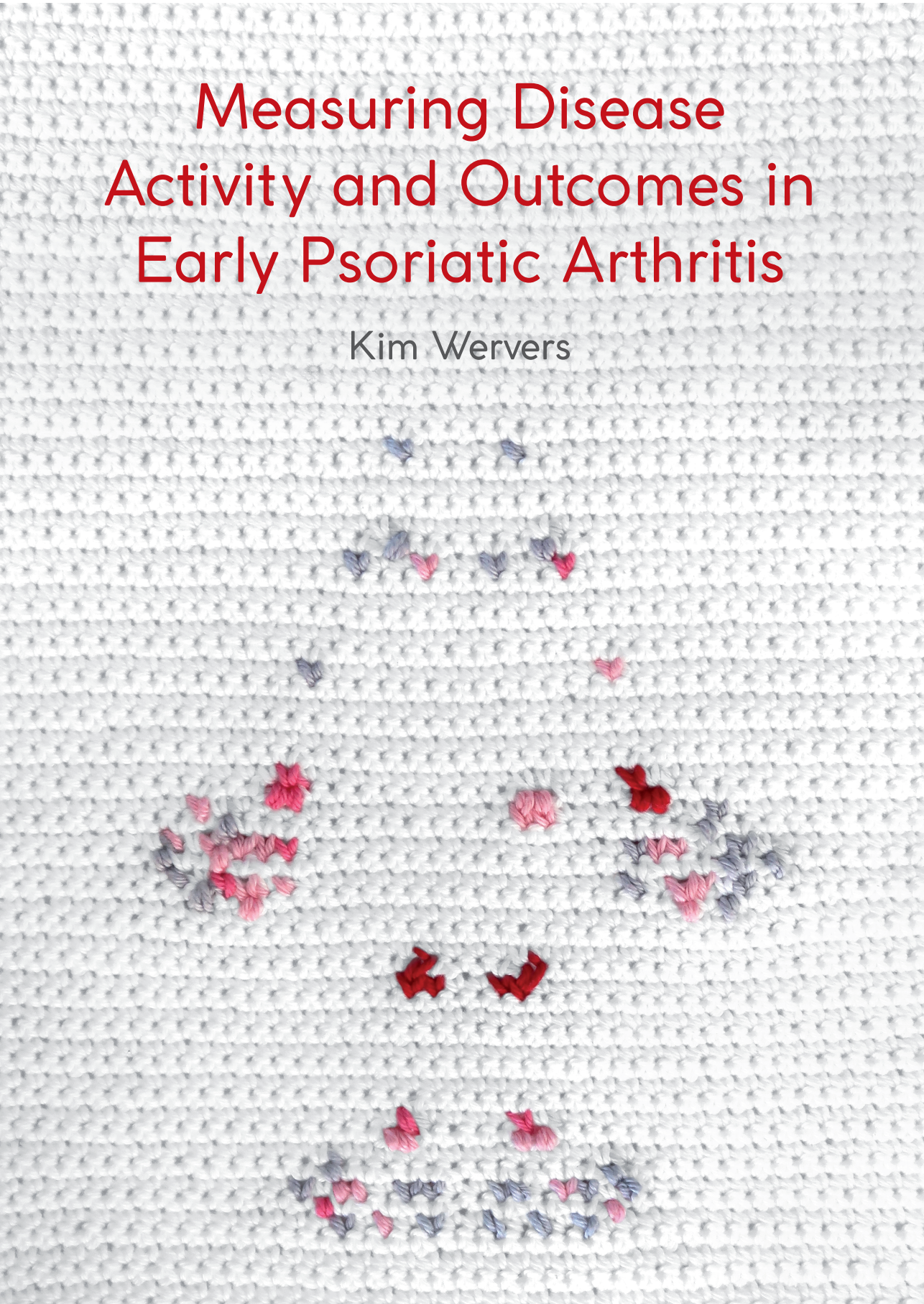
Measuring Disease Activity and Outcomes in Early Psoriatic Arthritis

Kim Wervers



Measuring Disease Activity and Outcomes in Early Psoriatic Arthritis

Het meten van ziekteactiviteit en uitkomsten in patiënten met vroege artritis psoriatica

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The cover represents the distribution of joint involvement of patients with oligoarticular psoriatic arthritis, with the swollen joints crocheted on the left side and the tender joints on the right side. Inspired by Figure 1 of Coates 2013 A&R 1504-9.

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CHAPTER 1

General Introduction

PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease with heterogenic manifestations (Figure 1). It presents with musculoskeletal manifestations of peripheral arthritis, dactylitis, enthesitis, and spondylitis. Peripheral arthritis can occur in any joint; the pattern of arthritis in PsA is often oligoarticular (i.e. four or less joints) and asymmetrical, and has more often a ray pattern (i.e. joints of a single digit involved) and involvement of distal interphalangeal (DIP) joints than is seen in other rheumatic diseases.[1, 2] Dactylitis is the inflammation of an entire digit, in which joints, tendons, and soft tissue are affected. This results in diffuse, painful swelling of a digit, and is therefore often referred to as sausage-toe or sausage-finger. Presence of dactylitis is very specific to PsA.[3] Enthesitis is inflammation of the insertion of a tendon, ligament or joint capsule. Patients often present with pain at insertion of the Achilles tendon or plantar fascia.[4] Patients with axial involvement have inflammation of the sacroiliac joints or the spine, either causing symptoms of chronic back pain or being asymptomatic.[5] The pattern of musculoskeletal manifestations differs greatly between patients and within patients over time.

