65)	54 (68)	41 (64)
Inflammatory back pain (current)	29 (19)	18 (23)	10 (16)
Peripheral disease, no. (%)			
Arthralgia (current)	48 (32)	27 (34)	19 (30)
Peripheral arthritis (ever)	5 (3)	2 (3)	3 (5)
Enthesitis (ever)	8 (5)	5 (6)	3 (5)
Dactylitis (ever)	1 (1)	1 (1)	0
Extra-articular disease, no. (%)			
Psoriasis (ever)	2 (1)	1 (1)	1 (2)
IBD (ever)	0	0	0
Urethritis/diarrhea (ever)	1 (1)	0	0
Uveitis (ever)	1 (1)	0	1 (2)
Family history, no. (%)			
Psoriatic arthritis	1 (1)	0	1 (2)
Psoriasis	12 (8)	4 (5)	8 (13)

		HLA-B27 status*	
	Baseline (n=151)	**Positive (n=80)**	**Negative (n=64)**
IBD	12 (8)	5 (6)	7 (11)
Uveitis	9 (6)	7 (9)	2 (3)
Disease activity measures			
PhGA, 0-100mm VAS	0 (0-7)	0.5 (0-20)	0 (0-6.8)
PtGA, 0-100mm VAS	2 (0-26)	5 (0-25)	1 (0-36)
Pt total back pain, 0-100mm VAS	13 (0-33)	12.5 (0-28)	15 (0-42)
Pt nocturnal pain, 0-100mm VAS	0 (0-9)	0 (0-12)	0 (0-5)
BASDAI	1.4 (0.7-2.7)	1.3 (0.7-3)	1.4 (0.7-2.7)
ASDAS-CRP	1.0 (0.6-1.7)	1.1 (0.5-1.7)	0.9 (0.6-1.7)
BASFI score, range 0-10	0.1 (0-0.9)	0.2 (0-0.8)	0 (0-0.9)
Clinical findings			
Modified Schober <4.5cm, no. (%)	5 (3)	3 (4)	2(3)
Chest expansion <3.6cm, no. (%)	3 (2)	2 (3)	1(2)
TJC >0, range 0-68	16 (11)	11 (14)	5 (8)
SJC >0, range 0-66	0	0	0
MASES >0, no. (%)	35 (23)	19 (24)	25 (25)
Laboratory test results			
CRP, mg/L	2 (1-3)	2 (1-3)	2 (1-3)
ESR, mm/hour	2 (2-8)	2 (2-8)	2 (2-10)
Imaging, no.(%)			
High-grade sacroiliitis on X-ray	2 (1)	2 (3)	0
SPARCC score ≥2 on MRI	14/139 (10)	10 (13)	4 (6)
SPARCC score ≥5 on MRI	5/139 (4)	4 (5)	1 (2)
Deep lesions on MRI	5/139 (4)	3 (4)	2 (3)

All values are presented as median (interquartile range) unless indicated otherwise.
IBD inflammatory bowel disease; PhGA physician global disease activity; PtGA patient global disease activity; VAS visual analogue scale; BASDAI Bath Ankylosing Spondylitis Disease Activity Index; ASDAS Ankylosing Spondylitis Disease Activity Score; CRP C-reactive protein; BASFI Bath Ankyosing Spondylitis Function Index; TJC tender joint count; SJC swollen joint count; MASES Maastricht Ankylosing Spondylitis Enthesitis Score; ESR erythrocyte sedimentation rate, SPARCC Spondyloarthritis Research Consortium of Canada
*HLA-B27 status is missing for n=7

Presence of highly specific MRI lesions in the original cohort of FDRs

We previously reported a higher incidence of MRI lesions in a first cohort of 51 FDRs using a less stringent scoring method, namely according to the ASAS definition. To assess if this difference in incidence of MRI lesions was due to the cohort or to the scoring methodology, we re-assessed the MRI SIJ of all 51 FDRs from the original cohort using the more stringent methodology used above to assess the presence of abnormalities suggestive of SpA. Eight FDRs (16%) had a SPARCC score ≥2 and 4 (8%) a SPARCC score ≥5. One FDR (2%) had a deep lesion on MRI, this FDR had a total SPARCC score of 9.5. The distribution was equal between HLA-B27 positive and negative FDRs. Inter-reader agreement on absolute SPARCC scores was excellent (ICC 0.877). These data are in line with the findings reported above in the cohort of 151 FDR showing imaging findings highly specific of axSpA in up to 15% of seemingly healthy FDR.

Evolution towards clinical SpA during 1 year follow-up

At the time of analysis, 123 FDRs had completed 1 year of follow-up. None were lost to follow up during the first year. Characteristics after one year of follow-up are shown in Table 2. One participant had developed new onset IBD, all other SpA-related features and disease activity parameters remained stable. Within the first year of follow-up, 7(6%) FDRs were referred to a rheumatologist because they were suspected of axSpA as the intensity and frequency of their back pain had increased. All were clinically diagnosed with axSpA. Six out of 7 FDRs with a clinical diagnosis of axSpA after one year were HLA-B27 positive. In all FDRs with a clinical diagnosis after one year, disease activity measures had increased at the one year follow-up visit compared to baseline: VAS patient global disease activity (0-100mm) from median(IQR) 18 (0-28) to 44 (19-60) (p=0.043), VAS total back pain from 19 (0-27) to 44 (16-54)(p=0.063), VAS nocturnal back pain from 4 (0-25) to 27 (11-50)(p=0.028) and BASDAI from 1.4 (1.0-2.1) to 3.9 (2.2-4.9)(p=0.018).

Table 2. Demographic and clinical characteristics, laboratory test results and imaging signs of spondyloarthritis at baseline and after one year of follow-up of 123 FDRs with one year follow up

	Baseline (n=123)	**Year 1 (n=123)**
Male sex, no. (%)	72 (59)	
Caucasian, no. (%)	114 (93)	
HLA-B27 positive, no. (%)	65 (53)	
Current smoker, no. (%)	33 (27)	33 (27)
Axial disease, no. (%)		
Back pain (current)	70 (57)	57 (46)
Inflammatory back pain (current)	22 (18)	22 (18)
Peripheral disease, no. (%)		
Arthralgia (current)	40 (33)	20 (16)
Peripheral arthritis (ever)	5 (4)	4 (3)
Enthesitis (ever)	5 (4)	5 (4)
Dactylitis (ever)	0	0
Extra-articular disease, no. (%)		
Psoriasis (ever)	3 (2)	3 (2)
IBD (ever)	0	1 (1)
Urethritis/diarrhea (past/present)	0	1 (1)
Uveitis (ever)	2 (2)	2 (2)
Family history, no. (%)		
Psoriatic arthritis	3 (2)	3 (2)
Psoriasis	11 (9)	11 (9)
IBD	8 (7)	8 (7)
Uveitis	4 (3)	4 (3)
Disease activity measures		
PhGA, 0-100mm VAS	0 (0-6)	0 (0-7)
PtGA, 0-100mm VAS	2 (0-15)	1 (0-12)
Pt total back pain, 0-100mm VAS	6 (0-21)	4 (0-24)
Pt nocturnal pain, 0-100mm VAS	0 (0-5)	0 (0-12)
BASDAI	1.0 (0.5-2.0)	1.1 (0.5-2.1)
ASDAS-CRP	0.9 (0.5-1.3)	0.8 (0.5-1.5)
BASFI score, range 0-10	0.1 (0-0.7)	0.1(0-0.6)
Clinical examinations findings		
Modified Schober <4.5cm, no. (%)	5 (4)	7 (6)
Chest expansion <3.6cm, no. (%)	1 (1)	2 (2)
TJC >0, range 0-68	15 (12)	7 (6)

	Baseline (n=123)	Year 1 (n=123)
SJC >0, range 0-66	0	0
MASES >0, no. (%)	30 (24)	30 (24)
Laboratory test results		
CRP, mg/L	2 (1-3)	2 (1-3)
ESR, mm/hour	5 (2-9)	5 (2-8)

All values are presented as median (interquartile range) unless indicated otherwise.
IBD inflammatory bowel disease; PhGA physician global disease activity; PtGA patient global disease activity; VAS visual analogue scale; BASDAI Bath Ankylosing Spondylitis Disease Activity Index; ASDAS Ankylosing Spondylitis Disease Activity Score; CRP C-reactive protein; BASFI Bath Ankyosing Spondylitis Function Index; TJC tender joint count; SJC swollen joint count; MASES Maastricht Ankylosing Spondylitis Enthesitis Score; ESR erythrocyte sedimentation rate

To assess whether specific baseline features may be associated with evolution to clinical axSpA, baseline characteristics of FDRs who developed clinical disease were compared to baseline characteristics of those who did not develop axSpA within the first year of follow-up (Table 3). All but one were HLA-B27 positive, none had extra-articular disease and 5 out of 7 were male. FDRs with a clinical diagnosis after one year had significantly more often inflammatory back pain (71 vs. 15%, p<0.001) and enthesitis (29 vs. 3%, p=0.001) at baseline, thus before a clinical diagnosis was made. Imaging abnormalities suggestive of axSpA were also more prevalent at baseline in FDRs with a clinical diagnosis after one year: high grade sacroiliitis on X-ray: 29 vs. 1%, p<0.001, a SPARCC ≥2: 43 vs. 12%, p=0.023 and deep lesions on MRI: 14 vs. 1%, p=0.006 at baseline.

Table 3. Baseline characteristics of FDRs with and without a clinical diagnosis of spondyloarthritis after one year of follow-up

	Clinical diagnosis		
	Yes (n=7)	**No (n=116)**	**p-value**
Male sex, no. (%)	5 (71)	67 (58)	0.476
Caucasian, no. (%)	7 (100)	107 (92)	0.586
Age, years	26.6 (6)	26.6 (6)	0.914
HLA-B27 positive, no. (%)	6 (86)	59 (51)	0.073
Current smoker, no. (%)	3 (43)	30 (26)	0.324
Axial disease, no. (%)			
Back pain (current)	6 (86)	64 (55)	0.113
Inflammatory back pain (current)	5 (71)	17 (15)	<0.001
Peripheral disease, no. (%)			

	Clinical diagnosis		
	Yes (n=7)	**No (n=116)**	**p-value**
Arthralgia (current)	3 (43)	37 (32)	0.548
Peripheral arthritis (ever)	0	5 (4)	0.575
Enthesitis (ever)	2 (29)	3 (3)	0.001
Dactylitis (ever)	0	0	-
Extra-articular disease, no. (%)			
Psoriasis (ever)	0	3 (3)	0.667
IBD (ever)	0	0	-
Urethritis/diarrhea (past/present)	0	0	-
Uveitis (ever)	0	2 (2)	0.726
Family history, no. (%)			
Psoriatic arthritis	0	3 (3)	0.667
Psoriasis	2 (29)	9 (8)	0.061
IBD	0	8 (7)	0.472
Uveitis	0	4 (3)	0.617
Disease activity measures			
PhGA, 0-100mm VAS	21 (0-23)	0 (0-5)	**0.021**
PtGA, 0-100mm VAS	18 (0-28)	2 (0-13)	0.158
Pt total back pain, 0-100mm VAS	19 (0-27)	5.5 (0-21)	0.380
Pt nocturnal pain, 0-100mm VAS	4 (0-25)	0 (0-5)	0.135
BASDAI	1.4 (1.0-2.1)	1.0 (0.5-1.9)	0.416
ASDAS-CRP	1.2 (1.1-1.5)	0.8 (0.5-1.3)	0.126
BASFI score, range 0-10	0.4 (0.2-1.4)	0(0-0.6)	0.050
Clinical examinations findings			
Modified Schober <4cm, no. (%)	1 (14)	4 (3)	0.159
Chest expansion 3.6cm, no. (%)	0	1 (1)	0.805
TJC >0, range 0-68	1 (14)	14 (12)	0.862
SJC >0, range 0-66	0	0	-
MASES >0, no. (%)	3 (43)	27 (23)	0.241
Laboratory test results			
CRP, mg/L	2 (1-6)	2 (1-3)	0.428
ESR, mm/hour	10 (2-16)	5 (2-8)	0.158
Imaging			
High-grade sacroiliitis on X-ray, no. (%)	2 (29)	1 (1)	<0.001
SPARCC score ≥2 on MRI, no. (%)	3 (43)	14 (12)	0.023

	Clinical diagnosis		
	Yes (n=7)	**No (n=116)**	**p-value**
SPARCC score ≥5 on MRI, no. (%)	1 (14)	6 (5)	0.317
Deep lesions on MRI, no. (%)	1 (14)	1 (1)	0.006

All values are presented as median (interquartile range) unless indicated otherwise.
IBD inflammatory bowel disease; PhGA physician global disease activity; PtGA patient global disease activity; VAS visual analogue scale; BASDAI Bath Ankylosing Spondylitis Disease Activity Index; ASDAS Ankylosing Spondylitis Disease Activity Score; CRP C-reactive protein; BASFI Bath Ankyosing Spondylitis Function Index; TJC tender joint count; SJC swollen joint count; MASES Maastricht Ankylosing Spondylitis Enthesitis Score; ESR erythrocyte sedimentation rate; SPARCC Spondyloarthritis Research Consortium of Canada

DISCUSSION

The Pre-SpA cohort is a prospective inception cohort of first-degree relatives (FDRs) of HLA-B27 positive axial spondyloarthritis (axSpA) patients. In this study, we evaluated clinical features and imaging abnormalities that are considered highly suggestive of SpA at baseline, as well as clinical features of SpA and evolution towards clinical disease within one year of follow-up. We showed that at baseline 19% of FDRs had inflammatory back pain, 32% had current arthralgia, 3% arthritis (ever), 5% enthesitis (ever) and 1% dactylitis (ever). In total, 3% of FDRs had extra-articular disease. Sixteen percent had an elevated CRP and 7% an elevated ESR. Up to 15% of FDRs had MRI findings highly suggestive of axSpA, but still without signs and symptoms that warranted a clinical diagnosis. All features were equally distributed between HLA-B27 positive and negative FDRs. Approximately 6% of FDRs developed a distinguishable clinical syndrome of axSpA over 1 year of follow-up, and all except one were HLA-B27 positive. Two of the FDRs who developed clinical axSpA had high-grade sacroiliitis on X-ray a baseline, and one of those additionally had abnormalities on MRI suggestive of SpA.

Even though the Pre-SpA cohort is a cohort of young, (seemingly) healthy FDRs, up to 65% reported current back pain of which 19% was inflammatory, and up to 30% current arthralgia. Probably these findings are not very specific in most individuals as tender joints are not observed at physical examination and, although inflammatory back pain is regarded as a spondyloarthritis feature, recent studies reported that the distinctive impact of inflammatory back pain was lower than previously thought with a specificity of 25-52% and sensitivity of 74-84%(20,21) Nevertheless, both the percentage of FDRs reporting arthralgia and back pain are high when considering the mean age at inception of 27. Also, serum inflammatory markers were elevated in a significant number of FDRs, which could be an indication of subclinical disease. In contrast, the number of FDRs

with extra-articular disease was low, which could partly be explained by the young age at inception. Taken together, (sub)clinical signs of SpA features were highly prevalent.

In this study, imaging abnormalities suggestive of subclincal inflammation were seen in up to 16% of the FDR. A recent study showed that scoring MRIs binomial as either highly suggestive of SpA or not according to the ASAS definition, lacks specificity (22), and MRI results should be interpreted with caution. We here used the SPARCC score with cutoff values of ≥2 and ≥5 which was previously shown to discriminate between axSpA patients and patients with non-specific back pain and healthy individuals with or without SI-strain(10).

The MRIs of the sacroiliac joints (SIJ) of 10-16% of FDRs were scored with a SPARCC score ≥2, a SPARCC score of ≥5 was seen in 4-8% of FDRs, and deep lesions in 2-4%, and all were equally distributed between HLA-B27 positive and negative FDRs. As these FDR have additional risk factors for development of axial disease it will be of great interest to follow these individuals over time to determine who will or will not develop clinically manifest disease and if these highly specific imaging findings pose the same risk for development of disease.

After one year of follow-up in the Pre-SpA cohort, 6% of FDRs was diagnosed with axSpA. Notably, the assessment of global disease activity by the study physician at baseline, thus before a clinical diagnosis was made, was higher in the FDRs with a clinical diagnosis at the visit after one year of follow-up, indicating that the study physicians already suspected subclinical disease. As expected, the number of FDRs developing SpA in our cohort is much higher than the yearly incidence in a non-selected healthy population (23). AxSpA usually develops before the age of 40, therefore, with the mean age at baseline being 27, we expect that more FDRs will develop axSpA in the coming years during 5-10 year follow up. Whether we can extrapolate the incidence of 6% to later years of follow-up, or whether this percentage will be lower in de following years remains to be seen. A recent study by Sepriano *et al* distinguished three groups within the clinical axSpA domain. One of these groups was 'SpA at risk', which shows a close resemblance to part of the Pre-SpA cohort. They reported that 11% switched from the 'SpA at risk' group to a group with clinical manifest disease(24). This suggests that possibly a large number of FDR in the Pre-SpA cohort stay at risk of SpA with some suggestive clinical symptoms, but without enough signs and symptoms to make a diagnosis.

Although clinical serological and imaging features suggestive of subclinical inflammation at baseline were independent of HLA-B27 status, 6 out of 7 FDRs who progressed towards clinical disease were HLA-B27 positive. A strong association between HLA-B27 and progression towards chronic disease was also shown several decades ago for reactive arthritis. The disease was mainly self-limiting in HLA-B27 negative patients, while the patients who progressed towards chronic disease were mainly HLA-B27 positive(25). Likewise, in animal studies similar findings have been observed where HLA-B27 transgenic rats after innate immune triggering with low dose heat inactivated Mycobacterium tuberculosis developed chronic disease that resembled human spondyloarthritis whereas HLA-B7 transgenic rats did not(26). If our finding that almost all FDRs who progress towards clinical disease are HLA-B27 positive is confirmed during further follow-up, this suggests that HLA-B27 is not responsible for initiation of (acute) subclinical inflammation (or susceptibility to inflammation) but rather determines the progression of (a-specific) subclinical inflammation to clinically manifest disease in axSpA. This hypothesis could also fit our previous imaging findings suggesting that sacroiliitis (BME according to ASAS) on MRI is a relative common feature as consequence of mechanical stress and is transcient in general(10), but preferentially in HLA-B27 positive individuals this stress-induced inflammation becomes extended and chronic with development of structural damage.

One of the limitations of this study is the possible channeling of specifically those FDR with complaints to participate in this study as a high number of FDRs reported back pain (65%). However, this back pain was reported upon active questioning and the majority had not visited a physician or used pain medication because of back pain. Furthermore, the FDRs with back pain reported a low VAS total back pain (median[IQR] 20.5(10-39.5)), indicating that back pain was not a major complaint in their daily lives and probably not the sole reason to participate in the Pre-SpA cohort. We did not formally record how many potential FDRs did not want to participate nor their reasons not to participate. Also, for ethical reasons we cannot formally check the information that FDRs give about family and medical history, thus we have to rely on the information the FDRs provide. As the number of FDRs included in the Pre-SpA cohort is still limited, we are recruiting more FDRs. Further follow-up will show which FDRs will develop clinical axSpA.

In conclusion, in seemingly healthy FDRs of axSpA patients, (sub)clinical signs of SpA features are frequently seen with an equal distribution between HLA-B27 positive and negatieve FDRs. However, progression towards clinical axSpA is seen mainly in FDRs with HLA-B27 positivity and inflammatory back pain. Further follow-up of the Pre-

SpA cohort will give more robust insight into the characteristics of FDRs that progress towards clinical SpA, thereby hopefully enabling the characterization of high-risk FDRs.

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4

FIRST-DEGREE RELATIVES OF AXIAL SPONDYLOARTHRITIS PATIENTS OF THE PRE-SPA COHORT WOULD CONSIDER USING MEDICATION IN A PREVENTIVE SETTING

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ABSTRACT

Objective

To study the willingness of first-degree relatives of axial spondyloarthritis (axSpA) patients to use preventive medication.

Methods

Participants of the Pre-SpA cohort (n=106) completed a survey including hypothetical scenarios varying in disease risk, side effects and treatment effect.

Results

The willingness to use preventive medication was 63.2-91.5% (with 30-70% SpA risk, respectively), and declined to 27.4-51.9% respectively, when side effects might occur. On a visual analogue scale (VAS) 0-100 (median;range) participants were not occupied by the thought of developing SpA (23;13-39), did not assume that they will eventually develop SpA (22;14-35) and consider SpA a severe disease (66;52-78). The willingness to use preventive medication was negatively influenced by their own risk assessment of developing SpA (OR=1.17, p=.001) and was not primarily influenced by costs and route of administration.