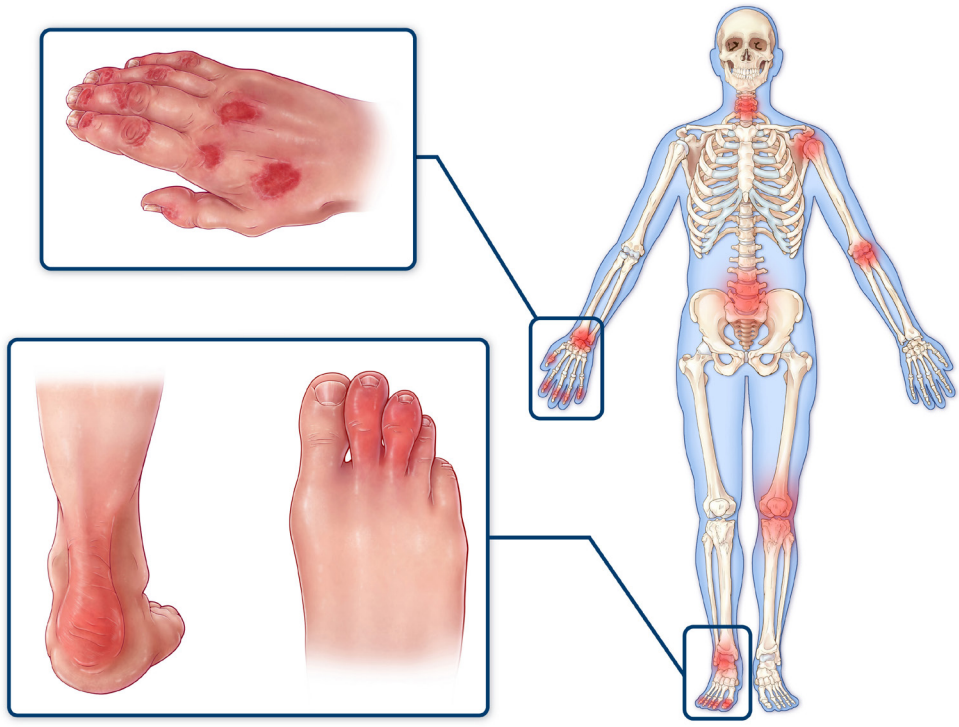

Figure 1. Manifestations of psoriatic arthritis

Besides musculoskeletal manifestations, most patients with PsA also suffer from psoriasis. Patients have erythematous, scaling plaques that can be itchy or painful.[6] These plaques are caused by hyperproliferation of keratinocytes, due to chronic inflammation of the skin. Chronic inflammation can also occur in the nails, leading to pitting, onycholysis, subungual hyperkeratosis and an oil-drop sign.[7] Most often psoriasis is diagnosed before or at time of diagnosis of PsA, but in 15% of cases psoriasis is not present at time of diagnosis.[8] Of the patients with psoriasis, an estimated 6-42% of patients will eventually developing PsA,[1] at a rate of 3% per year after diagnosis of psoriasis.[9] In the general population, the prevalence of PsA is estimated to be 0.19% in Europe and 0.13% in North America, but a lot lower in Asia (0.05-0.07%) and South America (0.07%).[10] Both men and women are equally affected by PsA and patients are often diagnosed between the ages of 30 and 50 years.[1]

DIAGNOSIS OF PSA

PsA is diagnosed by a rheumatologist, based on clinical assessment of PsA manifestations as described above, laboratory tests, and imaging. Elevation of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) is seen in about half of the patients.[11] With respect to serology, patients are usually negative for rheumatoid factor[3, 12] and antibodies to cyclic citrullinated peptides (anti-CCP).[13] No biomarkers specific to PsA are available. Radiographic signs of erosive disease of DIP joints, ankylosis (i.e. fusion of bones), new bone formation, resorption of distal phalanges, and 'pencil in cup' deformities are suggestive of PsA.[14] The diagnosis of PsA varies between rheumatologists,[15] which complicates comparing results of different study populations.

To ensure study populations are comparable, classification criteria have been developed in PsA (CASPAR: ClASsification criteria for Psoriatic ARthritis).[3] To meet these criteria, a patient must have inflammatory articular disease (joint, spine or entheseal) and in addition 3 out of the following 5 points: current psoriasis (2 points) or personal or family history of psoriasis (1 point), nail psoriasis, absence of rheumatoid factor, dactylitis either current or a history recorded by a rheumatologist, or radiographic evidence of juxtaarticular new bone formation. These criteria had a specificity of 98.7% and a sensitivity of 91.4% to diagnose PsA, where a clinical diagnosis was the gold standard. Patients can be classified as having one of five clinical patterns of PsA: distal arthritis (i.e. DIP arthritis of hand and feet), oligoarthritis, polyarthritis, arthritis mutilans (i.e. a destructive form of arthritis) and spondyloarthritis.[16] The most common clinical patterns have been reported to be oligoarthritis and polyarthritis,[17] but the clinical pattern of a patient can vary over time.[1]

DIAGNOSIS OF ENTHESITIS

Patients report pain or tenderness at insertion sites, but agreement on how to diagnose enthesitis in clinical practice is lacking. In clinical trials, a commonly accepted definition of enthesitis is entheseal tenderness at clinical examination using a scoring system, such as the Leeds Enthesitis Index (LEI).[18] Pain at the site of the enthesis is however a sign of enthesiopathy, which could have degenerative, metabolic, and mechanical causes besides enthesitis.[19] Tendon complaints are quite common in the healthy population,[20, 21] which complicates the diagnosis of PsA-related enthesitis.

Distinguishing inflammatory enthesitis from non-inflammatory enthesiopathy might be done using imaging. Entheses are located superficially and can therefore easily be scanned with ultrasound, which has the advantage that multiple sites can be scanned. Ultrasound abnormalities suggestive of enthesitis are increased thickness, calcifications, enthesophytes, structural changes (hypoechogenicity), erosions and sonographic signs of bursitis.[22] Further, increased vascularisation can be assessed using the power Doppler (PD) mode of ultrasound. Increased thickness, sonographic signs of bursitis and a PD signal are often considered inflammatory changes, while calcifications, enthesophytes, structural changes and erosions are considered structural changes.[23] These abnormalities can be scored in an enthesitis ultrasound score for diagnostic purposes, such as the MASEI (MAdrid Sonographic Enthesitis Index).[24] The MASEI was developed for the diagnosis in spondyloarthropathy (SpA): a score of 18 or higher had a sensitivity of 83.3% and a specificity of 82.8% to diagnose SpA.[24] Different studies have confirmed that the MASEI score is indeed higher in patients with SpA than in healthy volunteers.[25, 26]

The value of ultrasound in diagnosing enthesitis in PsA has been evaluated in a few studies. Eder et al. found that both structural and inflammatory MASEI scores were higher in PsA patients with established disease and in patients with psoriasis than in healthy volunteers.[27] Using a different scoring system, similar results were seen by Aydin at al.[28] Regarding patients with early disease, Bandinelli et al. found more structural changes and more often a PD signal in early PsA than in healthy controls.[29] The performance of the MASEI in early disease as compared with healthy volunteers or patients with established disease has not been studied yet.

The level of sonographic enthesis involvement differs greatly between patients, and is possibly related to disease activity or other factors influencing sonographic signs of enthesitis. Within PsA, it has been shown that the MASEI score was associated with LEI scores,[30] but on the enthesis-level, concordance between ultrasound and clinical examination is generally very poor.[31, 32] Associations with global assessment of disease activity are reported by some,[33] but not observed by others.[30, 34] A higher body mass index (BMI) and higher age were associated with more structural and inflammatory changes of the entheses in PsA, but also in psoriasis

and healthy controls.[27] In healthy controls, tendons and entheses displayed PD signal after intense physical stress,[35, 36] and preceding overuse injuries.[37, 38] The role of physical activity on entheses as seen on ultrasound has not been studied in PsA.

BURDEN OF PSA

Patients with PsA can experience loss of functional ability, decreased health-related quality of life (HRQOL), and loss of productivity. Disability is often assessed using the Health Assessment Questionnaire (HAQ) Disability Index, in which a score between 0 and 1 reflects mild to moderate disability, between 1 and 2 moderate to severe disability, and 2 to 3 severe to very severe disability. Husted et al. reported a mean HAQ of 0.58 in patients with established disease and The Swedish early PsA registry reported a mean HAQ score of 0.66.[39, 40] In both studies, disability in PsA was lower than in rheumatoid arthritis (RA), though it might be argued that the HAQ is better in capturing disability in RA because it was first developed for use in RA. The type of disability experienced by patients with RA as captured with the HAQ might differ from the type of disability experienced by patients with PsA. Further, patients with PsA report HRQOL to be lower than the general population and patients with psoriasis.[39, 41, 42] Both physical and mental aspects of HRQOL are affected and disease burden is as high as in RA and ankylosing spondylitis.[39, 41] Impact on HRQOL has been studied in patients with established disease, but it is unknown to what extent this burden is already present at time of diagnosis. In two studies assessing which disease manifestations were associated with worse HRQOL, a relation with the number of tender joints but not with psoriasis was found.[43, 44] Though PsA is a heterogeneous disease with many different manifestations, the impact of manifestations besides arthritis and psoriasis have not been studied. Unemployment and work disability occurs more often in PsA than in the general population, and is related to the level of disability.[45, 46] Of the employed patients, about 3 out of 10 patients report having short term sick leave in the past year.[47, 48]

TREATMENT

The goal of therapy is ultimately to optimize functioning and quality of life, and prevent structural damage. To prevent lasting structural and functional damage best, treatment should be started within three months if PsA is active.[49] This advice is based on a concept extensively studied in RA but less so in PsA: the window of opportunity. Treatment in this window of opportunity can alter the course of disease of RA which cannot be done as effectively outside this window.[50] It is unknown whether such a window of opportunity exists in PsA, though studies have shown that a short delay between onset of symptoms and diagnosis is a predictor

of good clinical outcomes in PsA,[51, 52] and therapy is more effective in patients with a shorter disease duration.[53, 54]

Pharmacological treatment options in PsA are non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and local injections or systemic treatment with glucocorticoids. There are three types of DMARDs: conventional synthetic DMARDs (csDMARDs), biological agents (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Of the csDMARDs, methotrexate is most often used in PsA and is specifically preferred in case of active psoriasis. The use is widespread because of the experience with methotrexate in RA – in which it is known to alter the course of peripheral arthritis – and clinical experience in PsA, rather than because of its proven efficacy in PsA. The bDMARDs have effects on distinct parts of the immune system: adalimumab, certolizumab pegol, etanercept, golimumab or infliximab are tumor necrosis factor inhibitors (TNFi), ustekinumab inhibits interleukin-12/23 (IL-12/23), and secukinumab and ixekizumab inhibit IL-17. Treatment with tsDMARDs is targeted at a specific molecule: apremilast is a phosphodiesterase-4 inhibitor, and tofacitinib inhibits Janus kinase. With these many treatment options, many more being developed for use in PsA, and no two patients being exactly the same, choosing the best treatment option can be challenging. It is why groups of experts have developed guidelines to aid treatment decisions.

The European League Against Rheumatism (EULAR) has developed an algorithm for treatment, in which different steps in therapy are taken depending on whether treatment was effective enough. Treatment should be escalated more quickly if adverse prognostic factors are present (i.e. polyarthritis, radiographic damage, elevated acute phase reactants, or dactylitis or other extra-articular manifestations). Treatment starts with NSAIDs, followed by a first csDMARD, a second csDMARD (either switch or a combination), TNFi, and lastly bDMARD therapy with IL-12/23 or IL-17 inhibitors, or a tsDMARDs. In case patients present with axial disease or enthesitis and NSAIDs do not suffice, a bDMARD should be the next step instead of csDMARD therapy. If patients suffer from psoriasis, topical treatment, followed by phototherapy and csDMARDs – especially methotrexate – are advised. Throughout the steps, treatment with corticosteroids can be considered as adjunctive therapy. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommends different steps of treatment escalation, depending on the manifestation, as some steps of therapy have not been proven to be beneficial for some of the symptoms.[55] The choice of treatment should cover as many manifestations as possible. Though the EULAR and GRAPPA recommendations have some differences, both agree that treatment depends on the type of manifestations a patient has. With more knowledge of how each manifestation is related to burden of disease, treatment might be chosen more appropriately.

The recommendations state that therapy should be evaluated and escalated if needed, and an international task force recommends to do so in a treat-to-target (T2T) strategy.[56] We

know that outcomes of patients improve if a T2T strategy is followed from experience with RA.[57] In a T2T strategy, patients are carefully monitored and if a target of remission is not met, treatment is intensified. In RA, the target Disease Activity Score with 28-joint count (DAS28) is often used.[57] It calculates a composite score based on the 28 tender and swollen joint count, an ESR or CRP level, and a patient's global assessment of disease activity on a visual analogue scale (VAS).[58] The continuous score is then translated to remission or minimal disease activity.[59] The TIght COntrol of Psoriatic ARthritis (TICOPA) trial is the only T2T trial in PsA; it has shown that a T2T strategy leads to better clinical and patient-reported outcomes than usual care in patients with PsA.[60, 61] Though a T2T approach aiming at remission or – if remission cannot be achieved – low or minimal disease activity is also recommended in PsA, remission or low disease activity is not defined in PsA.[49, 55, 56]

DISEASE ACTIVITY

Composite disease activity scores

The target in a T2T strategy is a composite score, in which different aspects of disease are combined in a single score. In line with the goals of therapy (i.e. optimizing functioning and preventing structural damage), treatment is indicated if either current functioning is impaired due to inflammation, or if the current level of inflammation could potentially cause structural damage. In order to use it as a target, a disease activity measure consists of both predictors of future damage (e.g. joint swelling, CRP or ESR) and predictors of current disability (e.g. patient VAS global score). For PsA, many disease activity measures are available, though there is no consensus on which measure should be used for T2T in PsA.

In clinical trials of PsA, the DAS28 has often been used as a measure of disease activity.[62] The use of the DAS28 has been validated RA, and the reduced joint count of 28 joints reflect joints that were typically affected.[58] PsA, however, has a different joint distribution, and experts feared that disease activity in patients with predominantly involvement of DIP joints or joints of the feet would be missed. It is why the Disease Activity score for Psoriatic Arthritis (DAPSA) has been developed: a measure summing the 66 swollen joint count, 68 tender joint count, patient VAS global and VAS pain (both in cm, range 0-10), and CRP level.[63] The clinical DAPSA (cDAPSA) has the same calculation but without CRP.[63] PsA is however a heterogeneous disease, and others have argued that a composite score should be reflective of inflammation in all domains of disease.[56] Composite scores combining multiple domains of the disease have been developed: the Composite Psoriatic Disease Activity Index (CPDAI),[64] Psoriatic ArthritiS Disease Activity Score (PASDAS),[65] the GRAppa Composite ScorE (GRACE),[66] and the Minimal Disease Activity (MDA).[67] The components needed to calculate all these scores are displayed in Table 1.