Conclusion

First-degree relatives of axSpA patients with a clearly increased disease risk (70%) would largely consider using preventive medication. Their willingness roughly halved by the possible occurrence of side effects. Participants' perceived risk to develop SpA and their assessment of the severity of SpA negatively influenced the willingness to use preventive medication.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease affecting the spine, peripheral joints and extra-articular sites. Early treatment of axSpA is important, since a delayed start of treatment is linked to worse clinical outcome (1,2).

In rheumatoid arthritis (RA) improving outcome was gained by early and aggressive treatment, which is nowadays standard of care (3). Moreover, attempts have been made (4) and trials are ongoing initiating treatment in the pre-clinical phase before the onset of clinical manifestations (5,6) aimed at preventing RA. In axSpA little is known about the possibilities, effects and desirability of early treatment, merely because of the difficult diagnostic process. Initiatives as the pre-SpA cohort (7), a prospective cohort of healthy first degree relatives of axSpA patients, and the SPACE (SPondyloArthritis Caught Early) cohort (8) might enable in a very early phase to identify, treat and thereby possibly even prevent axSpA. Therefore, also in axSpA, preventive treatment is an imaginable scenario.

To our knowledge, the willingness of first-degree relatives of axSpA patients to start preventive therapy has never been explored. If we know whether and under what circumstances at-risk individuals are willing to start preventive therapy, development of preventive treatment strategies could be targeted to that purpose.

The aim of this study was to investigate the willingness of individuals at increased risk of developing axSpA to initiate preventive treatment and evaluate which factors influence this decision.

METHODS

Study population

For this study all participants from the Pre-spondyloarthritis (Pre-SpA) cohort, known to have an increased risk to develop SpA, were approached regardless of their time of follow-up**.** This cohort has been described in detail previously (7). In short, Pre-SpA is an ongoing, prospective, multicenter inception cohort of healthy, first-degree relatives of HLA-B27-positive axSpA patients between 18-40 years of age. All were 1) not diagnosed as having SpA at the time of the baseline visit and 2) not treated for back pain by a physician. All participants gave their written informed consent and the ethics board of the Academic Medical Center Amsterdam approved the study protocol (Nl41248.018.12).

Survey

Participants completed a paper survey designed to assess their willingness to use treatment to prevent or delay the onset of SpA. The survey comprised six scenarios. In each scenario we changed one variable: 1) the likelihood of developing SpA varying from 30-70%, 2) the effectiveness of treatment; either complete prevention or 10 year delay of onset of SpA, 3) potential side effects, varying from none to mild to potential infections. For each scenario the participant could answer to what degree he or she wants to (hypothetically) initiate preventive treatment on a 5-point Likert scale (from 'No' to 'Yes'). We also included a question to investigate the most important factor for participants to decline using preventive treatment (partly multiple choice, partly open). Furthermore, participants scored their perception of the severity of SpA, their own risk to develop SpA, and whether they are preoccupied with the thought of developing SpA on a visual analogue scale (VAS) from 0-100. We conducted think-aloud interviews with SpA patients, healthy volunteers with a wide variety of age and educational level, and medical doctors and nurses to verify realistic and clear scenarios and questions.

Statistical analyses

Baseline data are presented as numbers (%) (categorical data) or the mean/median (SD/IQR/range) (continuous data) as appropriate. The data on treatment preference are shown as percentages and analyzed using the McNemar's test, enabling to compare two scenarios as paired data. To prepare the data for that analysis, the 'preference for treatment' outcome variable was dichotomized. A preference for treatment (the answers 'Yes' and 'I probably would') was assigned a score of 1, and a neutral preference ('I don't know) or preference for non-treatment ('I would probably not' and 'no') was assigned a score of 0.

To test for possible interactions of willingness to use preventive medication with age, gender, HLA-B27 status and the presence of back pain throughout the different scenarios, we used a generalized estimating equations (GEE) model with a logit link, binomial distribution and an exchangeable correlation. GEE enables analysis of repeatedly assessed preference scenarios. It corrects for the fact that patients' answers to each subsequent scenario are related to their answers in previous scenarios. Outcome measures of the GEE were odds ratios and 95% confidence intervals. We calculated whether age, gender, HLA-B27 status or the presence of back pain were significant predictors for (non)treatment preference.

We tested the correlation of disease perception (the own risk assessment of developing SpA) with the willingness to start using preventive medication in a linear regression model. We performed all analyses in SPSS version 24.0.

RESULTS

Study population and response

The study population has been described in detail earlier (7). Of all 130 Pre-SpA participants, 106 completed the survey (response rate 81.5%). Baseline characteristics are shown in Table 1. There were no missing values. Baseline characteristics between responders and non-responders did not differ (data not shown).

Evaluating participants' believes and perceptions of SpA (VAS -100) showed that they were not occupied by the thought of developing SpA (median 23, range 13-39), did not assume that they will eventually develop SpA 22 (14-35) and consider SpA as a severe disease 66 (52-78).

Table 1. Baseline characteristics of participants

	Participants (n=106)
Age, mean (SD)	28.7 (5.6)
Gender male, n (%)	47 (44)
Back pain, n (%)	58 (55)
HLA-B27 positive, n (%)	55 (52)
BASDAI, median (IQR)	1.0 (0.5-2.0)
CRP, median (IQR)	1.3 (0.7-2.7)
ESR, median (IQR)	5 (2-9)
Enthesitis, n (%)	4 (4)
Arthritis, n(%)	4 (4)
Dactylitis, n (%)	0
Psoriasis, n (%)	3 (3)
Inflammatory bowel disease, n (%)	1 (1)
Uveitis, n (%)	2 (2)
Reactive arthritis, n (%)	0

HLA-B27: human leukocyte antigen B27; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, IQR: interquartile range

The willingness to use preventive medication

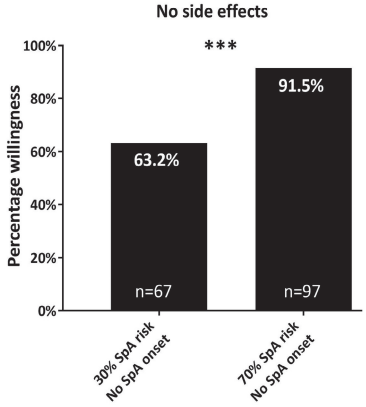
The percentage of participants willing to use preventive medication with 100% effectiveness causing no side effects varied between 63.2% (with 30% SpA risk) and 91.5% (with 70% SpA risk) (p<.0001, Figure 1A).

The percentage decreased depending on the possible occurrence of side effects. From 63.2% to 27.4% and 32.1% (with 30% SpA risk) if the medication would possibly cause mild side effects or infections respectively (p<.001, Figure 1B) and from 91.5% to 51.9% with 70% SpA risk if the medication would possibly cause infections (p<.0001, Figure 1C). When medication would cause a delay in SpA onset of 10 years (with 70% SpA risk), the percentage willing to use preventive medication decreased from 91.5% to 67.9% (p<.0001, Figure 1C).

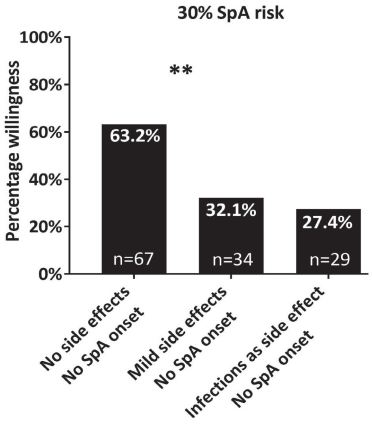
The willingness to use preventive medication was negatively influenced by their own risk assessment of developing SpA (OR=1.17, *p*=.001). The GEE model showed no correlation between choice for preventive medication and age (OR 1.0, p=.96), HLA-B27 positivity (OR 1.45, p=.69) or the presence of back pain (OR 1.17, p=.58).

The willingness to use preventive medication was primarily influenced by the certainty of the risk to develop SpA (34.0%), followed by the risk of side effects (32.1%) and the effectiveness of the medication (25.5%). Medication costs (0.9%) and the route of administration (0%) had no influence.

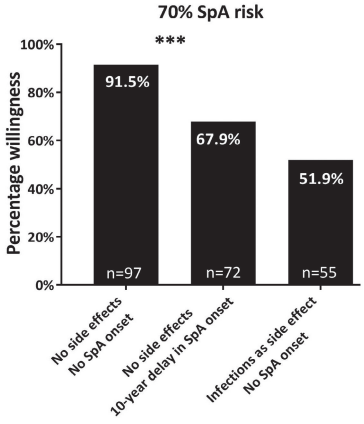
Figure 1. Percentage of at-risk individuals willing to use preventive medication.



A without side effects ***p<0.0001. The percentage of first-degree relatives of axSpA patients that is willing to use preventive medication without any side effects and with 30 or 70% risk of ever developing SpA.



B with 30% risk of developing SpA ** p<0.001. The percentage of first-degree relatives of axSpA patients that is willing to use preventive medication with a 30% risk of ever developing SpA and with either none, mild side effects or infections as a side effects, all with a 100% effectiveness of the medication.



C with 70% risk of developing SpA*** p<0.0001. The percentage of first-degree relatives of axSpA patients that is willing to use preventive medication with a 70% risk of ever developing SpA and with either no side effects and no onset of SpA, no side effects and a 10 year delay of SpA onset, or infections as a side effect and no SpA onset.

axSpA, axial spondyloarthritis; SpA, spondyloarthritis

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DISCUSSION

The results of our study suggest that: 1) 67% of individuals at increased risk to develop SpA is willing to use preventive medication when the hypothetical risk to develop SpA is 30%, increasing to 91.5% when this risk is 70%, if the medication would not cause any side effects. 2) Potential side effects lower the willingness to use preventive medication to 27% and 52% with 30% and 70% disease risk, respectively. And 3) the willingness to use preventive medication is influenced by the participants' own perception of the severity of the disease and the disease risk, regardless of the given hypothetical risk.

In a previous study in rheumatoid arthritis (RA) using a comparable study population, approximately one third of the participants chose to take preventive medication if the risk of developing RA was 20-40%, with a varying risk of side effects (9). This is

concordant with the findings of our study that approximately 30% of participants is willing to use medication with a 30% risk of developing SpA and the possibility of side effects.

Studies to investigate the willingness of individuals to use medication in a preventive setting have been performed in other diseases than axSpA. Port *et al* investigated the willingness of women eligible to use tamoxifen for breast cancer prophylaxis, and showed that the vast majority declined because of side effects (10). Another study performed in Denmark investigated whether individuals would use preventive treatment for cardiovascular disease; in this study, more than half of respondents who were initially willing to use this medication declined after hearing about side effects (11). Interestingly, in our study the willingness to use preventive medication also dropped by 50% when mild side effects might occur, despite the fact that these side effects would stop directly after quitting the preventive medication. Together with our study results, these results emphasize the importance of thorough education of at-risk individuals with regard to their risk profile and the preventive therapy that is offered.

Our study has several strengths. First, the Pre-SpA cohort is by our knowledge the only cohort of first-degree relatives (FDRs) of axSpA patients, representing a unique opportunity to study a population at increased risk for developing SpA. Second, the high response rate (81.5%) suggests that the subject is of relevance for participants.

Our study has also limitations. First, some of the theoretical values that were used in this study are extremes (e.g. the efficacy of medication (100%) and risk to develop SpA (70%)). However, the scope of this study is not to deduct a fixed willingness, but to conclude that there is a reasonable willingness that is fluctuating with the magnitude of the risk to develop SpA, the risk to develop side effects and the effectiveness of the medication. Previous research showed that participants may encounter difficulties in interpreting percentages and complex hypothetical scenarios (12), therefore we chose a limited amount of scenarios and chances. Second, FDRs of axSpA patients included in Pre-SpA might be more inclined to take preventive medication than non-participating FDRs because of symptoms possibly relating to SpA. This suggestion is contradicted by the fact that the willingness to use preventive medication is not influenced by HLA-B27 status or by the presence of back pain. Moreover, data between participants and non-participants did not differ, suggesting that the data are representative for the study population. Third, despite being composed thoroughly, we might have not included all important variables in our study scenarios. For example, our study did not show a difference in willingness to use preventive medication between men and women, whilst

in daily practice, women might fear becoming unfertile because of certain therapies. At some point we had to compromise between length and clarity of the survey and completeness.

In conclusion, when the axSpA risk is clearly increased (70%) or when preventive medication has no side effects, the vast majority of first-degree relatives of axSpA patients seems willing to use preventive medication. This willingness roughly drops by 50% by the possible occurrence of mild side effects. Further research will have to focus on highly effective medication with an acceptable safety profile and on selecting individuals at clearly increased risk to develop SpA

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5

ACHIEVING REMISSION IN PSORIATIC ARTHRITIS BY EARLY INITIATION OF TNF INHIBITION: A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL OF GOLIMUMAB PLUS METHOTREXATE VERSUS PLACEBO PLUS METHOTREXATE

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ABSTRACT

Objectives

Early initiation of effective treatment favours remission in rheumatoid arthritis, but it remains unknown if the same concept applies to psoriatic arthritis (PsA). Therefore, this study investigated whether the combination of golimumab plus methotrexate (MTX) as a first-line treatment is superior to MTX alone in inducing remission in PsA.

Methods

This investigator-initiated, multicentre, double-blind, randomised, placebo-controlled trial included 51 MTX and bDMARD-naïve patients with PsA fulfilling the CASPAR criteria and with active disease at baseline (≥3 swollen joint count/tender joint count). Patients were randomised to golimumab (50 mg SC monthly)+MTX (n=26) (TNFi arm) or matched placebo+MTX (n=25) (MTX arm). MTX was started 15 mg/week and increased to 25 mg/week over 8 weeks. The primary endpoint was percentage of patients achieving Disease Activity Score (DAS) remission (<1.6) at week 22. Safety was assessed throughout the study.

Results

The primary efficacy endpoint was achieved by 81% in the TNFi arm versus 42 % in the MTX arm (p=0.004). This difference in DAS remission was already observed at week 8. A significant difference in favour of the golimumab+MTX arm at week 22 was also observed for other response criteria such as MDA, ACR20/50/70, disease measures and patient-reported outcomes. The occurrence rates of adverse event and treatment-emergent adverse event were similar in both arms.

Conclusion

In patients with early PsA, DAS remission at week 22 was almost doubled with golimumab+MTX versus MTX alone. This double-blind, randomised, placebo-controlled study supports the concept that early initiation of TNFi in patients with PsA favours remission.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of skin and nails. Treatment options for PsA have tremendously increased over the last two decades. The initial treatment in most patients consists of conventional synthetic disease-modifying antirheumatic drugs (csDMARDS). Patients with PsA with persistent moderate to high disease activity are eligible for tumour necrosis factor inhibitors (TNFi). In rheumatoid arthritis (RA), there is ample evidence for strategies aiming to reach and maintain remission of inflammation (ie, treat to target) (1-4). Also, the early start of treatment improved outcomes, as the earlier the start of treatment, the higher the remission rates were seen (5,6).

Whether initiation of potent targeted therapies in an early disease phase favours remission in other types of inflammatory arthritis, including PsA, remains unknown. The current treatment paradigm in PsA still consists of a step-up approach with non-steroidal anti-inflammatory drugs (NSAIDs) and/or non-biological DMARDs, mostly methotrexate (MTX) or leflunomide, as a first-line treatment (7,8). MTX is most commonly used as first-line treatment despite the fact that its potential efficacy is not supported by randomised, placebo-controlled studies (9). TNFi, which have demonstrated strong efficacy in multiple randomised, placebo-controlled studies in PsA (10-13), are merely recommended as second-line therapy for patients with PsA failing to respond to first-line therapy (7,8). More recently, other targeted therapies such as interleukine(IL)-12/ /IL-23 p40 inhibition, IL-17A inhibition and Janus kinase (JAK) inhibition have become available as second-line or third-line options (14-17).

A couple of studies have started to explore if early initiation TNFi favours remission in PsA. Baranauskaite *et al* investigated the use of early MTX with or without infliximab in an open-label study in patients with early PsA. They showed high response in both arms, with a significantly greater improvement in the MTX plus infliximab arm compared with the MTX alone arm (American College of Rheumatology response criteria (ACR20): 86.3% vs 66.7%). Larger differences were seen between the treatment arms with more stringent outcome measures such as ACR50, ACR70 and Minimal Disease Activity (MDA) (18). However, the important limitation of this study was the open-label design and these data have not yet been confirmed in a placebo-controlled setting in PsA. Exploring the same concept in a slightly different population, Carron *et al* investigated the early initiation of TNFi treatment in a placebo-controlled study in a mixed population of patients with early peripheral spondyloarthritis, of which 40% had concomitant nail or

skin psoriasis (19). Patients achieved clinical remission (defined as absence of arthritis, enthesitis and dactylitis) in 75% in the TNFi-treated arm versus 20% in the placebo arm.

Based on this circumstantial evidence that early treatment with TNFi could favour high remission rates in PsA, the current double-blind placebo-controlled randomised study was initiated to investigate whether the combination of golimumab plus MTX as a first-line treatment is superior in achieving remission compared with treatment with MTX alone in patients with PsA who are naïve to MTX and TNFi.

METHODS

Study design

This investigator-initiated, randomised, placebo-controlled, double-blind study was conducted at three centres in the Netherlands between September 2013 and September 2017. Patients were randomly assigned in a 1:1 ratio to receive either five injections with golimumab (50 mg subcutaneous monthly) or matched placebo. In both arms, MTX was started at 15 mg/week orally and increased to 25 mg/week over 8 weeks. Statistical minimisation was applied for centre, number of swollen joints and disease duration using a software program ALEA, a validated randomisation tool (NKI, Amsterdam, the Netherlands). The primary endpoint of the study was measured at the end of the 22-week blinded treatment period.

Patients

Patients aged 18–70 years were eligible if they had PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and current active disease, defined as the presence of at least three swollen and three tender joints at baseline (20). Patients previously treated with MTX or any biological DMARD were excluded. Allowed co-medication included NSAIDs and/or systemic steroids <10 mg/daily at stable dosages from 2 weeks prior to baseline. Local corticosteroids were not allowed within 4 weeks prior to baseline. Three patients used concomitant fumaric acid and one patient used concomitant sulphasalazine (Table 1). Key exclusion criteria were the presence of latent or active tuberculosis, malignancy in the past 5 years (other than basal cell carcinoma of the skin), recent severe infections or other severe diseases that may affect patient's participation to the study in the opinion of the investigator. The study was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.

Table 1. Baseline demographics and clinical characteristics of the study patients by treatment arm

	Golimumab + MTX (n=26)	**Placebo + MTX (n=25)**
Age, years	47.5 (11.8)	45.8 (11.0)
Gender (male:female)	18:8	20:5
Disease duration arthritis, years	0.5 (0.5-1.8)	0.5 (0.4-3.0)
Disease duration skin, years	6.0 (1-20)	11 (4-19)
Prior use of csDMARDs (leflunomide), n	1	0
Concomitant use of topical psoriasis treatment, n	6	13
Concomitant use of fumaric acid, n	1	2
Concomitant use of sulphasalazine, n	0	1
Concomitant use of NSAID, n	16	17
Concomitant use of corticosteroid, n	0	0
DAS-CRP	2.3 (1.0)	2.5 (0.9)
Swollen joint count, median (IQR)	7.0 (4.0-8.3)	5.0 (4.0-9.5)
Tender joint count, median (IQR)	9.5 (4.0-15.3)	10.0 (5.5-17.0)
PASI score, median (IQR)	1.6 (0.3-3.3)	2.3 (0.3-6.8)
PASI > 2.5, n	10	10
Enthesitis, n	4	7
Dactylitis, n	9	8
Inflammatory axial symptoms, n	4	2
ESR (mm/hr), median (IQR)	20.5 (6.5-33.3)	15.0 (5.0-29.0)
ESR > 20 mm/hr, n	13	14
CRP (mg/L)	4.5 (1.2-13.3)	7.0 (2.0-15.9)
CRP > 5 mg/L, n	14	9
Patient global VAS (mm)	44.7 (24.7)	39.3 (23.4)
Patient pain VAS (mm)	43.5 (24.2)	41.3 (28.4)
Physician VAS (mm)	44.5 (14.5)	47.0 (19.7)
Morning stiffness (minutes)	44.0 (32.5)	42.3 (33.3)
BASDAI	41.0 (18.6)	41.3 (23.3)

Values are presented as mean (SD) unless indicated otherwise
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PASI, psoriasis activity and severity index; VAS, visual analogue scale

Assessments

The primary efficacy endpoint of this study was the proportion of patients achieving a status of Disease Activity Score (DAS) remission at week 22, defined by a DAS C reactive protein (CRP) score <1.6 (0.54 × SQRT(Ritchie Articular Index) + 0.065 × swollen joint count (SJC) 44 + 0.17 × ln(CRP+1) + 0.0072 ×Visual Analogue Scale (VAS) global health + 0.45) (21). Secondary endpoints included additional response criteria such as MDA(22), DAS score low disease activity (LDA) (<2.4), DAPSA LDA and ACR20/50/70 responses. Disease activity measures included 66/68 swollen and tender joint count (SJC/TJC), dactylitis count, Leeds Enthesitis Index (LEI) including the plantar fascii (23), Psoriasis activity and severity index (PASI) and PASI75 (≥75% improvement in the PASI score) for subjects with baseline PASI ≥2.5, CRP, ESR and VAS physician. Patient-reported outcomes (PROs) were patient pain and patient global score on a VAS from 0 to 100 mm, morning stiffness duration, and Bath Ankylosing Spondylitis Index (BASDAI). Function and quality of life were assessed using the Short Form 36 (SF36), Health Assessment Questionnaire (HAQ) and Dermatology Life Quality Index (DLQI) scores. All efficacy endpoints were evaluated at week 22 as well as at week 8.