Table 1. Components in calculation of disease activity measures

	DAS28	DAPSA	CPDAI	PASDAS	GRACE	MDA
Clinical Assessment						
Tender joint count	28	68	68	68	68	68
Swollen joint count	28	66	66	66	66	66
PASI			x		x	x
LEI			x	x		x
Dactylitis count			x	x		
VAS physician				x		
Patient Questionnaire						
VAS global	x	x		x	x	x
VAS skin					x	
VAS joints					x	
VAS pain		x				x
HAQ			x		x	x
DLQI			x			
BASDAI			x			
ASQoL			x			
SF-36 PCS				x		
PsAQoL					x	
Laboratory Assessment						
CRP	x	x		x		

DAS28: Disease Activity Score 28; DAPSA: Disease Activity index for PSoriatic Arthritis; CPDAI: Composite Psoriatic Disease Activity Index; PASDAS: Psoriatic ArthritiS Disease Activity Score; GRACE: GRAppa Composite ScorE; MDA: Minimal Disease Activity; PASI: Psoriasis Area and Severity Index; LEI: Leeds Enthesitis Index; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire; DLQI: Dermatology Life Quality Index; BASDAI: Bath Ankylosing Spondylitis Disease Actvitivity Index; ASQoL: Ankylosing Spondylitis Quality of Life; SF-36 PCS: Short Form 36 Physical Component Summary; PsAQoL: Psoriatic Arthritis-specific Quality of Life; CRP: C-reactive protein.

The CPDAI, PASDAS and GRACE are continuous measures of disease activity using multiple domains of disease. In the CPDAI, severity of involvement of five domains of PsA is assessed and scored as not involved, or with mild, moderate or severe involvement (range 0-3 per domain: joints, skin, entheses, dactylitis and spine). In each domain, a clinical evaluation is combined with patient-reported impact of disease.[64] The PASDAS is calculated with a joint, enthesitis and dactylitis count, both patient and physician global VAS score, CRP and a SF-36 PCS (Short Form 36 Physical Component Summary). These variables are transformed and weighted to result in a total score.[65] The GRACE score uses joint counts, patient global, psoriasis and pain VAS, HAQ, PASI (Psoriasis Area and Severity Index), and PsAQoL (PsA-specific Quality of Life). Each of these scores are transformed to desirability function in which 0 is completely unacceptable and 1 is normal, and scores in between correspond to desirability states. For example, moderate disease activity corresponds to a desirability score of 0.63 on all scales,

which is a swollen joint count of 3, a tender joint count of 5, a HAQ score of 1.0 and VAS scores of 30. The average of all these desirability scores is calculated (arithmetic mean of desirability function: AMDF), and the GRACE score is then transformed to a 0-10 scale with a higher score representing higher disease activity: (1-AMDF) x 10.[65, 68]

MDA is a state rather than a composite disease activity measure. A patient is considered to be in MDA if at least 5 out of 7 remission criteria are met: swollen joints, tender joints, enthesitis count, and PASI scores have to be 1 or lower, patient VAS pain 15 or lower, patient VAS global 20 or lower, and HAQ 0.5 or lower.[67] The remission variant is Very Low Disease Activity (VLDA), in which all remission criteria need to be achieved. MDA is the target that has been used in the only T2T trial in PsA, the TICOPA trial.[60] In addition, cross-sectional studies have shown that patients in MDA report lower impact of disease and better HRQOL than patients not in MDA.[69, 70] In such a cross-sectional analysis of patient outcomes however, it is not completely ruled out that factors not related to inflammation could lower both HRQoL and the probability of having low disease activity. Longitudinal data showing that achievement of MDA is related to an improvement of disease burden are lacking.

Though T2T with MDA and being in MDA are shown to be associated with better outcomes for patients with PsA, it is still debated whether MDA should be the target. Recently, a task force has recommended the use of either MDA or DAPSA in clinical practice.[56]

Comparison of Composite Disease Activity Scores

For all composite scores, lower disease activity is associated with a lower burden of disease and less structural progression. In an observational study of established PsA patients, Coates et al. showed that MDA is associated with less radiological progression,[71] which was also seen in patients with low disease activity according to DAPSA, GRACE and PASDAS in data from a trial with golimumab.[72] Using data from the same trial, it was shown that PASDAS, AMDF, CPDAI, DAS28, and DAPSA were all able to distinguish the treatment group from the placebo group.[73] They were also all associated with changing treatment as a measure of active disease in routine clinical care.[65] Michielsen et al. compared disease activity scores between patients finding their disease status acceptable and those who did not, and found that all the measures investigated (i.e. DAPSA, CDPAI, PASDAS, DAS28) were lower in patients with an acceptable disease status.[74]

Though all composite measures are related to indicators of inflammation, they are not always in agreement for a single patient: whether a patient has high disease activity and hence a treatment intensification is indicated depends on the measure used. In general, MDA is the strictest definition of low disease activity,[75-79] and agreement between measures is often only moderate.[74, 75] This disagreement between measures indicates that the question of which measure to choose is a relevant one; if all would give the same treatment indication, it would not matter which one is used. As treatment for PsA is aimed at optimizing functioning and HRQOL,

we need to know which composite measure best reflects these outcomes. To guide treatment decisions, the composite measures need to be sensitive to change when disease activity improves after effective treatment. In addition, most studies have assessed the performance of measures in observational studies of established PsA patients and in randomized clinical trials, but it is unknown how these measures perform in an early course of disease. Bearing in mind the possible window of opportunity in treatment of PsA, it is especially relevant to know how disease activity measures perform in that crucial early stage of disease, in current clinical practice.

DEPAR STUDY

In order to study current clinical practice of treatment, disease activity measures, and outcomes in patients with PsA, the DEPAR study (Dutch southwest Early Psoriatic Arthritis cohoRt) was set up in 2013. Patients were eligible to participate if they had a new diagnosis of PsA, were not yet treated with DMARDs for PsA before baseline assessment, were 18 years or older, and had sufficient understanding of the Dutch language. DMARD treatment with indication of psoriasis, and use of NSAIDs were allowed. Classification criteria were not included in the eligibility criteria, to ensure a sample representative of daily clinical practice. In the first year, patients were seen by their rheumatologist every 3 months and subsequently visited a research nurse for clinical evaluation. They were asked to complete questionnaires shortly before or after their visit. Laboratory values were collected every 3 months, and radiographs of hand and feet were collected yearly. Though the data of the first year of follow up are analysed in this thesis, the DEPAR study also collects data after 18 and 24 months, and yearly after that.

OBJECTIVES AND OUTLINE OF THIS THESIS

In order to improve outcomes for patients with PsA, good measures of disease activity are needed. As we suspect the chances to change the disease course are highest soon after diagnosis, more information on disease activity and outcomes at time of diagnosis and immediately after diagnosis is needed. Therefore, the aims of this thesis are to investigate in early PsA:

- ultrasound abnormalities of the entheses
- burden of disease at time of diagnosis and its relation with disease manifestations
- the relation between time to minimal disease activity and outcomes
- performance of disease activity measures

First, we explore whether ultrasound could aid in the diagnosis of enthesitis in PsA. We show the results of a comparison of extremes in **Chapter 2**: we compare the prevalence of ultrasound abnormalities of the entheses at time of diagnosis of PsA, in patients with established disease, and in young, healthy volunteers. These results are then validated in **Chapter 3**, in which we compare established disease with older healthy volunteers. In addition, we investigate which factors are associated with ultrasound abnormalities of the entheses in patients with established PsA.

In **Chapter 4** we study the impact of PsA on HRQoL at time of diagnosis in a cross-sectional analysis, and assess which of the disease manifestations are related with higher impact of disease.

The longitudinal relation between achieving a state of MDA and burden of disease in the first year after diagnosis is studied in **Chapter 5**. We also investigate whether time to achieving MDA is related to better outcomes.

We then proceed to comparing different disease activity measures. In **Chapter 6** we describe low disease activity 1 year after diagnosis of PsA using 2 disease measures recently recommended for use in clinical practice: MDA and DAPSA. These 2 measures are compared by assessing burden of disease in the different definitions of low disease activity. **Chapter 7** shows a comparison of the performance of multiple disease activity measures in early PsA.

In **Chapter 8**, these results, their implications on clinical practice and suggestions for future research are discussed.

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CHAPTER 2

Modification of a sonographic enthesitis score to differentiate between psoriatic arthritis and young healthy volunteers

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ABSTRACT

Objectives: We aimed to describe sonographic structural and inflammatory changes in entheses of patients with recently diagnosed psoriatic arthritis (PsA), patients with established PsA, and young healthy volunteers, and to investigate whether the MAdrid Sonographic Enthesitis Index (MASEI) enables us to distinguish these groups in an extreme comparison.

Method: New and established PsA patients and healthy volunteers (aged 20-30 years) were recruited. The triceps, quadriceps, patellar, Achilles and elbow extensor tendon insertion, and plantar fascia entheses were investigated sonographically for structural changes, erosions, calcifications, increased thickness, bursitis, and power Doppler (PD) signal according to the MASEI.

Results: The study included 25 new and 25 established PsA patients, and 25 healthy volunteers. Increased thickness and PD signal in knee entheses were common for patients and healthy volunteers, while changes at other locations predominantly occurred in patients only. PD was recoded (1, 1 spot; 1.5, 2 or 3 spots; 2,confluent signal; 3, severe confluent signal) and thickness of knee entheses excluded. This resulted in different modified MASEI scores between PsA patients and young healthy controls: median (interquartile range) modified MASEI of 13 (10-22.5) in new PsA, 13.5 (9.5-18) in established PsA, and 3 (1-8.5) in healthy volunteers ($p = 0.002$).

Conclusions: Structural ultrasound changes and PD in entheses are common in both new and established PsA and healthy controls. MASEI score did not differentiate PsA patients from young healthy volunteers. After recoding of PD severity and excluding thickness of knee entheses, marked differences between PsA patients and healthy controls were observed.

INTRODUCTION

Enthesitis is an entry criterion of the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria.[1] It is an inflammation of tendon, ligament or joint capsule insertion, with an estimated prevalence of 25% to 78% .[2] The presentation is similar to other tendon complaints that are quite common in the healthy population.[3] Therefore, general practitioners, dermatologists, and rheumatologists do not always recognize the presence of enthesitis or its association with psoriatic arthritis (PsA).[2]

In research, enthesitis is scored by counting the number of tender entheses. Tenderness does not occur in inflammatory enthesiopathy alone.[4,5] Other means may help to differentiate inflammatory from non-inflammatory entheseal tenderness. Ultrasound can be used to investigate multiple superficially located entheses. Abnormalities can be quantified with a combined score, for example the MAdrid Sonographic Enthesitis Index (MASEI).[6]

The main objective of this cross-sectional study was to investigate the frequency of ultrasound changes at the entheses of patients with recently diagnosed PsA, patient with established PsA, and young healthy volunteers (aged 20-30 years). In this extreme comparison, we aimed to describe sonographic signs of enthesitis in clearly diseased and clearly non-diseased entheses. The secondary objective was to investigate whether an enthesitis score (using the MASEI) was able to distinguish the 3 groups. We chose a control group of young healthy volunteers because their tendons have matured but have had limited exposure to the other causes of enthesiopathy.

METHOD

Patients and setting

Three groups of participants were investigated: new PsA patients, established PsA patients and healthy volunteers (aged 20-30 years). Consecutive newly diagnosed and established patients were included in hospitals in the south-west of the Netherlands. Established disease was defined as having been diagnosed with PsA for at least 2 years. Those patients were included irrespective of disease activity. To reduce the impact of age on ultrasound readings and clinical evaluation, an age limit of 55 years was set in the established PsA group. Healthy 20-30-year-old volunteers were recruited via advertisement at the medical faculty and by word of mouth. Exclusion criteria for healthy volunteers were familiar hypercholesterolemia, diabetes mellitus, and having any rheumatological disease. Participants were recruited from May 2015 to January 2016. Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study was approved by the local medical research ethics committee of Erasmus MC, University Medical Center Rotterdam, the Netherlands (MEC-2012-

549).

Data collection

Ultrasound examination of the entheses was performed by a trained sonographer (KW) who was blinded to the clinical information. An Esaote MyLab60 with the Probe LA-435 (6-18 MHz; Doppler frequency of 8.3 MHz, pulse repetition frequency of 750 Hz and a wall filter of 3) and Probe LA-523 (4-13 MHz; 6,3 MHz, 750 Hz and a wall filter of 4) was used. A color gain was set at the disappearance of color noise in the bone underneath the enthesis. The 6 MASEI locations and the common extensor insertion at the lateral epicondyle of the elbow (increased thickness cut-off 4.2 mm[7]) were assessed bilaterally. Each ultrasound location was scored for calcifications, erosions, increased thickness, structure, power Doppler (PD) signal, and bursitis, in accordance with the MASEI.[6]

Positioning of patients followed the recommendations of the MASEI developers, but with the knee flexed at approximately 30° instead of 70° in order to improve PD signal detection.[8] The lateral epicondyle was examined in 90° elbow flexion. PD was scored with a semi-quantitative scoring system similar to the method used in arthritis:[9] 0, absent; 1, 1 color spot; 1.5, 2 color spots; 2, confluent signal; and 3, severe signal (Supplemental Figure 1). Interrater agreement of rescoring was 93% and weighted Cohen's kappa with linear weights was 0.92.

Statistical methods

Simple descriptive techniques fitting the distribution were used to describe the study results and determine whether ultrasound data differed in the 3 groups, in STATA 14.0.