Safety endpoints included adverse events (AEs) and serious AEs (SAEs), and discontinuation or interruption of study treatments because of AEs. Routine laboratory investigations, vital signs and physical examination findings were recorded at screening and at every visit (baseline, weeks 4, 8, 14 and 22).

Statistical analyses

The sample size was calculated based on the results of the RESPOND study. This open-label study of Baranauskaite *et al* showed a DAS remission rate of 68.6% in the TNFi+MTX arm versus 29.2% in the MTX arm (18). Therefore, we estimated an expected 40% difference in response rate between both treatment arms. Considering a two-sided significance level of 0.05 and a power of 80%, the power analysis indicated 24 patients each arm.

Baseline characteristics and safety analyses included all randomised patients who received at least one dose of trial medication (51 patients). For efficacy analyses, one individual with wrong administration of golimumab versus placebo due to protocol violation was excluded from the MTX arm. Therefore, the intention-to-treat population for efficacy included 50 patients. Missing data were handled using non-responder imputation for the primary endpoint as well as all other binary endpoints and using last observation carried forward for continuous variables. Values are reported as mean (SD) or median (IQR) as applicable. At each time point, differences between placebo

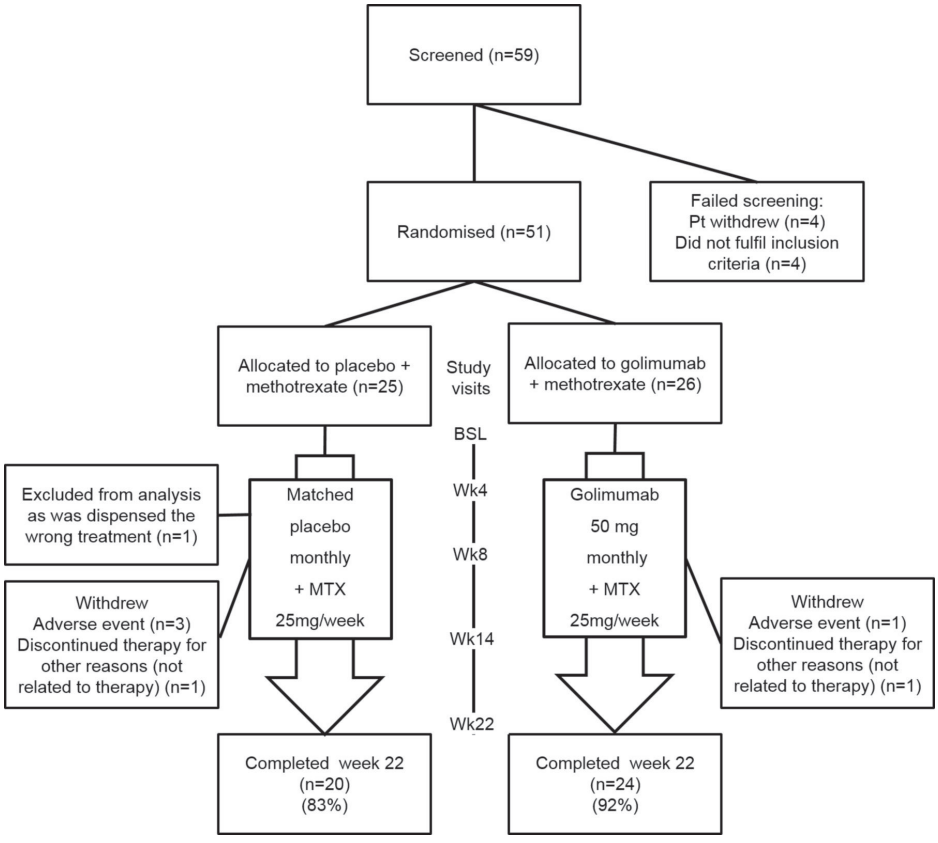
and golimumab were tested using a χ^2 test for the categorical variables, and an ANCOVA with the baseline variable as covariate for continuous variables. All statistical tests were two sided and p values of <0.05 were considered statistically significant.

RESULTS

Study population and patient disposition

A total of 59 patients were screened at three rheumatology clinics in The Netherlands between September 2013 and September 2017 (Figure 1). Fifty-one patients were randomised to receive either golimumab and MTX (n=26) (TNFi arm) or placebo and MTX (n=25) (MTX arm). The baseline characteristics were similar in the two treatment arms (Table 1).

Figure 1. Overview of patient disposition and study design. Patients were randomly assigned in a 1:1 ratio to receive either five injections with golimumab (50 mg SC montly) or matched placebo. In both arms, methotrexate (MTX) was started at 15 mg/week orally and increased to 25 mg/week over 8 weeks.



Median time since diagnosis was 0.5 (0.5–2) years, most patients (35/50) presented with a polyarticular disease pattern, and the median SJC and TJC were 5 (4–8) and 10 (5-15), respectively. Twenty patients had a PASI score ≥2.5 at baseline, and enthesitis was present in 11 patients and dactylitis in 17 patients.

Prior to unblinding, one patient from the MTX arm was excluded from all efficacy analyses due to an error at the pharmacy causing the wrong treatment to be administered. The efficacy analyses are therefore based on data of 50 patients: golimumab+MTX (n=26) and placebo+MTX (n=24).

During the 22-week period, in total six patients did not complete the study period as scheduled; reasons reported for drop out were adverse events: two patients (one in the TNFi arm and one in the MTX arm, both at week 14 of the study) and withdrawal of informed consent: four patients (one in the TNFi arm and three in the MTX arm).

All patients completing the 22-week study period received the full 5/5 of assigned study injections. The overall mean dosage of MTX during the full 22-week period was mean (SD) 19.2 (4.5) mg/week in the TNFi arm and 21.2 (2.4) mg/week in the MTX arm.

Efficacy

The study met the primary efficacy endpoint with DAS remission at week 22 achieved by a greater number of patients in the TNFi arm (21/26;81%) versus the MTX arm (10/24;42%) (p=0.004) (Figure 2). This difference in favour of the TNFi arm was confirmed by other composite response criteria at week 22 (Figure 2): patients in the TNFi arm reached an MDA in 21/26 (81%) versus 7/24 (29%) in the MTX arm (p<0.001). Although not reaching statistical significance, a similar trend was seen for DAS CRP LDA (85% vs 64%, p=0.072), and a DAPSA LDA was achieved in 92% versus 54% (p=0.001). An ACR 20/50/70 response was achieved by respectively 85%, 81% and 58% in the TNFi arm versus 58%, 33% and 13% in the MTX arm (p=0.039, p=0.001 and p=0.001, respectively). With exception of DAS CRP LDA, statistically significant differences were already seen by week 8 for all these response measures (Figure 2). Disease activity measures, PROs, and measures of physical function and quality of life are listed in Table 2.

Significant differences in response on PROs included VAS patient pain, VAS patient global, morning stiffness duration and BASDAI. This effect was already seen at week 8 for VAS global. No significant differences were seen in physical functioning and in health-related quality of life between both arms at week 22. No significant differences were seen in the achievement of PASI75 and DLQI scores.

Figure 2. Primary and secondary response measures; upper panel: percentage of patients in DAS CRP remission after 8 and 22 weeks in the golimumab+MTX and the placebo+MTX arm, respectively. Other panels: percentage of patients reaching DAS CRP LDA, MDA, DAPSA LDA and ACR20/50 and 70 responses.

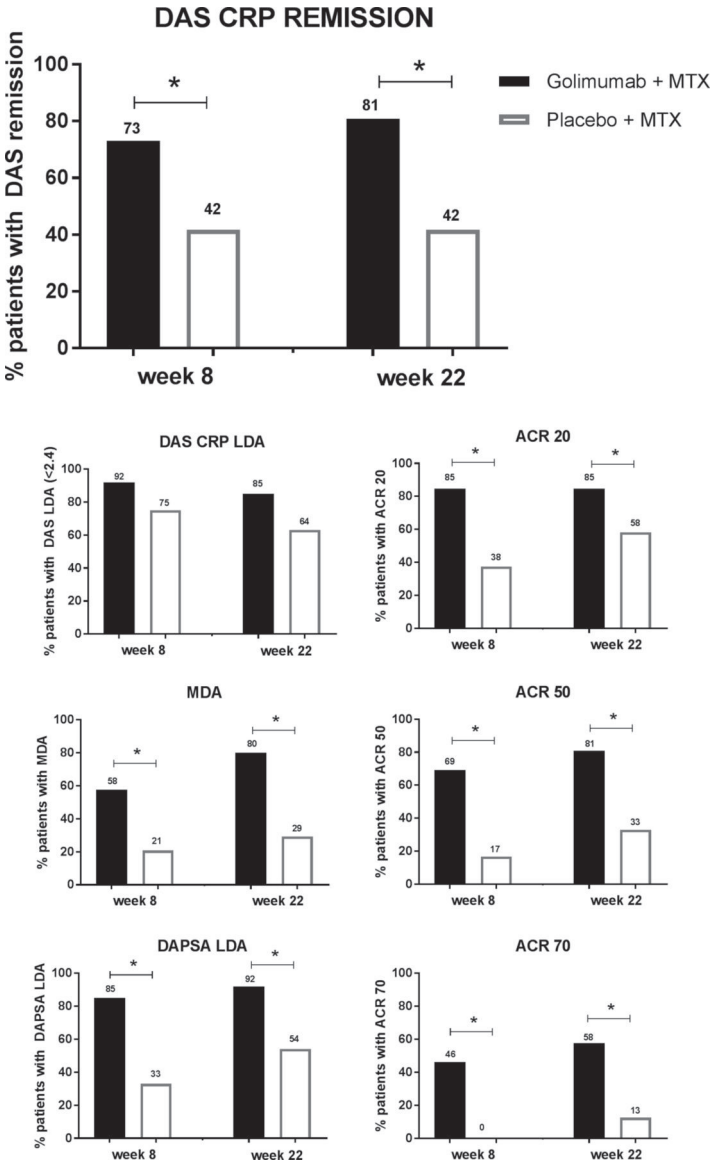


Table 2. Disease activity and patient-reported outcomes at baseline, week 8 and week 22

	Baseline		Week 8			Week 22		
Efficacy measures	**Golimumab + MTX**	**Placebo + MTX**	**Golimumab + MTX**	**Placebo + MTX**	**p value group difference**	**Golimumab + MTX**	**Placebo + MTX**	**p value group difference**
DAS CRP	2.1 (1.7-2.7)	2.4 (1.9-2.9)	1.1 (0.7-1.6)	1.8 (1.3-2.3)	0.002	0.9 (0.7-1.4)	1.8 (1.2-2.2)	<0.001
Swollen joint count	7 (4-8.3)	5 (4-10.3)	1 (0-3)	4 (1.5-8)	0.003	0 (0-1.3)	2 (0-4)	0.042
Tender joint count	9.5 (4-15.3)	10 (5.3-15.5)	1 (0-4)	5 (3-9.8)	0.019	0 (0-4)	3 (1-5)	0.019
PASI (in group with BSL PASI >2.5)	5.75 (4.0–7.55)	4.95 (3.50–8.45)	0.65 (0–3.05)	2.7 (0.75–4.25)	0.210	0.55 (0–1.90)	0.50 (0–1.95)	0.924
Patients with enthesitis, n	4	7	4	3	0.594	2	4	0.209
Patients with dactylitis, n	9	8	5	5	0.836	0	1	0.313
ESR (mm/hr)	20.5 (6.5-33.3)	15.5 (5.0-30.5)	2.0 (2.0-5.0)	8.0 (5.0-19.0)	0.003	2.0 (2.0-18.0)	8.0 (2.0-13.0)	0.566
CRP (mg/L)	4.5 (1.2-13.0)	7.1 (2.2-16.6)	0.8 (0.3-3.0)	2.9 (1.3-7.8)	0.079	1.1 (1.5-4.9)	3.6 (1.2-7.0)	0.144
VAS patient global (mm)	48 (26-59)	36 (25-54)	21 (6-36)	31 (16-46)	0.184	9 (4-32)	31 (14-57)	0.038
VAS patient pain (mm)	44 (29–64)	34 (17–7)	11 (3–24)	30 (16–38)	0.003	6 (2–18)	34 (6–58)	0.001
VAS physician (mm)	48 (37–53)	46 (37–64	10 (6–25)	33 (19–50)	<0.001	4 (1–20)	18 (9–33)	0.047
BASDAI	40.5 (29.9–56.3)	47.1 (19.1–56.9)	36.5 (16.3–59.6)	41.6 (22.5–61.0)	0.287	18.1 (4.9–23)	24.6 (11.7–49.5)	0.022

	Baseline		Week 8			Week 22		
Efficacy measures	**Golimumab + MTX**	**Placebo + MTX**	**Golimumab + MTX**	**Placebo + MTX**	**p value group difference**	**Golimumab + MTX**	**Placebo + MTX**	**p value group difference**
HAQ	0.38 (0.19–1.0)	0.63 (0.19–1.47)	0 (0–0.3)	0.43 (0.03–0.84)	0.003	0 (0–0.125)	0.25 (0–0.5)	0.403
SF36 PCS	41.1 (35.8–48.1)	43.6 (36.1–48.5)	47.0 (40.9–55.1)	48.8 (45.3–53.0)	0.056	50.1 (43.7–52.2)	50.7 (44.5–52.1)	0.543
SF36 MCS	47.9 (40.7–55.4)	51.6 (47.4–56.6)	51.7 (40.7–56.8)	50.3 (44.2–56.5)	0.041	50.7 (40.0–55.5)	50.9 (37.8–52.7)	0.125
DLQI	2 (0–7)	2 (0–5.8)	1 (0–3.5)	1 (0–5)	0.891	1 (0–3)	0 (0–3.5)	0.272

Values are presented as median (IQR) unless indicated otherwise

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PASI, psoriasis activity and severity index; VAS, visual analogue scale; SF36, Short form 36 Physical Component Score; SF36 MCS, Short form 36 Mental Component Score; DLQI, Dermatology Life Quality Index

Safety and adverse events

One serious adverse event (AE) occurred in a patient in the MTX arm (cervical spine stenosis, requiring surgery), which was considered not to be study related and did not result in early withdrawal. AEs occurring during the study period are described in Table 3.

The incidence of adverse events was similar between arms. In total, 43/50 patients experienced at least one AE during the trial period (range 1–7), all of which were graded mild to moderate. The most frequent AE involved nausea and occurred in similar incidences in both treatment arms and was considered likely to be treatment related. In 18 patients, an AE led to temporary halt and/or lowering of MTX dosage, and four AEs led to early withdrawal from the trial. No deaths occurred.

Table 3. Adverse event types and incidence up to 22 weeks

	Golimumab + MTX (n=26)	**Placebo + MTX (n=25)**
Patients with SAE (not study drug related), n	0	1
Patients with AE/event leading to lowering or quitting MTX, n		
Total	8	11
ALAT elevation	2	6
Nausea/vomiting	4	2
Infection	2	3
Patients with other treatment related AE, n	21	22
Liver toxicity	2	5
Upper airway infections	5	5
Other infections	3	8
Headaches	1	1
Malaise/tiredness around MTX intake	5	5
Nausea/vomiting	17	13
Other	8	8

SAE, serious adverse event; AE, adverse event; MTX, methotrexate

DISCUSSION

The major finding of this randomised, double-blind, placebo-controlled study was that the combination of golimumab plus MTX as a first-line treatment is superior to treatment with MTX alone in patients with early PsA who are naïve to MTX.

When interpreting the data of this study, two factors related to study design should be carefully considered. First, the study was specifically designed to compare the combination of a TNFi+MTX with MTX monotherapy and not to study the efficacy of MTX monotherapy itself. Monotherapy with MTX was chosen as the control arm for the sole reason that this is currently the most frequently used first-line therapy in PsA and is recommended by several guidelines (8,24). Therefore, MTX reflects the current standard of care despite the fact that previous trials of MTX in PsA failed to unequivocally establish its efficacy (9,18). As one of the potential reasons for the lack of efficacy in previous trials was the relatively low dosage of MTX (up to 15 mg/week), we used a more aggressive dosing scheme with a starting dose of 15 mg/kg and a rapid dose increase to 25 mg/week over 8 weeks, which resulted in a mean dose of around 20 mg/week over the 22-week study period. Whereas this was aimed to reflect the full potential of MTX in early PsA, the absence of a non-treated placebo arm and the powering (aimed for the golimumab+MTX vs. MTX alone) precludes meaningful conclusions on the potential efficacy of MTX as standalone treatment.

Also, we used golimumab as a prototype TNFi; although not formally demonstrated, there is no scientific or clinical evidence suggesting that the concept demonstrated here would not apply to all TNFi. Whether the concept also applies to other biologic targeted therapies used in PsA (anti-IL-17A, anti-p40, anti-p19) remains to be investigated.

Second, the population included in this trial of patients with early, MTX-naïve PsA differs considerably from previous pivotal large phase III randomised controlled trials. As expected, disease duration was much shorter (0.5 years in our study vs. 6–7 years in the large phase III studies) and, in line with the inclusion criterium of a minimum SJC/TJC of 3 at baseline, both SJC (median 5 vs 12) and TJC (10 vs 21) were lower in this trial in early, MTX-naïve disease(10,16,25). Whereas the population we included here is likely more representative of early untreated PsA, the differences in baseline features do not allow to compare the outcomes between this study and previous pivotal phase III trials.

Within this particular framework of the study design, the study met its primary endpoint by demonstrating that almost double the number of patients treated with

golimumab+MTX achieved DAS remission at week 22 versus MTX alone. Similar or even more pronounced differences were confirmed by other outcome measurements such as DAPSA LDA, MDA, ACR50 and ACR70, as well as by several PROs. Moreover, most of these differences were already observed at week 8. The early and consistent improvement in stringent response criteria in favour of the golimumab+MTX arm confirms and extends the results of the open-label RESPOND study (18) that early initiation of TNFi contributes to achieve low disease activity or even remission in PsA.

The DAS remission was chosen as the primary endpoint as this measures a 'depth of response' instead of a decrease of disease activity as measured by ACR response. We included several secondary endpoints, including the traditional response measures, showing similar results.

Our data raise a number of additional questions. First, clear effects were already seen at week 8, but most outcomes were even more pronounced at week 22. It remains unknown if the responses—in particular the stringent responses such as remission—have already plateaued at week 22 or could even further increase over time. Similarly, it remains to be determined if the combination of TNFi and MTX is only needed for the induction of remission or is also needed to maintain this state of remission over time. To this purpose, golimumab (or placebo) was stopped at week 22 in those patients achieving DAS CRP remission and an extension of the present study will explore if responses are maintained up to week 50 on MTX monotherapy.

Second, the improvement in outcome measurements was paralleled by significant improvement of single disease parameters such as SJC and TJC, but not enthesitis, dactylitis and PASI. This could of course be due to the fact that only a fraction of the patients included in this proof-of-concept study had these disease manifestations and, accordingly, that the study was underpowered to detect potential differences. Alternatively, MTX could be more effective for these disease manifestations than for pure articular disease, as suggested for skin by the proven efficacy of MTX in psoriasis (26).

Third, HAQ showed a significantly larger improvement in golimumab+MTX versus placebo+MTX at week 8 but that was not maintained at week 22, with a gradual improvement in HAQ also observed in the MTX alone arm. More intriguingly, there was no difference at all in SF36 and DLQI scores between both treatment arms. Obviously, the study was not powered to this purpose, but the total absence of numerical trends suggest that the improvements in disease outcome measures are not reflected in

function and QoL in this population with early disease. Further research is needed to fully explore this disconnect.

Fourth, in this study we did not include MRI or ultrasound to evaluate the presence or absence of active synovitis or enthesitis or their resolution over time. Arthritis and enthesitis was scored by joint and enthesitis counts. These types of assessments would have required a much larger study population. An interesting follow-up question would be if the observed clinical remission in peripheral PsA truly represents a resolution of inflammation without any signs of subclinical inflammation on imaging, and second, if the differences in achieved remission rates also protect from development of structural damage.