RESULTS

Participants

In total, 75 participants were evaluated: 25 new PsA and 25 established PsA patients, and 25 young healthy volunteers. Median disease duration was 2.9 weeks in new PsA and 8.0 years in established PsA (Table 1). Median symptom duration of musculoskeletal complaints as reported by the new patients was 1.2 years (interquartile range [IQR] 0.6-3.1 years).

Structural ultrasound findings

Calcifications were seen in all locations of entheses in patients, with the highest prevalence at the lateral epicondyle (entheses of new 56% vs established 28%), quadriceps tendon (68% vs 50%), and Achilles tendon (70% vs 56%) (Table 2 and Supplemental Table 1). In entheses of healthy volunteers, calcifications were seen far less frequently and they mainly occurred in the

quadriceps tendon (30%). Increased thickness was seen at all locations in patient entheses, with the highest prevalence at the lateral epicondyle (entheses of new 80% vs established 74%) and at the knee entheses (prevalence range 52-82%). In healthy volunteers, only knee entheses had an increased thickness (range 50-70%).

Table 1. Participant characteristics of the three groups

	New PsA (n=25)	Established PsA (n=25)	Healthy volunteer (n=25)
Male, n (%)	13 (52)	13 (52)	12 (48)
Age, years, median (range)	52 (30-72)	44 (26-53)	22 (20-26)
Time since PsA diagnosis, median (IQR)	2.9 (0.7-5.3) weeks	8.0 (5.0-11.0) years	
Medication, n (%)			
DMARDs	4 (16)*	17 (68)	
Biologicals	0 (0)	5 (20)	
DMARDs and biologicals	0 (0)	3 (12)	
LEI, median (IQR)	1 (0-1)	1 (0-2)	0 (0-0)
MASES, median (IQR)	0 (0-4)	1 (1-3)	0 (0-0)

*all DMARD use duration < 1 week.

PsA: psoriatic arthritis; IQR: interquartile range; DMARD: disease-modifying antirheumatic drug; LEI: Leeds Enthesitis Index (range 0-6); MASES: Maastricht Ankylosing Spondylitis Enthesis Score (range: 0-13).

Inflammatory ultrasound findings

The majority of patients and half of the healthy volunteers had a PD signal present in at least 1 enthesis (Table 3, Supplemental Table 2). A PD score of 2 or more in at least 1 enthesis was present in 52% of new and 44% of established PsA patients, and in 28% of healthy volunteers. The lateral epicondyle and the quadriceps tendon were affected in one-third of the entheses in patients (Table 2). In healthy volunteers, one-third of the quadriceps entheses and distal patellar entheses showed a PD signal.

MASEI

The median MASEI score with the lateral epicondyle added was 18 (IQR 15-31) in new PsA, 22 (IQR 15-27) in established PsA, and 10 (IQR 5-15) in healthy volunteers ($p = 0.002$). As described before, the main contributors to the MASEI scores in healthy volunteers were increased thickness and PD signal in knee entheses. After we excluded knee entheseal thickness and used the new PD scores, the IQRs were no longer overlapping. The scores of the modified MASEI were 13 (IQR 10-22.5), 13.5 (IQR 9.5-18) and 3 (IQR 1-8.5, $p = 0.002$) (Table 3).

Table 2. Madrid Sonographic Enthesitis Index (MASEI) score per component per enthesis location (n=50 per group)

	Structure			Thickness			Erosion		
	A	B	C	A	B	C	A	B	C
Lateral epicondyle tendon		4		80	74	20		2	
Triceps tendon	2	2		16	14	2		6	4
Quadriceps tendon	2	8	2	66	56	50			2
Proximal patella tendon		4		52	60	58		2	
Distal patella tendon		12		82	74	70		2	
Achilles tendon				8	26		4	8	4
Plantar fascia				24	28	4			

	Calcification*			PD signal			Bursitis		
	A	B	C	A	B	C	A	B	C
Lateral epicondyle tendon	56	28	8	36	34				
Triceps tendon	16	22	2		10				
Quadriceps tendon	68	50	30	28	30	34			
Proximal patella tendon	22	12	6	8	12	2			
Distal patella tendon	18	16		16	14	30			
Achilles tendon	70	56	8	8	10	2	8	6	
Plantar fascia	16	2	6						

Data are shown as the number of abnormalities (%) per group. A: new PsA patients; B: established PsA patients; C: healthy volunteers.

*Calcification is expressed as the number of tendons with a score > 0. PD: power Doppler.

Table 3. Outcome of the Madrid Sonographic Enthesitis Index (MASEI) scoring system and different adjustments to the MASEI scoring system in the 3 participant groups

	new PsA (n=25)	established PsA (n=25)	healthy volunteer (n=25)
Ultrasound Examination			
MASEI*	15 (11-25)	16 (11-26)	10 (5-13)
PD			
PD in any enthesis	76%	96%	56%
PD≥2 in any enthesis	52%	44%	28%
≥ 3 entheses with PD	20%	32%	24%
Amendments (stepwise)			
+ Lateral epicondyle	18 (15-31)	22 (15-27)	10 (5-15)
- Quadriceps thickness	13 (11-28)	17 (12-23)	5 (2-12)
Amending PD score#	13 (10-22.5)	13.5 (9.5-18)	3 (1-8.5)

Data are shown as median (interquartile range) or percentage of participants.

*Range 0-136.

#Using new scoring system to award points for PD: 1a was given 1 point and 1b 1.5 points. PsA: psoriatic arthritis; PD: power Doppler.

DISCUSSION

Sonographic changes in the entheses were observed in young, healthy volunteers, patients with recently diagnosed PsA, and patients with established PsA. Increased thickness and a subtle positive PD signal in knee entheses were common in healthy volunteers and patients, while abnormalities at other locations predominantly occurred in patients. After we excluded patellar tendon enthesis thickness and applied a new method of scoring PD, the modified MASEI was able to distinguish between PsA patients and healthy controls. Furthermore, we showed that ultrasound abnormalities are already very common in early PsA.

The extreme contrast we expected between young healthy volunteers and PsA was not reflected in the MASEI score. We chose to compare PsA patients and clearly non-diseased young subjects, expecting a big contrast owing to difference in disease status and age. Tendon thickness reference values explained part of the overlap, especially in the case of the knee entheses. The reference values originate from an ultrasound study of human cadaveric limbs aged 67-87 years[10] and probably underestimate enthesis thickness. Small spots of PD signal in healthy volunteers further diminished the expected extreme contrast. Our findings seem to suggest that a single spot of PD is not of value in identifying active entheseal inflammation and that at least a confluent signal is necessary. Furthermore, the patellar tendon is susceptible to showing hypervascularity after acute physical stress. A study performing PD examination on runners showed hypervascularity in the patellar tendon directly after a marathon.[11]

Our results raise questions and challenges for the future. First, our controls were not age-matched. Therefore, the differences between controls and patients cannot solely be ascribed to entheseal inflammation due to PsA. The effect of aging is likely to play a role as well, which is also reflected in higher scores in the slightly older new PsA group. The effect of factors such as obesity, physical exercise, age, and gender could not be analyzed, as the subgroups would be too small to analyze. Secondly, compared to other studies in early PsA, we found slightly higher scores on PD, possibly due to differences in study design and the machines used.[12, 13]

CONCLUSION

Ultrasound structural changes and inflammation in the enthesis were common in both new and established PsA patients, and in the knees of healthy young adults, using the MASEI score. Excluding knee entheses thickness and refinement of PD signal scores provided discrimination of PsA from healthy young volunteers in terms of enthesis pathology.

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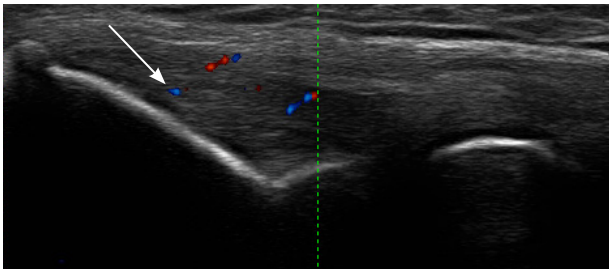
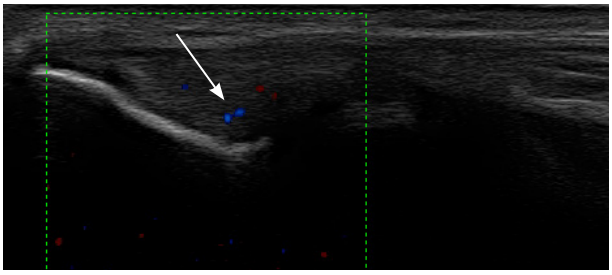
SUPPLEMENTAL DATA

Supplemental Figure 1. Recoding of power Doppler score within 2 mm of the cortex
1a (1 color spot) for A, 1b (2 color spots) for B, 2 (confluent signal) for C and 3 (severe signal) for D. Ultrasound of lateral epicondyle of the humerus (A-C) and quadriceps insertion (D)

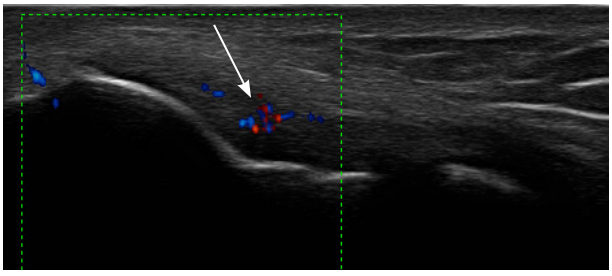
A



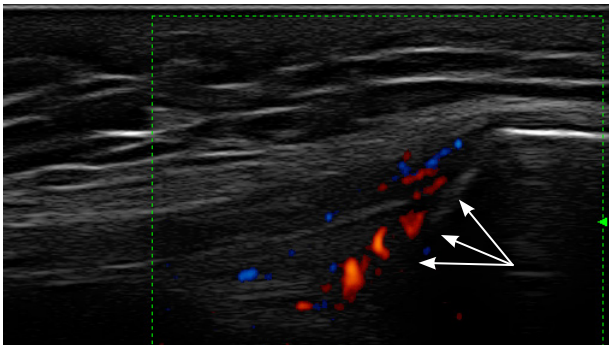
B



C



D



Supplemental Table 1. Calcification scores per individual using the Madrid Sonographic Enthesitis Index (MASEI) scoring system

New PsA																									
Age	37	66	64	35	35	55	46	68	59	45	52	46	55	48	69	37	53	30	46	52	46	58	72	62	52
Gender	F	F	M	F	F	M	M	M	F	F	F	M	F	M	M	M	M	F	F	F	F	M	M	M	M
Right lateral epicondyl tendon	1	1	1			2		1	1	1	1		1									1	1	1	1
Left lateral epicondyl tendon		1	1	1		1			1	1	1		1		1		1		1			1	1		3
Right triceps tendon																			1						3
Left triceps tendon			1			3									1				1			2			3
Right quadriceps tendon		3	2	3	2	3			2			2	3	1	3	1					1	2	2	2	3
Left quadriceps tendon	1	3	2		1	3	1	1	1				3	1	3	1			2		3	1	3	3	3
Right proximal patella tendon				1		2			1														3		3
Left proximal patella tendon				1		3		2											3				3		3
Right distal patella tendon						1		1									2		1				2		
Left distal patella tendon						3											3						1		3
Right Achilles tendon	1	3	1		1	3			2	2				2	3	2			3		2		3	2	3
Left Achilles tendon	2	2	2	3	1	3			1	1		1	2	3	3	1	2		1	2	1		3	3	2
Right plantar fascia	2	2							2														3		
Left plantar fascia	2	2				2									2										

Supplemental Table 1. (continued)

Established PsA																									
Age	40	44	38	53	51	34	30	40	47	52	46	33	45	49	28	42	26	36	45	42	48	45	47	52	32
Gender	F	F	M	M	F	F	M	M	M	F	F	F	F	M	F	M	F	M	M	M	M	F	M	F	M
Right lateral epicondyl tendon	1		1	1	1			1	1			1							1			1		1	
Left lateral epicondyl tendon				1	1																			1	2
Right triceps tendon	1		2				1	1						2											
Left triceps tendon							1	2					1	3				1						1	
Right quadriceps tendon	2		3	2	3			2			1		1	3		1		3			3		2		2
Left quadriceps tendon			3	2	3			1			3		2	3	1			3			3		1		2
Right proximal patella tendon					1									1							1				
Left proximal patella tendon								1			1							3							
Right distal patella tendon	1	1	1		1								2												
Left distal patella tendon							1						1					2							
Right Achilles tendon	2	2	2	2	3	1	3	2	2			2		2				2			3			1	
Left Achilles tendon	2	2	2	2	3		2		3			2		2	1			2			3		1	2	
Right plantar fascia																									
Left plantar fascia																									2

Supplemental Table 1. (continued)

Healthy Volunteers																									
Age	22	22	25	23	22	23	22	22	22	21	22	25	22	23	22	24	26	22	22	26	22	24	22	20	24
Gender	F	F	M	M	M	M	F	M	F	M	M	F	M	M	F	M	F	F	F	M	F	F	F	M	F
Right lateral epicondyl tendon	1			1												1									
Left lateral epicondyl tendon																1									
Right triceps tendon																				1					
Left triceps tendon																									
Right quadriceps tendon			2		1			1	1	1		1	1	2											
Left quadriceps tendon	1		2		1					2	2			2											2
Right proximal patella tendon					1								1								1				
Left proximal patella tendon																									
Right distal patella tendon																									
Left distal patella tendon																									
Right Achilles tendon				1										1											
Left Achilles tendon			1			1																			
Right plantar fascia								1																	
Left plantar fascia								1	1																

F: female; M: male; 1: small calcification or ossification; 2: enthesophytes or medium-sized calcification or ossification; 3: large calcification or ossifications.