Finally, the potential benefit of early initiation of TNFi should be balanced against potential risks. In this study, treatment with either golimumab+MTX or placebo+MTX was well tolerated, only a small number of patients withdrew from the study due to AEs and no treatment-related severe AEs occurred during the study period. The AEs in this study were similar in both treatment arms and were consistent with previous studies with TNFi and MTX (mostly in longer standing disease)(10,13,27,28), without any novel safety signal. However, the study size and duration limits the interpretation of safety and tolerability.

In conclusion, initiation of combination therapy with golimumab+MTX in patients with early, MTX-naïve PsA doubled the number of patients achieving DAS remission when compared with placebo+MTX. This was confirmed by additional outcome measures, as well as by larger improvement in clinical disease activity measures and PROs but not function or QoL. Taken together with the good tolerability and absence of novel safety signals, these results—in line with the results of an open-label study in PsA(9) and a randomised controlled trial in pSpA(19)—suggest the value of early intervention in PsA rather than the classical step-up approach.

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6

SUSTAINED REMISSION WITH METHOTREXATE MONOTHERAPY AFTER 22 WEEKS INDUCTION TREATMENT WITH TNF-ALPHA INHIBITOR AND METHOTREXATE IN EARLY PSORIATIC ARTHRITIS: AN OPEN LABEL EXTENSION OF A RANDOMIZED PLACEBO-CONTROLLED TRIAL

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ABSTRACT

Background

If TNF inhibitors are initiated in the early stages of psoriatic arthritis, this could potentially modulate disease and therefore allow us to discontinue the TNF inhibitor after achieving remission.

Objective

To investigate whether remission induced by TNFi and methotrexate in patients with early psoriatic arthritis is sustained after withdrawal of TNFi.

Methods

Open-label extension of a recently published double-blind, randomised placebo-controlled trial. Patients with psoriatic arthritis fulfilling the CASPAR criteria and with active disease at baseline (swollen and tender joint count ≥3) were randomised to either golimumab and methotrexate or matched placebo and methotrexate. Patients in DAS remission at week 22 continued in the open-label extension on methotrexate monotherapy. The primary endpoint was the percentage of patients in DAS-CRP remission (DAS <1.6) at week 50.

Results

Eight patients from the original placebo group and 18 patients from the original TNFi group continued in the extension phase. At week 50, 6 out of 8 (75%) patients from the original MTX group versus 10 out of 18 (56%) patients from the original MTX+TNFi group were in DAS-CRP remission (p=0.347). Considering the total study population, 6 out of 24 (25%) of the original MTX group versus 10 out of 26 (38.5%) of the original MTX+TNFi group were in DAS remission at week 50 (p=0.308).

Conclusions

Remission achieved by initial combination treatment with TNFi and methotrexate in early psoriatic arthritis is maintained on MTX monotherapy in approximately half of the patients.

INTRODUCTION

Biologics have drastically changed the field of rheumatology. Whereas they have originally been used to treat patients who were refractory to classical Disease Modifying Anti Rheumatic Drugs (DMARDs) such as methotrexate (MTX), increasing evidence shows that their use in early disease allows to achieve high remission rates (1–4). Moreover, it has been postulated that if biologics are initiated in the early stages of disease, during the so called "window of opportunity" (5), this could promote an immune reset rather than merely suppression of inflammation, and thereby alter the course of the disease and allow for discontinuation of treatment in patients who achieve remission.

Most of the studies exploring these concepts have been conducted in rheumatoid arthritis. It remains unclear to what extent these concepts may also apply to psoriatic arthritis (PsA), a subgroup of spondyloarthritis that can present with skin and nail psoriasis, arthritis, enthesitis, dactylitis, and axial disease (6).

We recently demonstrated that initiation of TNF inhibition with golimumab in combination with MTX doubled the number of early PsA patients achieving DAS remission at week 22 in comparison with MTX monotherapy: from 42% with MTX alone to 81% with golimumab plus MTX combination therapy (4). To explore the hypothesis that remission induced by TNFi plus methotrexate in patients with early psoriatic arthritis can be sustained after withdrawal of TNFi, we conducted an open label extension study of this trial with patients that were in DAS-CRP remission at week 22 and continued on MTX monotherapy. Disease activity was assessed at week 36 and 50.

METHODS

Study design and patients

The original study design and baseline characteristics have been described in detail (4). In short, 51 patients with psoriatic arthritis (PsA), fulfilling the CASPAR criteria and with active disease (defined as swollen and tender joint count ≥3), were included. During the double-blind phase (up to week 22) all patients received methotrexate (MTX) up to 25mg/week and were randomised to either golimumab 50mg/month (n=26) or matched placebo (n=24). Patients with a status of DAS-CRP remission at week 22, defined by a DAS-CRP score <1.6, were offered to enter the open label extension phase up to week 50 on MTX monotherapy. A clinical assessment was done at week 36 and week 50, an additional visit was done in the case of worsening or recurrence of symptoms. Participants who had loss of remission were withdrawn from the trial. The group that

originally used MTX and placebo will further be referred to as 'original MTX group', the group that used methotrexate and golimumab will further be referred to as 'original MTX+TNFi group'.

This study was conducted at three centres in the Netherlands between September 2013 and September 2017, and was approved by the medical ethics committee of the Academic Medical Centre in Amsterdam. Written informed consent was obtained from each patient before enrolment. The study was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki and is registered at clinicaltrials.gov under NCT01871649.

Assessments

The primary efficacy end point of this study was the proportion of patients who sustained a status of DAS-CRP remission (7) (DAS-CRP score <1.6) at week 50. Secondary efficacy end points included Low Disease Activity (LDA) status (DAS-CRP <2.4), criteria for Minimal Disease Activity (MDA) (8), and Disease Activity in Psoriatic Arthritis Low Disease Activity (DAPSA-LDA) (9). Clinical evaluations, patient reported outcomes and standard laboratory tests were done at every study visit. Safety endpoints included adverse events (AEs) and serious AEs (SAEs), and discontinuation or interruption of study treatment.

Statistical analysis

Data are presented as mean (SD) unless indicated otherwise. Differences between both groups were analysed with a Chi-square test for categorical data and a Mann-Whitney U test for continuous data. The primary and secondary outcomes were analysed with an intention-to-treat analysis. Patients that discontinued for any reason during the extension study were considered non-responders, as were patients that were in remission at week 22 but did not attend a study visit during the extension study. All statistical tests were two sided and a p value of <0.05 was considered statistically significant.

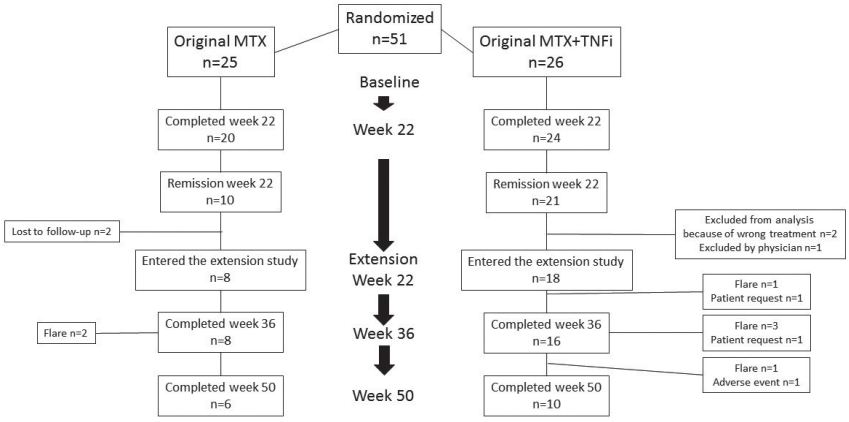
RESULTS

Study population and patient disposition

The patient disposition and flow chart is summarized in Figure 1. Ten patients from the original MTX group achieved remission in the first 22 weeks of the study. Of those, 2 were lost to follow-up. Therefore, 8 patients from the original MTX group entered the extension phase, of whom 6 completed week 50. For the original MTX+TNFi group, 21

patients achieved remission in the first 22 weeks of the study. Three were excluded before the start of the extension phase, therefore 18 patients entered the extension phase, of whom 10 completed week 50.

Figure 1. Patient disposition and flow chart



Baseline characteristics of the total study cohort have been described previously (4). Table 1 shows demographics, disease characteristics and disease activity measures of the 26 patients (18 on MTX + TNFi and 8 on MTX alone) continuing in the extension phase for baseline, week 22, 36 and 50 (data as observed). Demographics did not differ between both groups. At baseline VAS patient pain was lower in the original MTX group compared to the original MTX+TNFi group(p=0.011), as was the BASDAI (p=0.047). At week 22, PASI score was significantly higher in the original MTX group(p=0.001). At week 36 and 50 there were no differences between both groups. The overall mean(SD) dosage of methotrexate in the extension phase was comparable in both groups; 22.5(4.9)mg/week in the original MTX group and 20.9(6.2) mg/week in the original MTX+TNFi group (non-significant).

Safety

During the extension phase one serious adverse event (SAE) occurred in a patient from the original MTX+TNFi group: a small bowel obstruction with surgical intervention, which was judged unrelated to the study and did not lead to early termination. Eighteen AEs occurred during the extension phase; 9 in the original MTX+TNFi group and 9 in the original MTX group. One patient from the original MTX+TNFi group discontinued after week 40 because of an AE related to the study medication (liver enzymes >2 times the upper limit of normal).

Efficacy

Six out of 8 (75%) patients from the original MTX group completed the extension study and maintained DAS remission at week 50. Five out of 6 fulfilled criteria for MDA and all were in DAPSA-LDA. Two patients had a loss of DAS remission at week 36; 1 had a status of LDA according to the DAS, 1 was in DAPSA-LDA and none were in MDA.

Ten out of 18 patients (56%) from the original MTX+TNFi group completed the extension study and maintained DAS remission at week 50. Six out of 10 fulfilled criteria for MDA and 7 out of 10 were in DAPSA-LDA. Of the 8 patients dropping out of this arm of the study, 3 patients discontinued while still in DAS remission but were considered non-responders in the intention-to-treat analysis: 1 discontinued because of an AE (week 40) and 2 discontinued upon their own request (week 29 and 36)(Figure 1). Five patients had a loss of DAS remission (1 at week 29, 3 at week 36, and 1 at week 45); 4/5 patients had a status of LDA according to the DAS, 1/5 was in MDA and 3/5 in DAPSA-LDA.

In the intention-to-treat analysis, 6/8(75%) patients from the original MTX group versus 10/18(56%) patients from the original MTX+TNFi group were in DAS-CRP remission at week 50 (p=0.347). Considering not only the extension phase but the complete study from baseline to week 50, 6/24(25%) patients from the original MTX group had a status of DAS-CRP remission at week 50 compared to 10/26 (38%) patients from the original MTX+TNFi group (p=0.308).

Table 1. Demographics, characteristics and disease activity measures as observed of patients who entered the extension study

	Baseline			Week 22			Week 36			Week 50		
	Original MTX (n=8)	**Original MTX+TNFi (n=18)**	**p**	**Original MTX (n=8)**	**Original MTX+TNFi (n=18)**	**p**	**Original MTX (n=8)**	**Original MTX+TNFi (n=16)**	**p**	**Original MTX (n=6)**	**Original MTX+TNFi (n=10)**	**p**
Age	46(13.1)	48.7(10)	NS									
Gender (male/ female)	7/1	13/5	NS	7/1	13/5	NS	7/1	13/3	NS	5/1	9/1	NS
Disease duration <2 years, n(%)	5(62.5)	14(77.8)	NS	5(62.5)	14(77.8)	NS	5(62.5)	12(75)	NS	4(66.7)	6(60)	NS
SJC 66, median(IQR)	3.5(3-7.3)	7(4-8.3)	NS	0.5(0-2)	0(0-1)	NS	1(0.3-2)	0(0-1.3)	NS	0(0-1.3)	0(0-3.3)	NS
TJC 68, median(IQR)	5(4-13.8)	10(4.8-14.3)	NS	1(0.3-3.3)	0(0-3.3)	NS	1.5(0.3-2.8)	1.5(0-4.5)	NS	0(0-1.5)	1.5(0-4.3)	NS
PASI score, median(IQR)	2.7(0.5-6)	1.9(0.8-3.8)	NS	0.8(0.4-1.7)	0	0.001	0.5(0.5-1.8)	0	NS	1(0.3-1.9)	0.6(0-1.3)	NS
PASI >2.5, n(%)	4(50)	8(44.4)	NS	1(12.5)	0	NS	0	1(6.3)	NS	0	1(10)	NS
Pts with enthesitis, n(%)	0	2(11.1)	NS	1(12.5)	1(5.6)	NS	1(12.5)	3(18.9)	NS	0	1(10)	NS
Pts with dactylitis, n(%)	4(50)	4(22.2)	NS	1(12.5)	0	NS	4(50)	1(6.3)	NS	1(16.7)	1(10)	NS
ESR (mm/hr), median (IQR)	15.5(5.5-24.3)	20.5(4.3-31.8)	NS	7(3.5-15.8)	2(2-18)	NS	5.5(2-10.8)	5(2-6.5)	NS	5(2.5-11.5)	6(2-12)	NS
CRP (mg/L), median(IQR)	9.5(2.1-14)	4(1.3-14.5)	NS	3.1(0.9-15)	1.1(0.4-2.9)	NS	1.8(0.7-8)	1.5(0.4-4)	NS	4.2(0.9-7.4)	2(1-5)	NS

	Baseline			Week 22			Week 36			Week 50		
	Original MTX (n=8)	**Original MTX+TNFi (n=18)**	**p**	**Original MTX (n=8)**	**Original MTX+TNFi (n=18)**	**p**	**Original MTX (n=8)**	**Original MTX+TNFi (n=16)**	**p**	**Original MTX (n=6)**	**Original MTX+TNFi (n=10)**	**p**
VAS patient global (mm)	26.9(17.8)	46.3(24.9)	NS	23.4(25.9)	17.7(17.6)	NS	18.3(20.9)	24.1(23.8)	NS	17.4(15.2)	19.8(20)	NS
VAS patient pain (mm)	20(15.8)	47.7(26.1)	0.011	8.1(12.7)	13.6(17.5)	NS	9.4(8.7)	23(21.6)	NS	6.2(4)	21(27.1)	NS
VAS physician (mm)	43.1(14.0)	45.3(15.6)	NS	12.6(10.2)	8.1(9.3)	NS	8.9(8.1)	13.8(19.6)	NS	15.6(12.1)	13(17.5)	NS
BASDAI	2.4(1.8)	4.1(1.9)	0.047	1.5(1.6)	1.8(1.5)	NS	1.7(1.5)	2(1.7)	NS	1.8(1.7)	1.7(1.4)	NS

DISCUSSION

We recently reported that initiating combination therapy with MTX+TNFi resulted in doubling the rate of DAS-CRP remission at week 22 (81%) compared to MTX alone in patients (42%) with early psoriatic arthritis (PsA). We hypothesized that achieving remission in this 'window of opportunity' would allow to maintain clinical benefit in a substantial number of patients even after stopping the TNFi at week 22. Here we report that 56% of those patients indeed maintained remission up to week 50, whereas 75% of the patient achieving remission at week 22 on MTX monotherapy maintained remission over time. Taking into account the total study population, 38% of the original MTX+TNFi group versus 25% of the original MTX group achieved and maintained remission up to week 50.

A number of important aspects should be taken into consideration when interpreting the data of the present study. First, the number of patients included in the extension phase of the study was small, especially in the original MTX monotherapy group. Second, the study did not assess drug-free remission as all patients were on continuous MTX therapy from baseline to week 50 to reflect standard of care; the study was not designed to assess the real efficacy of MTX. Continuation of MTX in all patients also explains the high maintenance of remission in the original MTX group, as: there was no drug withdrawal in this group, only withdrawal of the placebo. Third, the patients and investigators remained blinded during the whole study (up to week 50) for the golimumab versus placebo treatment in the induction phase of the study, but were aware that this initial treatment was withdrawn at week 22. Fourth, we used the most conservative version of the data to do the analyses. Two patients from the original MTX+TNFi group who experienced a flare during the extension phase were actually still in DAS remission, but were nevertheless withdrawn from the study by the study physician because of arthritis in multiple joints not included in the DAS. Although still formally in DAS remission, these patients were considered as having a loss of remission in the analyses. Also patients dropping out for other reasons were considered as non-responders.

Despite these caveats, our findings are concordant with several other studies in PsA and other types of spondyloarthritis (10–12)). Huynh *et al* reported that 55.1% of patients with PsA who discontinued TNFi had persistent clinical benefit of TNFi therapy at the last clinical visit. In this study smoking and higher disease activity at the time of discontinuation were predictors of loss of clinical benefit, but disease duration did not affect the outcome (10).

The data of the current trial fail to support the hypothesis of immune reset by early TNFi treatment in PsA. In summary, our findings indicate that it is possible to maintain remission on MTX monotherapy in a substantial number of patients with early PsA achieving remission by initial combination treatment with TNFi and methotrexate. However, for how long this remission can be maintained, and whether the maintained remission in these patients is due to an immune reset or merely due to suppression of inflammation is not known. Moreover, a fair number of patients in the original MTX+TNFi lost remission after stopping TNFi, which shows that our treatment strategy did not provide the 'window of opportunity" to change the disease course in all patients. Whether even earlier initiated (combination) treatment, or other targeted treatment could provide a "window of opportunity" with sustained remission in all patients needs further assessment in future treatment strategy trials.

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7

AN ADD-ON TRAINING PROGRAM INVOLVING BREATHING EXERCISES, COLD EXPOSURE, AND MEDITATION ATTENUATES INFLAMMATION AND DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS – A PROOF OF CONCEPT TRIAL

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ABSTRACT

Objectives

The primary objective of this trial was to assess safety and anti-inflammatory effects of an add-on training program involving breathing exercises, cold exposure, and meditation in patients with axial spondyloarthritis

Methods

This study was an open-label, randomised, one-way crossover clinical proof-of-concept trial. Twenty-four patients with moderately active axial spondyloarthritis(ASDAS >2.1) and hs-CRP ≥5mg/L were included and randomised to an intervention (n=13) and control group (n=11) group that additionally received the intervention after the control period. The intervention period lasted for 8 weeks. The primary endpoint was safety, secondary endpoints were change in hs-CRP, serum calprotectin levels and ESR over the 8-week period. Exploratory endpoints included disease activity measured by ASDAS-CRP and BASDAI, quality of life (SF-36, EQ-5D, EQ-5D VAS), and hospital anxiety and depression (HADS).

Results

We found no significant differences in adverse events between groups, with one serious adverse event occurring 8 weeks after end of the intervention and judged 'unrelated'. During the 8-week intervention period, there was a significant decline of ESR from (median [interquartile range] to 16 [9-26.5] to 9 [5-23] mm/hr, p=0.040, whereas no effect was found in the control group (from 14 [8.3-27.3] to 16 [5-37] m/hr, p=0.406). ASDAS-CRP declined from 3.1 [2.5-3.6] to 2.3 [1.9-3.2] in the intervention group (p=0.044). A similar trend was observed for serum calprotectin (p=0.064 in the intervention group versus p=0.182 in the control group), but not for hs-CRP.

Conclusions

This proof-of-concept study in axial spondyloarthritis met its primary endpoint with no safety signals during the intervention. There was a significant decrease in ESR levels and ASDAS-CRP upon the add-on training program in the intervention group. These findings warrant full-scale randomised controlled trials of this novel therapeutic approach in patients with inflammatory conditions.

INTRODUCTION

Previous research in healthy individuals exposed to experimental endotoxemia showed that the innate immune response can be voluntarily modulated by a training program involving breathing exercises, exposure to cold and meditation (further referred to as: 'add-on training program').[1,2] Practicing the techniques learned in the add-on training program induced intermittent respiratory alkalosis and hypoxia, as well as profoundly increased plasma epinephrine levels, indicating activation of the sympathetic nervous system. These changes correlated with increased plasma levels of the anti-inflammatory cytokine IL-10 and attenuated levels of pro-inflammatory mediators such as TNF-α, IL-6, and IL-8 during experimental endotoxemia.[2]

The study of Kox et al[2] evaluated short term effects of this add-on training program in a controlled experimental model of acute inflammation in healthy individuals. It is unknown whether the same intervention could potentially lead to suppression of inflammation in patients with chronic inflammatory diseases. And, more importantly, it is not known whether this training program can safely be applied in patients with a chronic inflammatory disorder.

We designed a proof of concept (PoC) trial aimed to assess whether this well-defined add-on training program could modulate innate immune responses in a prototypical chronic inflammatory disease. We selected axial spondyloarthritis (axSpA)[3] as model disease since this chronic rheumatic inflammation of the spine a) involves altered innate immune responses,[4, 5] b) affects mainly young adults with few comorbidities and concomitant medication, allowing for an unbiased efficacy and safety assessment, and c) persists often for years as stable mild-to-moderate disease. Despite recent advances in therapeutic options for axSpA it is still not possible to sufficiently control disease activity in all patients, as only 60-70% of the patients respond to treatment, of whom 30% only partially. Remission is only achieved in 20% of the patients. This indicates a clear opportunity for additional treatment options, such as the add-on training program, to improve the outcome in these patients.

This study addresses the following primary research question: Can this add-on training program safely be applied in patients with active axial spondyloarthritis? C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and calprotectin levels are evaluated as secondary biological endpoints to investigate potential impact on inflammatory response. The exploratory outcomes are other inflammatory markers and the patient-reported outcomes ASDAS-CRP, Bath Ankylosing Spondylitis Disease Activity

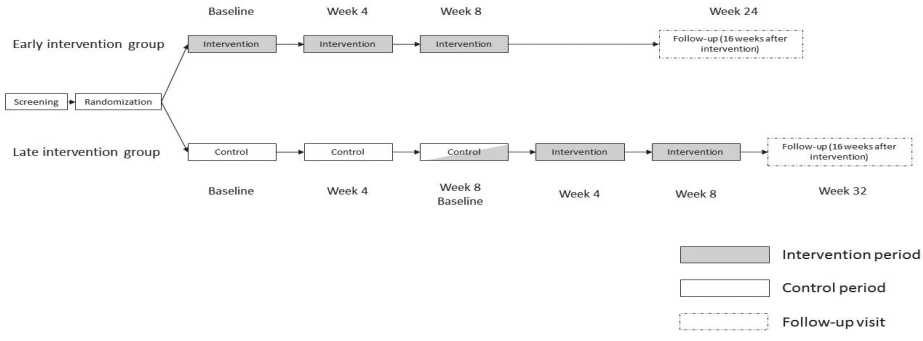
Index (BASDAI), quality of life measures (SF-36, EQ-5D, EQ-5D VAS), and hospital anxiety and depression (HADS). As this is the first study to investigate the safety and efficacy of this intervention in patients with a chronic inflammatory disease, we did not attempt to decipher the mechanism of action of the add-on training program.

METHODS

Study design

The study design used for this proof-of-concept trial was an open-label randomised one-way crossover design to rule out regression to the mean (Figure 1). This intervention is not suitable to compare to a genuine placebo effect. A concealed computer-based system randomised participants to an early intervention group or late intervention group in a 1:1 ratio. Stratification was performed for duration of disease and disease activity by ASDAS-CRP.

Figure 1. Study flow-chart



The early intervention group started with the intervention at baseline and continued with the intervention until week 8. Study visits in the intervention period were done at baseline, week 4 and week 8. Sixteen weeks after the intervention period, thus at week 24, a follow-up visit was done. The total study duration for the early intervention group was 24 weeks, in which 4 study visits were done.

The late intervention group started with the control period that lasted for 8 weeks. Study visits were performed at baseline, week 4 and week 8. After 8 weeks, the late intervention group started with the intervention and continued with the intervention

for 8 weeks. The week 8 visit of the control period also served as the baseline visit for the intervention period. Study visits in the intervention period for the late control group were done after 4 and 8 weeks of intervention (thus at week 12 and week 16). Sixteen weeks after the intervention period, thus at week 32, a follow-up visit was done. The total study duration for the late intervention group was 32 weeks, in which 6 study visits were done.

Data from the first 8 weeks of study participation of the late intervention group were used as control data. Data from both intervention periods (of the early and late intervention group) were combined in the analysis. In both groups, the 8-week intervention period was followed by a 16-week safety follow-up period. Patients were enrolled between May and December 2016. Participating centres were the Academic Medical Centre (AMC) and Bernhoven Hospital. All training sessions took place in the AMC.

Patients

Patients aged between 18 and 55 years were eligible if they had a clinical diagnosis of axSpA according to the treating physician, fulfilled the ASAS classification criteria[6] and had active disease defined as ASDAS>2.1[7] and a high-sensitive CRP (hs-CRP) ≥5mg/L. Patients were allowed to use concomitant non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (prednisone equivalent up to 10mg/day) and disease modifying anti-rheumatic drugs (DMARDs) (both synthetic and biologic) provided they have been initiated at least 8 weeks before screening (exception: two weeks for NSAIDs) and that the dose had been stable for at least 6 weeks prior to screening. Doses also had to remain stable throughout the study (from screening to end of intervention at week 8). Exclusion criteria were significant comorbidities that, in the opinion of the investigators, could interfere with the study or lead to deleterious effects for the patient, a recent history or persistence of an infection requiring hospitalization or antibiotic treatment within 4 weeks of baseline and pregnancy.

All participants gave written informed consent. Patients received a travel allowance that was dependent on the distance of the patients' residence to the training site, but no other reimbursement. This study was approved by the Medical Ethics Committee of the Academic Medical Centre in Amsterdam under reference number 2015_328.

Intervention

The intervention consisted of an 8-weeks add-on training program comprising three elements: 1) breathing exercises (further detailed below), 2) gradual cold exposure (immersions in ice cold water), and 3) meditation (third eye meditation).

The breathing techniques consisted of two exercises. First, patients were asked to hyperventilate for an average of 30 breaths. Subsequently, the patient exhaled and held their breath in an unforced manor for ~2-3 min until they felt a stimulus to inhale ("retention phase"). The duration of breath retention was entirely at the discretion of the patient himself. For safety reasons, it was instructed to not hold the breath longer than 3.5 minutes. Breath retention was followed by a deep inhalation breath, which was held for 10 s. Subsequently a new cycle of hyper/hypoventilation began. After the last cycle, patients were instructed to do a strenuous exercise such as push-ups. The induced state of intermittent respiratory alkalosis and hypoxia typically "empowers" the patient to outperform their standard capability in any physical exercise. The second breathing exercise consisted of deep inhalations and exhalations in which every inhalation and exhalation was followed by breath holding for 10 s, during which the patient tightened all his body muscles. An additional element this part of the training program consisted of strength exercises (e.g., push-ups and yoga balance techniques).

During the intervention period, patients voluntarily exposed themselves to cold in two ways. During weekly training sessions, the patients immersed whole-body in ice-cold water (0-1 °C) for several minutes, incrementally up to a maximum of 5 minutes (for safety reasons). At home, daily cold showers were taken incrementally up to 5 minutes (10-14 °C).

The so-called "third eye meditation," is a form of meditation including visualizations aimed at total relaxation. It consisted of an unguided meditation (in silence) with the eyes closed in any posture as desired by the patient for a period of 15-20 minutes. It was generally used at the end of each training session.

Consistent with the previous study,[2] patients were trained at the academic rehabilitation centre by a Dutch individual Wim Hof and four trainers who previously received an instructor course by Wim Hof to become a trainer. Medical personnel were present during all training sessions. During the first 4 weeks, participants had group trainings twice weekly, the second 4 weeks once weekly. During the intervention period, and after extensive written and oral instructions, participants practiced the exercises daily at home and registered their progression in a diary. In this diary the participants reported

per day a) their progression in breath retention at home and b) their mental and physical state. The adherence to the training program was discussed and assessed weekly by the trainers and during the study visits by the medical personnel.

Assessments

Primary safety assessments included vital signs, physical examination, electrocardiogram, haematology and chemistry at baseline, 4, 8, and 24 weeks and upon indication, and recording of adverse events (AEs) and serious adverse events (SAEs). The number and severity of adverse events was used to assess safety, other safety assessments, such as measuring blood pressure, heart rate, body temperature and physical exam, were done to detect potential adverse events that were not reported by the participants. Secondary endpoints were the change in serum hs-CRP (mg/L) levels between baseline and week 8 of the intervention/control period as a quick response measure, and erythrocyte sedimentation rate (ESR, mm/hr) and serum calprotectin levels[8] (measured by ELISA). Exploratory end-points were disease activity measured by ASDAS-CRP[6] and BASDAI[9], quality of life measured by the short-form 36 (SF-36)[10] and the EuroQol-5D (EQ-5D)[11] and depressive symptoms measured by the Hospital Anxiety Depression Score (HADS)[12]. All questionnaires were self-administered and used and scored according to the test manuals.

Statistical analysis

Because of the PoC design with safety as primary outcome, sample size could not be calculated and was estimated based on previous work[2]. All patients are included in the analysis of the primary outcome. For the primary outcome, safety, Mann-Whitney U tests were performed. For the secondary and exploratory outcome, a per protocol analysis was performed in which only patients that completed the intervention period were included. For the analyses of the intervention period, the intervention periods of the early and late intervention group were combined. The control group consisted of the first 8 weeks of the late intervention group. Secondary and exploratory outcomes were primarily assessed within groups over the 8-week intervention/control period using Wilcoxon signed rank tests comparing baseline and week 8. Because of the proof-of-concept nature of this trial, we did not adjust for multiple testing. A p value of <0.05 was considered statistically significant.

Patient and Public Involvement

This intervention has received extensive media attention in the past years, resulting in patients with various conditions practicing this intervention. However there was little known about safety and putative immunomodulatory effects. The importance of a

research project that would increase insight into these matters was highly appreciated by patients as mentioned in patient panels. To properly set the training program for patients with axSpA, 3 patient experts were consulted. As their strong preference was that all patients would receive the intervention, the study was designed as a one-way crossover open-label randomized (within-group) controlled trial. The results will be disseminated to study participants by personal communication and press release.

RESULTS

Study population

Thirty-one patients were screened and 24 patients were randomised to either the early (n=13) or late intervention (n=11) group (Figure 2). There were no statistical differences between both groups in demographics, baseline characteristics and concomitant medication (Table 1). Two patients in the early intervention group discontinued after 4 weeks of training: 1 because of an adverse event (AE) and 1 because of a change in medication for a persisting arthritis. In the control group, 3 patients discontinued after the control period (week 8). Two because of insufficient motivation for the intervention, 1 was lost to follow-up. In total 21 participants started with the intervention, of whom 19 completed the intervention period. All 11 patients in the late intervention group completed the control period.

Table 1. Demographics, characteristics and medication use at baseline

	Total study population (n=24)	**Early intervention group (n=13)**	**Late intervention group (n=11)**
Male sex, n(%)	15 (62.5)	8 (61.5)	7 (63.6)
Age, years	35.00 ± 7.31	35.46 ±8.29	34.45 ± 6.30
BMI, kg/m²	23.22 ± 6.39	24.46 ±3.22	21.44 ±9.25
HLA-B27 positive, n(%)[#]	16/21 (76.1)	11/12 (91.7)	5/9 (55.5)
Hs-CRP at baseline, mg/L, median (IQR)	8.3 (5.4-16.4)	7.9 (6.3-16)	8.7 (5.2-17.2)
ASDAS-CRP	3.02 ± 0.89	3.10 ±0.97	2.93 ± 0.81
Fulfill mNY, n(%)	16 (66.7)	9 (69.2)	7 (63.6)
IBP, n(%)	23 (95.8)	13 (100)	10 (90.9)
Psoriasis, n(%)	1 (4.2)	1 (7.7)	0 (0)
IBD, n(%)	2 (8.3)	1 (7.7)	1 (9.1)
Enthesitis, n(%)	5 (20.8)	4 (30.8)	1 (9.1)
Arthritis, n(%)	9 (37.5)	5 (38.5)	4 (36.4)

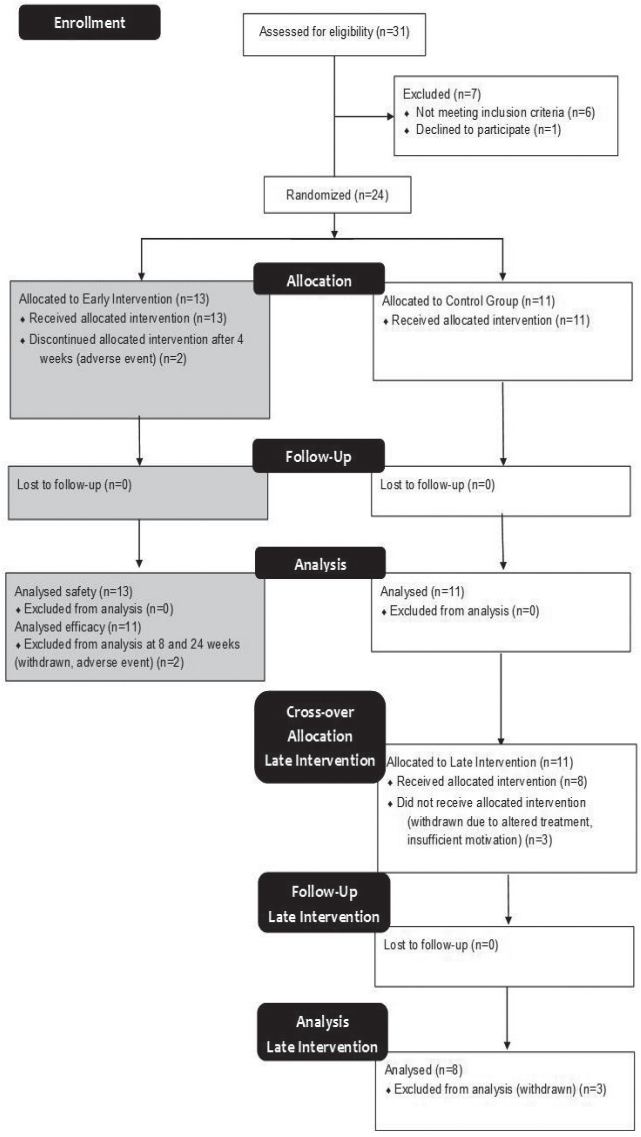
	Total study population (n=24)	**Early intervention group (n=13)**	**Late intervention group (n=11)**
Dactylitis, n(%)	1 (4.2)	1 (7.7)	0 (0)
Uveitis, n(%)	6 (25.0)	5 (38.5)	1 (9.1)
Family history positive for SpA, n(%)	8 (33.3)	6 (46.2)	2 (18.2)
Good response to NSAIDs, n(%)	22 (91.7)	11 (84.6)	11 (100)
Elevated hs-CRP, n(%)	24 (100)	13 (100)	11 (100)
NSAIDs, n(%)	22 (91.7)	11 (84.6)	11 (100)
Anti-TNFα, n(%)	3 (12.5)	2 (15.4)	1 (9.1)
Anti-IL17, n(%)	2 (8.3)	1 (7.7)	1 (9.1)
cDMARDs, n(%)	2 (8.3)	2 (15.4)	0 (0)
Corticosteroids, n(%)	1 (4.2)	1 (7.7)	0 (0)
General medication, n(%)	9 (37.5)	5 (38.5)	4 (36.4)

***** Except where indicated otherwise, values are mean ± SD

[#]HLA-B27 status is missing in 3 patients

IBP inflammatory back pain, IBD inflammatory bowel disease, mNY criteria modified New York criteria, cDMARDs conventional disease modifying anti-rheumatic drugs, NSAIDs non-steroidal anti-inflammatory drugs

Figure 2. Flow-chart and patient disposition



Safety

No serious adverse events occurred during the intervention period. During the intervention period, 10 participants in the intervention group reported a total of 12 AEs (2 participants reported 2 AEs), and 7 participants of the control group reported

a total of 9 AEs (2 participants reported 2 AEs)(p=0.268). The most common AE was common cold (4 vs. 2, respectively, Table 2). Three AEs during the intervention period had a moderate severity (1 in the intervention group and 2 in the control group). During the follow-up period (n=19), there was one SAE of a participant who experienced a hypertensive crisis 8 weeks after end of the intervention and was hospitalised for one night. Upon further examination by a ophthalmologist there were signs of longstanding disease, therefore this SAE was judged 'unrelated' to the study procedures and did not lead to discontinuation of the study.

Table 2. Adverse events during the intervention period, control period and follow-up period in absolute numbers and percentages

	Intervention period (n=24)	**Control period (n=11)**	**Follow-up period (n=19)**
Serious adverse event, n(%)	0	0	1(5.3)
≥1 adverse event, n(%)	12(57.1)	9(81.2)	7(36.8)
Anterior uveitis, n(%)	0	1(9.1)*	1(5.3)*
Headache, n(%)	1(4.8)*	0	0
Common cold, n(%)	4(19.0)	2(18.2)	3(15.8)
Other infectious diseases, n(%)	2(9.5)	2(18.2)	1(5.3)
Other adverse events, n(%)	5(23.8)	4(36.4)**	2(10.5)

*Adverse events with moderate severity
**One out of four had a moderate severity

Secondary endpoints

All secondary endpoints are listed in Table 3. In the intervention group, ESR significantly declined over time: from 16[9-26.5] mm/hr at baseline to 9[5-23] mm/hr at week 8, p=0.040, while it did not in the control group: from 14[8.3-27.3] mm/hr to 16[5-37] mm/hr, p=0.406). Hs-CRP did not significantly change within both groups during the 8-week intervention period (intervention group: from median [IQR] 10.2[6.5-17.1] mg/L to 6[3.9-15.6] mg/L, p=0.103, control group: from 8.7[5.2-17.2] mg/L to 13.2[7.9-20.1] mg/L, p=0.286). Calprotectin tended to decline in the intervention group (from 2295[1648-4923] pg/mL to 2165[953-3734] pg/mL, p=0.064), whereas it remained stable in the control group (2115[1300-2571] pg/mL to 2279[1770-4989 pg/mL], p=0.307)

Exploratory endpoints

All exploratory endpoints are listed in Table 3. There was a significant improvement in the median ASDAS-CRP during the 8-week period in the intervention group (p=0.044),

but not in the control group (p=0.213). Median BASDAI declined significantly in the intervention group (p=0.012) but not in the control group (p=0.755). The physical component score (PCS) of the SF-36 increased significantly during the intervention period (p=0.004) but not in the control group (p=0.859).The MCS of the SF-36 increased significantly in the intervention group (p=0.004) but not in the control group (p=0.859). The EQ-5D did not significantly change in the intervention group (p=0.102) nor in the control group (p=0.933).A similar effect was observed for the EQ-5D VAS (p=0.090 and p=0.674 in the intervention and control groups, respectively. There was no significant effect on the HADS anxiety and depression scales within groups.

The main burden of the intervention assessed by patients themselves was the commuting time to the academic center for group training and follow-up visits. The time spent on group and personal trainings were assessed as purposeful and the burden of cold exposure was transient. The participation during the training sessions was judged as high by the trainers. The adherence to the exercises at home was discussed in the group sessions and reviewed in the diaries, and was also judged as high.

Table 3. Analysis of inflammatory markers in peripheral blood, ASDAS, BASDAI, SF-36, EQ-5D, EQ-5D VAS and HADS during the 8-week intervention period.

	Intervention group			**Intra-group p value**	**Control group**			**Intra-group p value**
	Baseline (n=21)	**4w (n=21)**	**8w (n=19)**		**Baseline (n=11)**	**4w (n=11)**	**8w (n=11)**	
hs-CRP (mg/l)	10.2 (6.5-17.1)	8.9 (3.5-13.1)	6 (3.9-15.6)	.103	8.7 (5.2-17.2)	11 (8.4-20.2)	13.2 (7.9-20.1)	.286
ESR (mm/hr)	16 (9-26.5)	10 (6.5-31.5)	9 (5-23)	.040*	14 (8.3-27.3)	12 (8-34)	16 (5-37)	.406
Calprotectin (pg/ml)	2295 (1648-4923)	2245 (1273-3245)	2165 (953-3734)	.064	2115 (1300-2571)	2086 (1221-3527)	2279 (1770-4989)	.182
ASDAS-CRP	3.1 (2.5-3.6)	2.5 (1.9-3.2)	2.3 (1.7-3.2)	.044*	2.9 (2.3-3.6)	3.4 (3-3.6)	3.1 (2.7-3.6)	.213
BASDAI	4.5 (3-5.9)	3.3 (2.1-5.8)	2.6 (1.4-3.5)	.012*	3.2 (2.8-5.5)	5.5 (3-6.2)	4.3 (2.5-5.7)	.755

	Intervention group			Intra-group p value	Control group			Intra-group p value
	Baseline (n=21)	**4w (n=21)**	**8w (n=19)**		**Baseline (n=11)**	**4w (n=11)**	**8w (n=11)**	
SF-36 PCS	44.8 (36.0-48.8)	44.6 (39.9-47.4)	49.3 (40.7-54.7)	.004*	41.8 (34.1-49.1)	42.1 (35.9-46.1)	42.8 (33.5-48.0)	.859
SF-36 MCS	45.5 (39.9-53.5)	50.4 (44.3-54.6)	53.5 (46.8-56.7)	.004*	42.0 (38.1-50.4)	45.0 (37.2-53.9)	42.6 (40.0-52.5)	.859
EQ-5D	.81 (.65-.84)	.81 (.67-.92)	0.84 (.81-1.00)	.102	.81 (.69-.84)	.81 (.25-.81)	.81 (.65-.84)	.933
EQ-5D VAS	66.5 (59.3-74.0)	70.0 (55.5-76.0)	75.5 (70.0-87.0)	.090	67.5 (48.3-76.3)	60.0 (45.0-72.5)	66.5 (62.0-75.5)	.674
HADS-Anxiety	5.0 (2.5-7.5)	4.0 (2.5-6.0)	4.0 (.5-6.0)	.369	5.0 (3.0-7.0)	5.0 (4.0-6.0)	3.0 (1.0-5.0)	.138
HADS-Depression	3(1-6)	3(1-6)	2(1-6)	.508	3(2-6)	4(1-5)	1(1-4)	.137

Values are presented as median (interquartile range)
*: p<.05

DISCUSSION

In the present trial we show that the add-on training program involving breathing exercises, cold exposure, and meditation can safely be applied in patients with axial spondyloarthritis, a prototype chronic inflammatory disease.

We observed no differences in the number and severity of adverse events in the intervention group compared to the control group. There was a significant decrease in ESR levels over time in the intervention group but not in the control group. This is in line with previous work showing that the immune response can be modulated through the add-on training program in healthy participants during experimental endotoxemia[2]. The intervention also tended to result in decreased serum calprotectin levels, a validated disease activity biomarker in axSpA[8], although this did not reach a statistical significance. Various measures of disease activity (ASDAS-CRP, BASDAI) and quality of life (SF-36) improved following the intervention. The effects observed in

the intervention group are unlikely to be due to regression to the mean as there were no effects in the control group. Therefore, our results are indicative that voluntary modulation of the immune response may not only be possible in acute inflammatory response due to microbial stimulation but also in chronic inflammation related to immune-mediated inflammatory diseases.

This study has several limitations. 1) As this study was a proof-of-concept trial the sample size was small and not powered to investigate efficacy. However, despite this small sample size, significant changes in the secondary and exploratory outcomes were found. Larger follow-up studies are required to formally assess clinical efficacy.

2) The unblinded design of the study renders our results susceptible for a placebo effect. As the studied intervention is not suitable for a genuine placebo treatment, we chose hs-CRP, ESR and calprotectin as a secondary biologic endpoint that does not suffer from subjective influences or variability in the measurements. Furthermore, we used a delayed intervention group to assess the impact of regression to the mean. With this design we neutralized the aforementioned components of placebo effect. Moreover, the data obtained did not suggest an effect of regression to the mean since we observed changes in the intervention but not in the control group.

3) Our study design was not aimed at and therefore does not allow us to decipher the mechanism of action of this intervention. The mechanism of action behind the add-on training program remains to be unraveled. Kox et al clearly showed the biological impact of the training program on the innate immune response[2]. Firstly it is unknown whether it is necessary to practice all three components of the training program, or whether the observed effect in immune response is attained by one of the components. Secondly it is unknown what the minimally required intensity or duration of the training program should be to see similar results. Future research should address these questions.

4) The adherence to the training program at home was not formally checked, although discussed weekly during the group sessions and study visits. The adherence to the group sessions was high as on average the participants missed 1.5 out of 12 group sessions, due to holidays, other obligations or sickness.

5) Although not a major part of the add-on training program, the strength exercises (performed in conjunction with the breathing exercises) might play a role in the improvements we found in the participants, since exercise is a pivotal part of the treatment of axial spondyloarthritis.

In conclusion, the present study demonstrates that the add-on training program used in this study can safely be applied in patients with axial spondyloarthritis and potentially modulates inflammatory response. These findings warrant further clinical assessment of this novel therapeutic approach. Future research should include a larger sample size to formally evaluate clinical efficacy and should by focussed on further elucidation of the mechanism of action of the combined and/or individual components of the training program.

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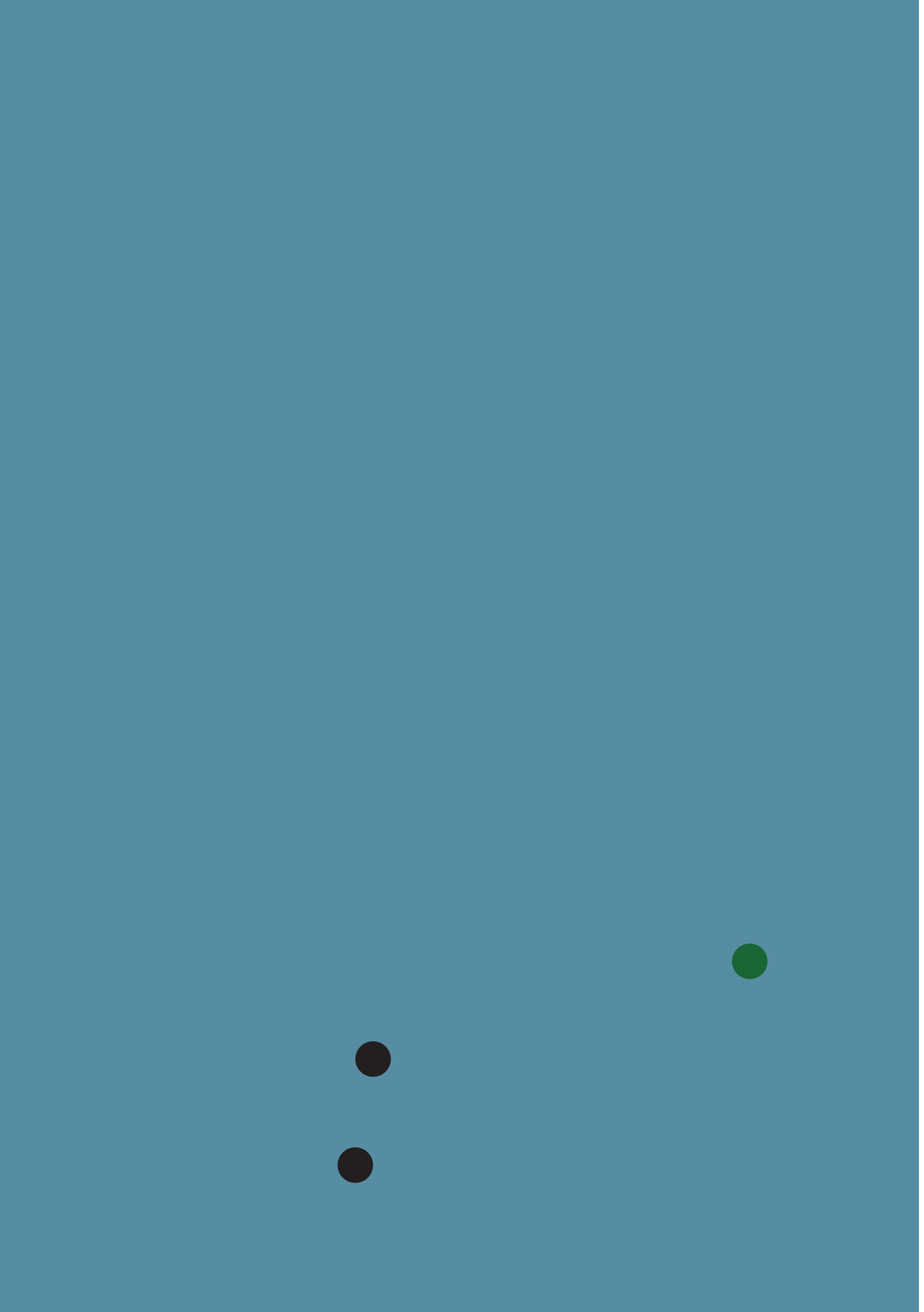
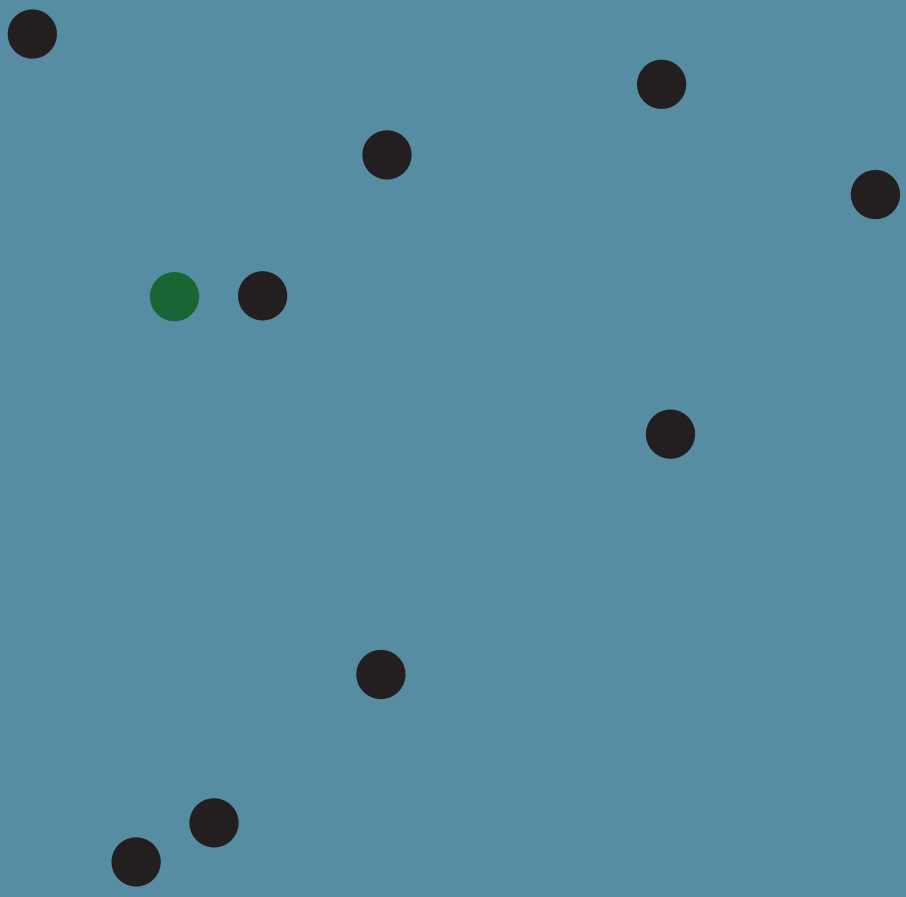


8

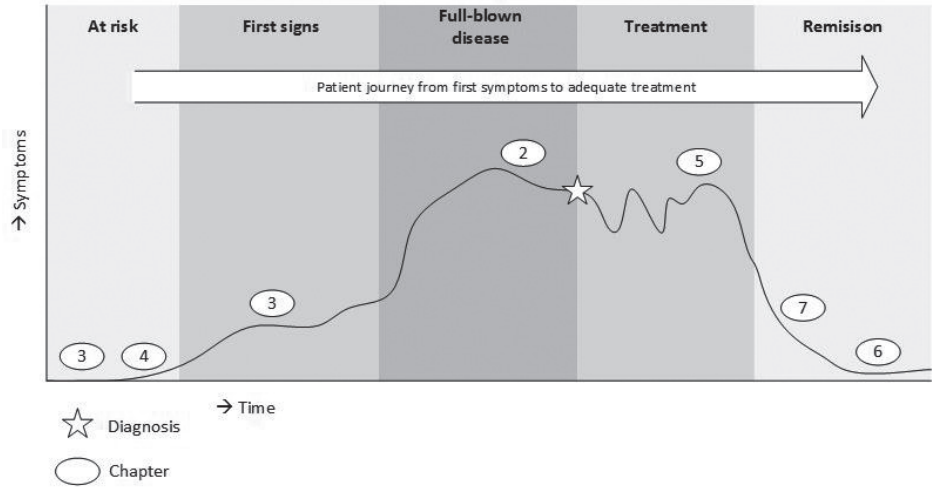
GENERAL DISCUSSION AND SUMMARY



GLOBAL AIM

The global aim of this thesis was to accelerate the patient journey from first symptoms to adequate treatment in spondyloarthritis (SpA) by a) tailoring the diagnostic process in order to enable an earlier diagnosis and b) tailoring the treatment strategy to shorten the time from diagnosis to remission and to increase remission rates in patients with SpA. To investigate which markers could aid in making an earlier diagnosis, we investigated which clinical features characterize females with SpA (**chapter 2**) and which clinical and imaging features are specifically present in individuals with an increased risk of developing SpA (**chapter 3**). Very early (pre-clinical) aggressive treatment as well as add-on treatment targeting low residual disease activity could induce remission in higher number of patients. To investigate tailored treatment strategies, we investigated the willingness of individuals at risk to develop SpA to use preventive treatment, if this would become available (**chapter 4**), if initial treatment with TNFα inhibitors induces higher remission rates in patients with early disease (**chapter 5**), if remission is sustained after discontinuing TNFα inhibitors which were started as initial treatment (**chapter 6**), and the safety and efficacy of an non-drug add-on treatment for patients with residual disease activity (**chapter 7**)(Figure 1).

Figure 1. The patient journey from first symptoms to adequate treatment



In this final chapter, we will summarize each chapter's main findings, discuss implications, and share our vision of challenges in the field for the coming years.

TAILORING THE DIAGNOSTIC PROCESS FOR SPA

Differences between females and males in disease presentation of SpA

Traditionally, ankylosing spondylitis (AS) was thought to be a predominantly male disease. Nowadays, the male:female ratio of axSpA is estimated to be 1:1 (1–3). However, females still experience a diagnostic delay of 6.5(5.6-7.4) years, while the diagnostic delay for males is significantly shorter(1). In **chapter 2,** we investigated the differences in disease characteristics between females and males in a real-life cohort of patients, in order to give a direction for a tailored diagnostic process for females. Our results show that females present with quite comparable disease characteristics except for having higher disease activity and less often radiographic sacroiliitis. This study was the first to compare differences between females and males in a real life cohort of patients, instead of patients fulfilling classification criteria for axial spondyloarthritis (axSpA), however our findings are concordant with previous studies that did use classification criteria as an entry criterion for the cohort (5–7). Our finding that females experience a higher disease activity is important, because it shows that the disease burden for females is at least equal to that of males. Besides the lower rates of sacroiliitis on X-ray, we did not find other differences in disease presentation that can explain the longer diagnostic delay for females. Therefore, other causes of this longer diagnostic delay should be investigated. A possible explanation is that physicians still believe that axSpA is a male disease and therefore are hesitant to diagnose females with axSpA. Another explanation could be that comorbidities, that are more prevalent in females, such as fibromyalgia, cloud the diagnosis of axSpA. Fibromyalgia and axSpA have an overlap in clinical symptoms and they can coexist (8–10). To exclude that the longer diagnostic delay for females is caused by physicians who are hesitant to diagnose axSpA in females, future research should investigate the believe of rheumatologists on this subject. Furthermore, it would be of interest to investigate the specific features that differ between females and males: why do females less often have sacroiliitis and structural damage compared to males? This could provide further insight into the pathophysiological mechanisms active in SpA and the differences between both sexes. A diagnostic delay as short as possible is important, since a delay in treatment has shown to negatively impact treatment outcomes (11), and a short time between onset of symptoms and diagnosis as well as male sex are important predictors of favorable clinical outcomes (12).

Earlier recognition of the disease facilitates early treatment, however we are still not able to induce remission in all patients, let alone to cure them. A possible explanation is that we are still not treating patients early enough, and that the disease has already fully developed with chronic inflammation and new bone formation. If we would be able

to identify individuals at high risk to develop SpA, before the onset of clinical disease, treatment in that stage could perhaps prevent SpA from developing. Early recognition and treatment of SpA is important to prevent structural damage from developing (13), and to improve treatment outcomes (11).

Exploring clinical features of preclinical SpA

The diagnosis of SpA is based on pattern recognition by the rheumatologist of a combination of clinical features and lab or imaging findings. Currently no clinical features or diagnostic (molecular or imaging) biomarkers are available that have sufficient sensitivity and specificity to make a certain diagnosis, or predict development of SpA (14). The Pre-SpA cohort is a cohort of first-degree relatives of HLA-B27 positive axSpA patients, aiming at identifying novel (bio)markers that can aid a very early diagnosis, or even identifying patients with preclinical disease. In the cohort, participants are followed for a period of 5 years, while clinical features and (bio)samples such as blood and radiological images are collected, and will be related to the development of clinically manifest disease over time. A previous report on the Pre-SpA cohort showed that up to 20% of the participants had imaging features highly suggestive of SpA, and that approximately one third of participants had clinical features related to SpA without having a clinical diagnosis (yet) (15). It is however not known if these features are stable over time and relate to development of clinically manifest disease. Moreover, recent studies have shown that MRI results should be interpreted with caution as it was shown that bone marrow edema of the sacroiliac joints according to the ASAS criteria can also be observed in individuals without a diagnosis of SpA (16). To validate our previous findings, and to further explore presence of imaging features related to SpA, we repeated the analyses of the previous report in **chapter 3** with thrice as many participants and included data of 1 year follow up. Also, we used a MRI scoring method which was recently suggested to be more specific for axSpA (16). Herein, we showed that at baseline 15% of the first degree relatives (FDRs) had MRI findings highly suggestive of SpA, with an equal distribution amongst HLA-B27 positive and negative FDRs. Up to 6% of FDRs developed symptoms and was clinically diagnosed with axSpA within the first year of follow-up.

An interesting finding in this report was that all but one of the FDRs that progressed towards clinical disease were HLA-B27 positive, while SpA features at baseline were equally distributed between HLA-B27 positive and negative FDRs. If we can confirm this finding in further follow-up, this would implicate that HLA-B27 is not responsible for initiation of subclinical inflammation but rather determines the progression of subclinical inflammation to clinically manifest disease in axSpA. This would be in line

with previous findings in reactive arthritis, which was shown to be self-limiting in HLA-B27 negative patients while patients who progressed towards chronic disease were mainly HLA-B27 positive (17), and animal studies where HLA-B27 transgenic rats after innate immune triggering with low dose heat inactivated Mycobacterium tuberculosis developed chronic disease that resembled human SpA whereas HLA-B7 transgenic rats did not (18).

Another finding that will hopefully be unravelled in further follow-up is whether we can extrapolate the incidence of 6% to the later years of follow-up, or whether there was a diagnostic bias and the incidence will be lower in the following years.

TAILORING THE TREATMENT OF SPA

Willingness of individuals at risk for SpA to use preventive medication

The focus of research on rheumatoid arthritis (RA), the most common form of inflammatory arthritis, has evolved from optimizing treatment strategies towards preventing disease, although so far no major breakthroughs were made (19,20). With the presence of specific autoantibodies, present before the onset of disease (IgM rheumatoid factor and anti-citrullinated peptide antibodies), and arthralgia without arthritis, it is possible to identify individuals at high risk to develop RA and include them in research. The Pre-SpA cohort has enabled us to also study individuals at high risk to develop SpA, before the onset of clinical symptoms. For SpA, in constrast to RA (21), it is not known if individuals at risk to develop axSpA would be willing to start preventive treatment. Therefore, in **chapter 4**, we explored the willingness of participants of the Pre-SpA cohort to use preventive medication. Preventive medication is not (yet) available, so the participants answered questions that referred to hypothetical scenarios. If the hypothetical risk of developing SpA was 70% without any side effects, then 92% would be willing to use preventive medication. This willingness dropped by almost 50% (to 52%) by the possible occurrence of side effects and to 27% if the risk of developing SpA was decreased to 30%. This is concordant with results of a study on preventive heart disease (22). As the participants in this study all have a first-degree relative with axSpA, as expected the willingness to use preventive medication increased with the participants' perception on the severity of axSpA and their own perception of the disease risk. The major influence of personal experience with a disease and the willingness to use preventive medication has also been shown in other diseases (23). This emphasizes the role of the physician in educating at risk individuals of the risks and disease burden of SpA. As participants answered questions to hypothetical scenario's our results give an idea on the range of the willingness, and which factors are important

to consider when developing and communicating on preventive treatment. Whether individuals at risk to develop SpA would also be willing to intervene in their lifestyle is currently being investigated in an additional study in the Pre-SpA cohort.

Early aggressive treatment with biologics in psoriatic arthritis

With the step-up approach for the treatment of SpA, highly effective treatment with biologics is currently reserved for patients with moderate to high disease activity who have failed treatment with conventional disease modifying anti-rheumatic drugs (cDMARDs). However, studies have shown that a delay in treatment can lead to significant damage and has worse clinical outcomes (11,12,24).

With the current treatment strategy not all patients achieve remission, which is why other treatment strategies should be investigated. To investigate whether early treatment with a TNF alpha inhibitor (TNFi) in combination with methotrexate is superior to methotrexate monotherapy in patients with early psoriatic arthritis, we conducted a randomized double-blind, placebo-controlled controlled trial which is described in **chapter 5**. Fifty-one patients were randomized in a 1:1 ratio to either treatment with a TNF alpha inhibitor and methotrexate or to treatment with placebo and methotrexate for the duration of 22 weeks. Patients who were treated with TNFi and methotrexate achieved a DAS remission up to a rate of 81% compared to 42% in the placebo combined with methotrexate treated patients. Improved outcomes for the initial TNFi treatment patients was confirmed by several other outcome measures. This study demonstrated that early treatment with a TNFα inhibitor and methotrexate is superior to methotrexate alone. These findings extend previous findings of the open label RESPOND trial in which 87% of patients who were treated with infliximab and methotrexate achieved an ACR20 response compared to 67% of patients receiving methotrexate alone (25), as well as other studies with similar results (26,27). There are some remarks to be made on this report. Firstly, the study design does not allow to investigate the efficacy of methotrexate. All patients used methotrexate continuously throughout the study as a standard of care. Secondly, the different outcome measures are still a subject of debate. Although we included several different outcome measures, we did not confirm remission by modalities such as MRI or ultrasound. Also, whether early treatment with biologics with another mechanism of action has the same effect as early treatment with TNFi needs further investigation.

Even the burden of early disease can be significant and thus have a significant impact on all aspects of quality of life, including work productivity and activity. Previous studies reported that treatment with TNFi treatment improved health economic parameters,

and work productivity and activity increased significantly (28,29). As SpA, and especially axSpA, affects young people, this is of major importance. The results of this study indicate that the sequence of different treatments for psoriatic arthritis should be reconsidered, or at least should not be as stringent as it is now.

Discontinuation of biologics after achieving remission with early aggressive treatment

Remission achieved by the use of highly effective treatment in early disease is part of the window of opportunity hypothesis. This hypothesis postulates that early treatment can modulate the disease, and therefore allow us to discontinue treatment while the patients retain their remission status. Safe discontinuation of TNFi therapy while sustaining remission is of major importance for several reasons. First, if medication could be discontinued safely after achieving remission for a significant period of time, this would decrease health care costs. Second, although so far TNFi have shown a reassuring safety profile on group level, decreasing immunosuppressants is expected to decrease the risk of potential side effects for the individual patients. Several studies have attempted to investigate the feasibility of discontinuing TNFα inhibitor after achieving remission, with varying success (30,31). Only one other study investigated the feasibility of discontinuing TNFα inhibitors in early peripheral SpA (26). To investigate whether early treatment with highly effective therapy such as TNF inhibitors actually results in an immune reset, in **chapter 6** we reported the results of the extension of the study in chapter 5. Patients who were in remission after 22 weeks of treatment with either TNFi and methotrexate or placebo and methotrexate continued in the extension phase, during which placebo and TNFi were withdrawn, but methotrexate was continued. Of the group originally treated with methotrexate and placebo (original MTX group), 8 patients continued in the extension phase. Of the group originally treated with TNFi and methotrexate (original MTX+TNFi group), 18 patients continued in the extension phase. At week 50, 75% of patients from the original MTX group versus 56% of patients from the original MTX+TNFi group were in DAS-CRP remission (p=0.347). Considering the total study population, 25% of the original MTX group versus 38.5% of the original MTX+TNFi group were in DAS remission at week 50 (p=0.308).

For the original MTX group, two things are important to realize. Only 10 patients who were initially treated with methotrexate and placebo achieved remission, and two of those were lost to follow-up after 22 weeks of treatment, therefore only 8 continued in the extension phase. This explains the small sample size of this group. Second, in contrast to the original TNFi+MTX group, no drugs were withdrawn in the methotrexate

and placebo group. Therefore we expected the remission rate in this group to remain stable during the extension phase.

In this study, we did not reinitiate TNFi treatment in patients who flared, however it is important to know whether patients who have a loss of remission after discontinuation of TNFi treatment can regain remission after reinitiation of TNFi treatment. We did not investigate this in the current trial, however, previous studies in psoriatic arthritis show that remission was restored after the reinitiation of TNFi treatment (30,32). In axSpA, studies investigating the reinitation of TNFi treatment after discontinuation show conflicting results: 57-100% of patients regain the clinical state they were in before discontinuation (33–35).

Our results indicate that it is possible to successfully discontinue TNFi treatment in about half of the patients, but further studies should investigate in which subsets of patients discontinuation is possible, to prevent unnecessary flares in patients in which discontinuation is not feasible.

Add-on treatment for patients with residual disease activity

Patients with axSpA show a growing interest in complementary and non-pharmaceutical medicine, before and even after a diagnosis is made (36). Although there is some skepticism among scientists on the basis and efficacy of these "alternative" therapies, non-pharmaceutical interventions could have a scientific basis and beneficial effect for patients (in which regular treatments (partly) fail). In **chapter 7**, we investigated the safety and efficacy of an add-on treatment with a combination of cold exposure, meditation and strenuous physical exercise. A previous report on this add-on training showed that, in healthy volunteers, voluntary activation of the sympathetic nervous system resulted in epinephrine release and subsequent suppression of the innate immune response after experimental endotoxemia (37). To investigate whether this add-on treatment can safely be applied on patients with axSpA and to explore whether it has a beneficial effect, we conducted a proof-of-concept study. The study design used was an open label, randomized, one-way crossover design, in which 24 patients participated. Herein, we showed that the erythrocyte sedimentation rate (ESR) and ASDAS-CRP significantly declined. A similar trend was seen for calprotectin. Although we found a decline in ESR and ASDAS-CRP, some considerations should be made. First, we did not have a blinded control group (how can one blind cold exposure?). Following the first point, and taking into account the group sessions in which patients exercised together and talked about experiences, we cannot exclude a placebo response. However, we did see a decline of ESR indicating that the measured effect is not solely

a placebo effect. Lastly, this training program consisted of three different components. We did not investigate whether any of these components alone have the same effect. In conclusion, the add-on training program used in this study can safely be applied in patients with axSpA and potentially modulates inflammatory response. Future research should include a larger sample size to formally evaluate clinical efficacy and should by focussed on further elucidation of the mechanism of action of the combined and/or individual components of the training program.

CONCLUDING REMARKS AND FUTURE DIRECTION

In the last couple of decades, major improvements have been made in the field of spondyloarthritis (SpA). Clearly defined referral strategies (38), the MRI as a diagnostic tool and the recognition of SpA in different subpopulations of patients have substantially helped in the improvement of the diagnostic process for patients with SpA. Also, the ASAS classification criteria have defined non-radiographic axSpA (39), which was not recognized as a disease entity before. Besides improvements in the diagnostic process, the development of biologics have made it possible to actually treat patients that failed treatment consisting of only NSAIDs and lifestyle advices. However, a significant diagnostic delay persists and the time from diagnosis to adequate treatment is consistently delayed by the use of a step-up approach for the treatment of SpA.

Accelerating the patient journey from first signs of SpA to a diagnosis

At this time, a one size fits all regime is being used for both the diagnostic process and the treatment of SpA. If a patient does not fit the full picture of SpA, chances are that the symptoms will be interpreted as signs of another disease, for example females that are diagnosed with fibromyalgia instead of SpA. Also, it can be challenging to distinguish symptoms of early axSpA from other explanations for the symptoms, because of the insidious onset of symptoms and other, more prevalent and therefore more logical explanations for the symptoms, such as mechanical back pain. Initiatives such as the Pre-SpA cohort, the DESIR (Devenir des spondyloarthritis indifférenciées récentes) cohort (40), the SPACE (SpondyloArthritis Caught Early) cohort (41) and GESPIC (German Spondyloarthritis Inception Cohort) (42) will hopefully add valuable information on the progress of early disease, prospectively as well as retrospectively.

One of the main challenges is the lack of a gold standard to diagnose SpA. As long as no (bio)marker, specific for SpA, that can significantly aid in making a diagnosis of SpA, has been found, other strategies should be used to make sure that no diagnoses will be missed and leave patients untreated. As the diagnosis is now based on the

clinical opinion of the rheumatologist, it could be helpful to refer patients with unclear disease to a specialized SpA center. By doing so, at least the diagnosis or lack thereof is based on disease recognition of a rheumatologist who is highly experienced with SpA. Furthermore, for patients who do not fit the complete picture but are significantly limited in their daily functioning, a biological could be used as a diagnostic tool. Although this option will not be possible in all countries because of the high costs of biologics, with the expired patents of biologicals the costs have significantly been reduced. This could be explored in trials investigating the efficacy of biologics in patients with significant disease burden but without the complete picture of SpA.

Accelerating the patient journey from diagnosis to adequate treatment

The currently used treatment strategy is a step-up approach that is used for all patients. Although some patients might benefit of treatment with NSAIDs or cDMARDs for a significant period of time, there are also patients for whom, soon after the initiation of treatment, it is clear that more effective treatment is needed to rapidly reduce symptoms and disease burden. In addition, in this thesis we have shown that early treatment with biologics is more effective than treatment with a cDMARD in patients with early disease; it induces a rapid reduction of disease activity and symptoms.

A more individualized treatment approach could be beneficial for many patients. Although research has shown repeatedly that a delay in treatment has negative effects on structural damage and treatment outcomes and early treatment with biologics is highly effective (25–27,35), with the current treatment strategy treatment with highly effective therapies is consistently delayed. One could argue that a step-down approach might be very beneficial for subsets of patients, especially those who present with high disease activity. If patients achieve remission or at least a state of low disease activity, the biologic therapy could be tapered or discontinued, and cDMARDs could be used to maintain the low disease activity state. Strategy trials investigating a step-down approach or individualized approach per patient would add valuable information for the feasibility of such an approach.

However, there are also many patients who experience residual disease activity despite adequate treatment. For example, the disease burden of patients with axSpA is highly influenced by the presence of peripheral disease such as dactylitis and enthesitis (43). With the increasing numbers of biologics with different mechanisms of action, strategy trials could be done to investigate the efficacy of switching biologics in patients with residual disease. This will help physicians to tailor the treatment of individual patients with residual disease activity. Also, patients who experience residual disease activity

despite adequate treatment could benefit from add-on therapies without extra pharmacological treatment. Exercising and moving already is a major recommendation for patients with SpA, and it is likely that other add-on treatments might be beneficial as well. To that purpose, research should look in to alternative treatments as well. Not to replace the standard of care, but to add to the standard of care. Highly popular training regimes or alternative treatments such as reported in this thesis should be investigated to at least make sure that they can safely be applied to patients with a chronic inflammatory disease. Hopefully some will prove to be truly effective as an add-on treatment for patients with residual disease, which will further add to the individualized treatment strategies.

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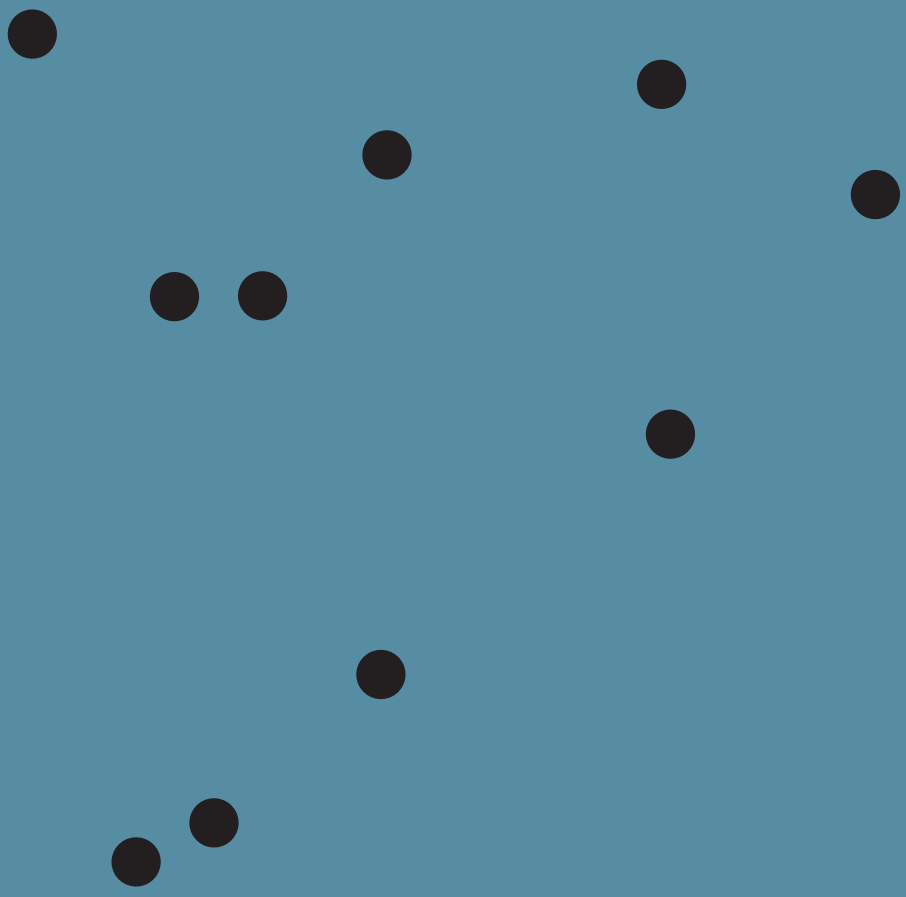
APPENDICES



NEDERLANDSE SAMENVATTING

Spondyloarthritis (SpA) is een van de meest voorkomende inflammatoire reumatische ziekten met een prevalentie van 0.2-1.6% (1). Op basis van het symptoom wat het meest op de voorgrond staat zijn er twee subgroepen SpA te onderscheiden: axiale spondyloartritis (axSpA) en perifere spondyloartritis (perSpA). De meest voorkomende en bekendste vorm van axSpA is de ziekte van Bechterew, de meest voorkomende vorm van perSpA is artritis psoriatica.

Het belangrijkste symptoom van axSpA is rugpijn. Deze rugpijn ontstaat meestal voor het 45ste levensjaar t en heeft vaak inflammatoire kenmerken. Inflammatoire rugpijn is door de Assessment of SpondyloArthritis Society werkgroep gedefinieerd als rugpijn met aanwezigheid van ten minste 4 van de 5 volgende kenmerken: ontstaan voor het 40ste levensjaar, sluipend begin, verbetering met bewegen, geen verbetering in rust en nachtelijke rugpijn welke verbetert bij bewegen(2). De belangrijkste symptomen van perSpA zijn artritis, dactylitis en/of enthesitis. Artritis is een ontsteking van een gewricht, dactylitis een ontsteking van een hele vinger of teen, en enthesitis een ontsteking van een peesaanhechting. Een belangrijk kenmerk van SpA is de vorming van nieuw bot, wat kan leiden tot vergroeiingen van de rug en/of perifere gewrichten(3,4). Inflammatoire rugpijn kan ook voorkomen bij perSpA, en artritis, dactylitis en enthesitis kunnen ook voorkomen bij axSpA. Naast deze symptomen kunnen er ook 'extra-articulaire manifestaties', dat wil zeggen manifestaties van ziekte buiten de gewrichten, voorkomen: psoriasis (een huidaandoening), uveitis anterior (oogontsteking van het vaatvlies van het oog) en ontstekingsziekten van de darmen zoals de ziekte van Crohn en colitis ulcerosa.

Beeldvormende technieken kunnen helpen bij het stellen van de diagnose SpA. Röntgenfoto's van de sacroiliacaal gewrichten, perifere gewrichten en de wervelkolom kunnen structurele schade als gevolg van ontsteking of vorming van nieuw bot laten zien. Op MRI kan ontsteking van de sacroiliacaal gewrichten of wervelkolom aangetoond worden. Echografie van de perifere gewrichten kan worden gebruikt om ontsteking van de gewrichten of de peesaanhechtingen in kaart te brengen.. Bij een gedeelte van de patiënten met SpA wordt er ook in het bloed verhoogde ontstekingswaarden, zoals het C-reactieve proteïne (CRP) of de bezinking (BSE) gezien. Daarnaast is HLA-B27 een gen wat een nauwe associatie heeft met SpA: in sommige onderzoeken is meer dan 90% van de axSpA patiënten HLA-B27 positief. Echter is in de algemene populatie 5-7% HLA-B27 positief; het is dus niet specifiek genoeg om een diagnose op te baseren.

Voordat de biologicals beschikbaar waren voor de behandeling van SpA waren de behandelopties erg beperkt. Sinds een paar decennia kunnen biologicals voorgeschreven worden aan patiënten met SpA met zeer goed effect. De huidige behandelstrategie bestaat uit een 'step-up approach': eerst worden patiënten behandeld met non-steroidal anti-inflammatory drugs (NSAIDs, ontstekingsremmers) en/of conventionele disease modifying antirheumatic drugs (cDMARDs) (methotrexaat, sulfasalazine of leflunomide). Bij onvoldoende effect van deze behandelingen kan er worden gestart met een biological. De eerst beschikbare biologicals voor de behandeling van SpA waren TNF-alfa remmers (TNFi), maar tegenwoordig zijn er ook andere biologicals met andere werkingsmechanismen beschikbaar. Dit is gunstig voor patiënten bij wie de behandeling met TNFi onvoldoende effectief is; de behandeling van deze patiënten kan worden verandert naar een biological met een ander werkingsmechanisme.

Doel van dit proefschrift

Het globale doel van dit proefschrift was om voor de patiënten met SpA de "reis" van eerste symptomen tot adequate behandeling te versnellen door a) het identificeren van mogelijke aanpassingen in het diagnostische proces zodat er sneller na het ontstaan van symptomen een diagnose gesteld kan worden, en b) de behandelstrategie voor patiënten met SpA aan te passen, zodat meer patiënten zo snel mogelijk in remissie komen.

HET DIAGNOSTISCHE PROCES

Verschillen tussen vrouwen en mannen in de ziektepresentatie van axSpA

Vroeger dacht men dat de ziekte de ziekte van Bechterew, de bekendste vorm van axSpA, een ziekte was die bijna uitsluitend bij mannen voorkwam. Tegenwoordig weten we dat de man:vrouw ratio van axSpA ongeveer 1:1 is(5–7). Desondanks duurt het voor vrouwen nog steeds gemiddeld 6.5(5.6-7.4) jaar voor ze een diagnose krijgen, terwijl deze duur tot diagnose voor mannen significant korter is (1).

In **hoofdstuk 2** hebben we de verschillen tussen vrouwen en mannen wat betreft ziekte karakteristieken onderzocht, zodat we een richting kunnen geven aan een aangepast diagnostisch proces voor vrouwen. Het resultaat van dit hoofdstuk laat zien dat axSpA zich presenteert met vrijwel dezelfde ziekte kenmerken bij vrouwen als bij mannen. Echter geven vrouwen een hogere ziekteactiviteit aan en hebben ze minder vaak sacroiliitis op röntgenfoto's van de sacroiliacaal gewrichten. Eerdere onderzoeken die het verschil in ziektepresentatie van SpA tussen vrouwen en mannen hebben onderzocht hebben hiervoor altijd een cohort gebruikt van patiënten die aan classificatie criteria moesten voldoen om deel te mogen nemen aan het cohort(9–11). Het onderzoek

beschreven in hoofdstuk 2 was het eerste onderzoek dat deze verschillen onderzocht in een cohort van patiënten die representatief zijn voor patiënten die behandeld worden in gespecialiseerde SpA poliklinieken.

Onze bevinding dat vrouwen een hogere ziekteactiviteit ervaren dan mannen is belangrijk omdat het laat zien dat de ziektelast voor vrouwen minstens gelijk is aan de ziektelast voor mannen. Naast het minder vaak voorkomen van sacroiliitis op röntgenfoto's van de sacroiliacaal gewrichten hebben we geen verschillen in ziektepresentatie gevonden die de langere duur tot diagnose voor vrouwen kunnen verklaren. Daarom zouden andere verklaringen voor dit verschil in duur tot diagnose onderzocht moeten worden. Een mogelijke verklaring kan zijn dat artsen nog steeds denken dat axSpA een ziekte is die met name bij mannen voorkomt, en dat ze daardoor terughoudend zijn om de diagnose bij vrouwen te stellen. Een andere verklaring zou kunnen zijn dat andere ziektes (zoals fibromyalgie) die meer voorkomen bij vrouwen, de diagnose SpA overschaduwen(12–14). Toekomstig onderzoek zou zich onder andere moeten richten op het onderzoeken van wat de gedachte is van artsen over de man/vrouw verhouding bij SpA, zodat aangetoond kan worden of terughoudendheid van artsen om axSpA te diagnosticeren bij vrouwen een oorzaak is van de langere duur tot diagnose. Daarnaast zou het interessant kunnen zijn om te onderzoeken waarom specifieke ziekte kenmerken verschillen tussen mannen en vrouwen, bijvoorbeeld: waarom hebben vrouwen minder vaak sacroiliitis en structurele schade dan mannen? Dit zou meer inzicht kunnen verschaffen in het pathofysiologische mechanisme van SpA en de verschillen tussen vrouwen en mannen met SpA.

Het is belangrijk om zo snel mogelijk na het ontstaan van symptomen een diagnose te stellen, omdat een vertraging in de diagnose een negatief effect heeft op behandeluitkomsten(15). Een korte tijd tussen eerste symptomen en diagnose is een belangrijke voorspeller van gunstige behandeluitkomsten(16). Vroege herkenning van de ziekte maakt een vroege behandeling mogelijk. Daarnaast zijn we nog steeds niet in staat om alle patiënten zo goed te behandelen dat ze allemaal geheel in remissie komen, laat staan om ze te genezen. Een mogelijke verklaring hiervoor is dat we patiënten niet vroeg genoeg in het ziekteproces behandelen, en dat de ziekte op het moment van behandeling al volledig ontwikkeld is met chronische ontsteking en vorming van nieuw bot tot gevolg. Als we mensen met een hoge kans op SpA zouden kunnen identificeren voordat de ziekte klinisch manifest is geworden, zouden we kunnen starten met behandelen in dit stadium voordat de eerste klinische kenmerken van ziekte aanwezig zijn. Dit stadium wordt ook wel het preklinische stadium of Pre-SpA genoemd. Mogelijk zouden we daarmee het beginnende ontstekingsproces kunnen remmen voordat de

ziekte volledig ontwikkeld is. Vroege herkenning en behandeling van SpA is belangrijk om structurele schade te voorkomen(17) en uitkomst na behandeling te verbeteren, zodat de kwaliteit van leven van patiënten met SpA beter wordt(15).

Het onderzoeken van preklinische kenmerken van vroege SpA

De diagnose SpA is gebaseerd op patroonherkenning door de behandelend reumatoloog. Er zijn momenteel geen klinische kenmerken of diagnostische (moleculair of op beeldvorming) biomarkers beschikbaar met voldoende sensitiviteit en specificiteit om een zekere diagnose te kunnen stellen, of om te kunnen voorspellen wie er SpA gaat ontwikkelen(18). Het Pre-SpA cohort is een cohort van eerstegraads familieleden van HLA-B27 positieve axSpA patiënten, gericht op het identificeren van nieuwe (bio) markers die kunnen helpen bij het stellen van een (hele) vroege diagnose, of zelfs om patiënten te kunnen identificeren met preklinische ziekte. Deelnemers van het Pre-SpA cohort worden voor een periode van 5 jaar gevolgd in de studie. Gedurende die 5 jaar worden klinische kenmerken die geassocieerd zijn met SpA en biosamples, zoals bloed en radiologische beelden verzameld. Deze zullen worden gerelateerd aan de ontwikkeling van klinisch manifeste ziekte gedurende de follow-up periode.

In een eerder artikel over het Pre-SpA cohort werd gerapporteerd dat bijna 20% van de deelnemers kenmerken van SpA had op beeldvorming, en dat ongeveer een derde van de deelnemers klinische kenmerken van SpA had zonder een diagnose van SpA (19). Het is nog niet bekend of deze kenmerken stabiel blijven en of ze gerelateerd zijn aan het ontstaan van klinisch manifeste ziekte. Daarnaast hebben recente onderzoeken laten zien dat resultaten van MRI met zorg geïnterpreteerd moeten worden; tekenen van ontsteking in de sacroiliacaal gewrichten, gescoord volgens de ASAS classificatie criteria, zijn ook frequent aanwezig bij mensen zonder SpA (20).

Om de eerdere bevindingen in het Pre-SpA cohort te valideren, en om de aanwezigheid van kenmerken van SpA op beeldvorming verder te onderzoeken, hebben we de analyses van het eerdere onderzoek herhaald in **hoofdstuk 3**, met drie keer zoveel deelnemers als in het eerste onderzoek. Ook hebben we data toegevoegd over de deelnemers na 1 jaar deelname in het Pre-SpA cohort. We hebben in dit artikel een andere scoringsmethode gebruikt voor het kwantificeren/evalueren van de ontsteking van de sacroiliacaal gewrichten op MRI dan in het eerste artikel, die meer specifiek zou zijn voor axSpA (20). De resultaten van dit hoofdstuk laten zien dat bij het begin van de studie ongeveer 15% van de deelnemers afwijkingen op MRI heeft die kunnen passen bij SpA, met een gelijke verdeling van deze afwijkingen tussen HLA-B27 positieve en negatieve eerstegraads familieleden. Bijna 6% van de deelnemers ontwikkelde

symptomen gedurende het eerste jaar van deelname aan het Pre-SpA cohort en werd gediagnosticeerd met SpA.

Een interessante bevinding van dit hoofdstuk was dat zes van de zeven deelnemers die SpA ontwikkelde binnen het eerste jaar van follow-up HLA-B27 positief waren, terwijl de kenmerken van SpA op baseline gelijk waren verdeeld tussen HLA-B27 positieve en negatieve deelnemers. Als we dit kunnen bevestigen bij verdere follow-up, dan zou dit impliceren dat HLA-B27 niet verantwoordelijk is voor de initiatie van subklinische inflammatie, maar vooral geassocieerd is met de progressie van subklinische ziekte naar klinisch manifeste ziekte. Eerdere onderzoeken bij een andere vorm van SpA, reactieve artritis, hadden vergelijkbare resultaten. Reactieve artritis bleek self-limiting te zijn bij HLA-B27 negatieve patiënten; alle patiënten die uiteindelijk chronische ziekte ontwikkelden waren HLA-B27 positief(21).

DE BEHANDELING VAN SPA

Bereidheid van mensen met een verhoogd risico op SpA om preventieve medicatie te gebruiken

De focus van het onderzoek naar reumatoïde artritis, de meest voorkomende vorm van inflammatoire reumatische ziekten, is verschoven van het optimaliseren van behandelstrategieën naar het voorkomen van ziekte. Bij reumatoïde artritis is het mogelijk om mensen met een verhoogd risico op SpA te identificeren met behulp van specifieke autoantilichamen (IgM reumafactor en anti-citrullinated peptide antilichamen) in combinatie met pijnlijke gewrichten. Hierdoor is het mogelijk om mensen met een verhoogd risico op reumatoïde artritis te onderzoeken voordat er klinische symptomen zijn. Het Pre-SpA cohort heeft ervoor gezorgd dat we nu ook in SpA mensen onderzoeken met een verhoogd risico op het ontwikkelen van ziekte. Voor reumatoïde artritis is al eerder onderzocht of mensen met een verhoogd risico op het ontwikkelen van ziekte bereid zouden zijn om preventieve medicatie te gebruiken(24). Voor SpA is dit niet bekend. Daarom hebben we in **hoofdstuk 4** onderzocht of deelnemers aan het Pre-SpA cohort bereid zouden zijn preventieve medicatie tegen SpA te gebruiken. Preventieve behandeling is vooralsnog niet beschikbaar, dus de deelnemers hebben vragen over hypothetische scenario's beantwoord. Als het hypothetische risico op het ontwikkelen van SpA 70% was, zonder bijwerkingen, zou 92% van de deelnemers bereid zijn om preventieve medicatie te gebruiken. Deze bereidheid om medicatie gebruiken daalde naar 52% als er mogelijk bijwerkingen zouden kunnen optreden, en naar 27% als de kans op ziekte werd verlaagd naar 30%. Deze resultaten zijn vergelijkbaar met onder andere onderzoeken naar de bereidheid van mensen om preventieve medicatie te gebruiken tegen cardiovasculaire ziekte(25).

Alle deelnemers aan het Pre-SpA cohort hebben eerstegraads familieleden met axSpA. Daarom was het te verwachten dat de bereidheid van de deelnemers om preventieve medicatie te gebruiken hoger werd naarmate de deelnemers de ernst van SpA hoger inschatten. Persoonlijke ervaring met een ziekte heeft een grote invloed op de bereidheid om preventieve medicatie gebruiken, zoals ook al eerder is aangetoond bij andere aandoeningen(26). Dit benadrukt de rol van de arts in het informeren van mensen met een verhoogd risico op ziekte op de risico's en ziektelast van SpA.

Omdat de deelnemers vragen hebben beantwoord over hypothetische scenario's hebben we nu een idee over de range van de bereidheid van de deelnemers, en welke factoren belangrijk zijn bij het ontwikkelen van en communiceren over preventieve medicatie. Of mensen met een verhoogd risico op SpA bereid zouden zijn om leefstijlinterventies te ondergaan wordt momenteel onderzocht in het Pre-SpA cohort.

Vroege, agressieve behandeling met biologicals bij artritis psoriatica

Met de huidige step-up benadering van de behandeling van SpA is behandeling met zeer effectieve medicijnen, zoals t biologicals, momenteel alleen beschikbaar voor patiënten met matig tot hoge ziekteactiviteit die niet goed genoeg hebben gereageerd op eerdere behandeling met csDMARDs. Onderzoeken hiernaar hebben laten zien dat een vertraging in behandeling kan leiden tot significante schade, en dat een vertraging in behandeling zorgt voor slechtere behandeluitkomsten (15,16,27).

Met de huidige behandelstrategie komen niet alle patiënten in remissie. Daarom moeten andere behandelstrategieën worden onderzocht. Om te onderzoeken of vroege behandeling met TNF alfa remmers (TNFi) in combinatie met methotrexaat beter is dan behandeling met methotrexaat alleen bij patiënten met vroege artritis psoriatica hebben we een gerandomiseerd, dubbel-blind, placebo gecontroleerd onderzoek uitgevoerd welke is beschreven in **hoofdstuk 5**. In totaal zijn 51 patiënten gerandomiseerd in 1) de groep die werd behandeld met TNFi en methotrexaat, of 2) de groep die behandeld werd met methotrexaat en placebo, voor een duur van 22 weken. Van de patiënten die met een combinatie van TNFi en methotrexaat werden behandeld kwam 81% in remissie op week 22, vergeleken met 42% in de placebo en methotrexaat groep. Deze uitkomst kon ook worden bevestigd met andere uitkomstmaten. Hiermee hebben we laten zien dat vroege behandeling met een TNFi en methotrexaat beter werkt dan methotrexaat alleen. Deze bevindingen bevestigen eerdere resultaten van het open label RESPOND onderzoek waarin 87% van de patiënten die werd behandeld met infliximab (een andere TNFi) en methotrexaat een ACR20 respons bereikte vergeleken met 67% van de patiënten die alleen met methotrexaat werd behandeld(28), alsook de resultaten van

andere studies (29,30). Er zijn een aantal belangrijke kanttekeningen bij dit onderzoek. Ten eerste is dit onderzoek is niet opgezet om de effectiviteit van methotrexaat te onderzoeken. Alle patiënten hebben gedurende het onderzoek methotrexaat gebruikt omdat dit momenteel over het algemeen ook op de poliklinieken zo wordt gedaan. Ook hebben we geen andere modaliteiten gebruikt om de remissie te bevestigen, zoals echografie of MRI. Als laatste kunnen we met dit onderzoek enkel uitspraken doen over TNFi, niet over biologicals met andere werkingsmechanismen.

Zelfs vroege SpA kan een significante ziektelast met zich meebrengen en een grote impact hebben op alle aspecten van kwaliteit van leven, zoals bijvoorbeeld ook werk productiviteit en activiteit (31,32). Omdat SpA, en dan voornamelijk axSpA, vaak op jonge leeftijd begint, is het dus belangrijk om te voorkomen dat de ziekteactiviteit hoog is of wordt. Het resultaat van dit onderzoek laat zien dat de volgorde van de verschillende behandelingen voor artritis psoriatica heroverwogen zou moeten worden, of in ieder geval niet zo strikt zou moeten zijn als nu het geval is.

Het staken van biologicals na het behalen van remissie van artritis psoriatica

Het bereiken van remissie door vroege behandeling met zeer effectieve medicijnen is onderdeel van de “window of opportunity” hypothese. Deze hypothese stelt dat behandeling in de vroege stadia van een ziekte de ziekte kan moduleren waardoor de chronische ontstekingsprocessen geheel gestopt worden. Hierdoor zou het mogelijk moeten zijn om de behandeling te staken als remissie van ziekte is bereikt. Staken van behandeling met biological zou de zorgkosten verlagen en de kans op (ernstige) bijwerkingen op de lange termijn verminderen, alhoewel biologicals een goed veiligheidsprofiel lijken te hebben. Verschillende onderzoekers hebben onderzocht of het mogelijk is om TNFi te staken na het bereiken van remissie bij patiënten met langer bestaande ziekte, met wisselend succes (33,34). Er is maar één onderzoek dat heeft gekeken naar het staken van TNFi in vroege perifere SpA(29). Om te onderzoeken of vroege behandeling met TNFi daadwerkelijk leidt tot immunomodulatie rapporteren we in **hoofdstuk 6** de resultaten van de extensie van het onderzoek genoemd in hoofdstuk 5. De patiënten die op week 22 (deel 1 van dit onderzoek, beschreven in hoofdstuk 5) in remissie waren gingen door in de extensie fase (deel 2 van dit onderzoek, beschreven in hoofdstuk 6), waarin placebo en TNFi werden gestaakt terwijl methotrexaat werd gecontinueerd. Van de oorspronkelijke groep die behandeld werd met TNFi en methotrexaat gingen er achttien door in de extensie, van de groep die behandeld werd met placebo en methotrexaat gingen er acht patiënten door in de extensie fase. Op week 50 was 75% van de patiënten uit de oorspronkelijke placebo groep vergeleken met 56% van de patiënten uit de TNFi en methotrexaat groep nog in DAS CRP remissie

(p=0.347). Als we kijken naar de hele studie populatie was 25% van de oorspronkelijke placebogroep versus 38.5% van de oorspronkelijke TNFi groep in remissie op week 50 (p=0.308)

Er zijn twee zaken belangrijk om te realiseren over de groep die in deel 1 van het onderzoek placebo en methotrexaat heeft gebruikt. Maar tien patiënten uit de oorspronkelijke groep waren in remissie op week 22,en twee daarvan zijn niet verder gegaan in de extensie fase. Daarom zijn er maar acht patiënten uit deze groep doorgegaan in de extensie van het onderzoek, wat het lage aantal patiënten in deze groep verklaart. Ten tweede zijn er in deze groep geen medicijnen gestaakt; alle patiënten in deze groep gebruikten immers al methotrexaat (en daarnaast placebo). Daarom is het huidige resultaat zoals we hadden verwacht: het grootste deel van de patiënten uit deze groep die zijn doorgegaan in de extensie fase zijn in remissie gebleven.

Als patiënten in dit onderzoek een opvlamming van de ziekte kregen werden ze uit de studie gehaald en verder behandeld op de poli. We hebben dus niet onderzocht of de ziekte opnieuw in remissie kan komen als de medicatie opnieuw wordt gestart na een opvlamming. Eerdere onderzoeken bij artritis psoriatica hebben laten zien dat dit wel het geval is: remissie wordt in een groot deel van de patiënten opnieuw bereikt na het herstarten van de biological(33,35). In het geval van axSpA laten onderzoeken wisselende resultaten hierover zien: 57-100% van de patiënten bereiken opnieuw de status waar ze in waren voor het staken van de medicatie(36–38).

Onze resultaten laten zien dat het mogelijk is om succesvol behandeling met TNFi te staken in ongeveer de helft van de patiënten. Verder onderzoek moet laten zien in welke subpopulaties van patiënten dit het geval is, om onnodige opvlammingen van ziekte te voorkomen bij patiënten waarbij het staken niet mogelijk is.

Extra behandeling voor patiënten met residuale ziekteactiviteit

Patiënten met axSpA laten een toenemende interesse zien in complementaire en niet-farmacologische behandelingen. Voor, maar ook nadat een diagnose van SpA is gesteld(39). Hoewel de medische wereld sceptisch tegen deze ‘alternatieve’ behandelingen aankijkt, zou het zo kunnen zijn dat sommigen van deze alternatieve behandelingen effectief zijn. Zeker bij patiënten waarbij de standaard behandelingen niet, of niet voldoende, werken. In **hoofdstuk 7** rapporteren we de resultaten van een onderzoek naar de veiligheid en effectiviteit van een ‘add-on’, dat wil zeggen extra, behandeling naast reguliere behandeling, bij patiënten met residuale ziekteactiviteit

ondanks behandeling. Deze extra behandeling bestond uit koude expositie, meditatie en fysieke inspanning. Een eerder onderzoek naar deze methode liet zien dat gezonde vrijwilligers in staat waren vrijwillig hun sympathische zenuwstelsel te activeren, wat resulteerde in de afgifte van adrenaline en daarmee onderdrukking van de aangeboren immuunreacties na experimentele endotoxemia (het inspuiten van eiwitten waardoor je ziek wordt)(40). Om te onderzoeken of deze extra behandeling veilig kan worden gedaan door patiënten met axSpA, en om te onderzoeken of het enig effect heeft op de ziekte, hebben we een proof-of-concept studie gedaan. In totaal hebben vierentwintig deelnemers meegedaan. Het resultaat van dit onderzoek laat zien dat deze methode veilig beoefend kan worden door patiënten met axSpA. Daarnaast daalden de bezinking en de ASDAS-CRP significant. Ondanks deze resultaten moeten we een paar zaken in overweging nemen. Ten eerste hebben we geen geblindeerde controlegroep gehad bij dit onderzoek (hoe kan je 'koude' blinderen?), dus kunnen we niet uitsluiten dat er sprake is van een placebo effect, hoewel de bezinking een objectieve maat is en de daling hiervan moeilijk te verklaren is door het placebo effect. Ook hebben we niet onderzocht of een van de componenten van deze methode alleen het gemeten effect kan veroorzaken, of dat de combinatie van alle drie de componenten echt nodig is.

De conclusie van dit hoofdstuk is dat deze methode veilig uitgevoerd kan worden door axSpA patiënten en mogelijk een modulerend effect heeft op het inflammatoire ziekteproces. Verder onderzoek naar deze methode zou grotere groepen patiënten moeten includeren om genoeg power te hebben om de effectiviteit te kunnen beoordelen, en zou zich meer moeten richten op het achterhalen van het werkingsmechanisme van deze methode.

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CURRICULUM VITAE

Henriëtte Miriam Ymke (Jet) de Jong werd geboren op 23 november 1990 in Utrecht. In 2008 deed zij eindexamen aan het Christelijk Gymnasium in Utrecht en is zij gestart met de bachelor Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. In 2009 is ze begonnen aan de studie Geneeskunde aan de Universiteit van Amsterdam. Tijdens de studie Geneeskunde was Jet lid van het skûtsjewedstrijdteam 'De Verwisseling' en is zij enkele jaren secretaris geweest van de bijbehorende vereniging. Tevens was zij penningmeester van het damesdispuut Fock van de studentenvereniging Orionis. Tussen de bachelor en master Geneeskunde heeft Jet in het OLVG gewerkt als medewerker bij de communicatieafdeling, waar zij de medisch specialisten in het OLVG interviewde voor de profielpagina's op website. In 2015 studeerde Jet af als basisarts en is ze begonnen aan haar promotietraject onder supervisie van prof. Dr. D.L.P. Baeten en dr. M.G.H. van de Sande met als focus verschillende aspecten van de diagnostiek en behandeling van spondyloartritis.

Momenteel is zij werkzaam bij de Nucleaire Geneeskunde in het Sint Antonius Ziekenhuis in Nieuwegein. Jet woont samen met Ewout en is moeder van Lotte (2017).

PORTFOLIO

PhD Portfolio

General courses	Year	Workload (ECTS)
Good Clinical Practice (GCP)	2015	0.1 ECTS
Basiscursus Regelgeving Klinisch Onderzoek (BROK)	2015	1.0 ECTS
Practical Biostatistics	2016	1.1 ECTS
Oral Presentation in English	2016	0.8 ECTS
Citation Analysis and Impact Factors	2016	0.1 ECTS
Searching for a Systematic Review	2016	0.1 ECTS
Clinical Epidemiology 4: Systematic Reviews	2017	0.7 ECTS
Advanced Biostatistics	2018	2.1 ECTS
Specific courses		
Advanced Immunology	2017	2.9 ECTS
Seminars, workshops and master classes		
Weekly department research seminars AMC	2015-2018	8 ECTS
Weekly department clinical education AMC	2015-2019	12 ECTS
Psoriatic Arthritis Masterclass Novartis	2015	0.5 ECTS
Presentations		
Annual European Congress of Rheumatology (EULAR), Madrid, Spain, poster tour presentation	2019	0.5 ECTS
Annual European Congress of Rheumatology (EULAR), Amsterdam, Netherlands, 2 poster presentations	2018	1.0 ECTS
(Inter)national conferences		
Annual European Congress of Rheumatology (EULAR), Madrid, Spain	2019	1.0 ECTS
International Congress on Spondyloarthritis, Ghent, Belgium	2018	1.0 ECTS
Annual European Congress of Rheumatology (EULAR), Amsterdam, Netherlands	2018	1.0 ECTS
Scientific meeting of the American College of Rheumatology, San Diego, USA	2017	1.0 ECTS
Other		
Student coaching	2016	1.0 ECTS

PUBLICATIONS

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