Supplemental Table 2. Power Doppler scores using the new scoring system per individual

New PsA																								
Age	37	66	64	35	35	55	46	68	59	45	52	46	55	48	69	37	53	30	46	52	46	58	72	62	52
Gender	F	F	M	F	F	M	M	M	F	F	F	M	F	M	M	M	M	F	F	F	F	M	M	M	M
Right lateral epicondyl tendon		1b		2	2	2	1a			2		1b													1a
Left lateral epicondyl tendon	1a	1b	1b	1b	1b		1b	1a		1b							2								2
Right triceps tendon																									
Left triceps tendon																									
Right quadriceps tendon		3				3						3			3					2				1b	
Left quadriceps tendon		3	2			2						2	1b		1b					3		2			
Right proximal patella tendon												1b												1b	
Left proximal patella tendon						1b						3													
Right distal patella tendon				1a								3							1a						
Left distal patella tendon				1a		1a						1a				3			1a						
Right Achilles tendon				1b															1b						
Left Achilles tendon				1b															1a						
Right plantar fascia																									
Left plantar fascia																									

Supplemental Table 2. (continued)

Established PsA																									
Age	40	44	38	53	51	34	30	40	47	52	46	33	45	49	28	42	26	36	45	42	48	45	47	52	32
Gender	F	F	M	M	F	F	M	M	M	F	F	F	F	M	F	M	F	M	M	M	M	F	M	F	M
Right lateral epicondyl tendon				1b		2		2	2		1b	2	1b					2							1b
Left lateral epicondyl tendon	2	2		2	1a				1a				1b									1b		2	
Right triceps tendon																1b									
Left triceps tendon			1a				1b													1b				1b	
Right quadriceps tendon							1b		2						1b				2	1b	1b	1a	1b		
Left quadriceps tendon			1a						1b	1b							1b	1a	1b				1b		
Right proximal patella tendon				1a		2			2												1a				
Left proximal patella tendon											2									1a					
Right distal patella tendon				1a																					
Left distal patella tendon	1a									1b							1b	1a		1a		1b			
Right Achilles tendon						2													1b						
Left Achilles tendon				1b		1a	1a																		
Right plantar fascia																									
Left plantar fascia																									

Supplemental Table 2. (continued)

Healthy Volunteers																									
Age	22	22	25	23	22	23	22	22	22	21	22	25	22	23	22	24	26	22	22	26	22	24	22	20	24
Gender	F	F	M	M	M	M	F	M	F	M	M	F	M	M	F	M	F	F	F	M	F	F	F	M	F
Right lateral epicondyl tendon																									
Left lateral epicondyl tendon																									
Right triceps tendon																									
Left triceps tendon																									
Right quadriceps tendon	1b	1a	2					1b		2		1a		1b		2									
Left quadriceps tendon		1b	1b					2		1b				1b	1a	1a		1b	1b						
Right proximal patella tendon																									
Left proximal patella tendon													1a												
Right distal patella tendon	1b		2					1a				2	1b			1b									2
Left distal patella tendon	2			1a				1a					1a	1a		1a			1a						2
Right Achilles tendon																									
Left Achilles tendon													1b												
Right plantar fascia																									
Left plantar fascia																									

F: female; M: male; PD signal was scored 0 if absent, 1a if only 1 color spot was detected (1 point), 1b if 2 color spots were detected (1.5 point), 2 in case of confluent signal and 3 in case of severe signal.

CHAPTER 3

Association of physical activity and medication with enthesitis on ultrasound in psoriatic arthritis

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ABSTRACT

Objective: Enthesitis is a manifestation of psoriatic arthritis (PsA), but its symptoms are difficult to interpret clinically. We investigated the associations of untrasonographic changes in entheses with clinical characteristics in PsA patients, and compared enthesis changes of PsA patients aged 35 to 60 with healthy volunteers of that age.

Methods: Consecutive PsA patients participated in this cross-sectional study, irrespective of enthesitis complaints and age. We collected data about complaints, physical activity and activity avoidance, medication, and clinical enthesitis. Inflammatory and structural enthesis changes were scored with the modified MAdrid Sonographic Enthesitis Index (MASEI). Among all PsA patients, associations between ultrasound scores and clinical characteristics were investigated using linear regression. We compared ultrasound scores of healthy volunteers and PsA patients aged 35 to 60 years using Wilcoxon rank tests.

Results: Eighty-four PsA patients and 25 healthy volunteers participated. In PsA patients, we found a small association between higher inflammatory modified MASEI score and higher age (β:0.07, 95% CI:0-0.13) and current use of biologicals (β:1.56 95% CI 0.16-2.95). Patients reporting avoiding activities had significantly lower inflammatory modified MASEI scores (β:-1.71, 95% CI:-3.1;-0.32) than those who did not. The PsA patients aged 35 to 60 years (n=50) had similar inflammatory scores as healthy volunteers, but higher structural scores (median 6 vs. 2, p=0.01).

Conclusion: Within PsA patients, avoiding physical activity, younger age and not using biologicals was associated with less entheses inflammation. PsA patients and healthy volunteers aged 35 to 60 years displayed similar levels of inflammatory changes of the entheses, but PsA patients had more structural damage.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease that belongs to the group of spondyloarthropathies. It has a heterogeneous presentation of arthritis, psoriasis, spondylitis, dactylitis and enthesitis.[1, 2] Enthesitis is one of the distinguishing features of spondyloarthropathies and is defined as inflammation of tendon, ligament or joint capsule insertion. Enthesitis is found at clinical examination in a third of PsA patients,[3] but tenderness of the enthesis does not necessarily have an inflammatory origin. A better technique is needed to distinguish PsA-related inflammatory enthesitis from other enthesiopathies, such as metabolic, degenerative and mechanical processes.[4]

With ultrasound, inflammatory and structural changes of the entheses can be assessed[5] and quantified with a composite ultrasound score, such as the MAdrid Sonographic Enthesitis Index (MASEI).[6] In a previous study we evaluated the value of use of the MASEI in an extreme comparison; we compared patients newly diagnosed with PsA, patients with established disease and young healthy volunteers.[7] We found that increased thickness of knee entheses and a subtle power Doppler (PD) signal were present in all groups, even in young healthy volunteers. We, therefore, modified the MASEI score: we excluded knee enthesis thickness (i.e. quadriceps and both patellar tendon insertions) from the evaluation and graded PD severity. This modified MASEI score showed a good discrimination between entheses of patients and those of young healthy volunteers. As the number of enthesis abnormalities varied within all groups, we suspected other factors than PsA-related inflammation could cause these ultrasound abnormalities. Previous studies, for example, showed that higher age and higher body mass index (BMI) were associated with more entheseal abnormalities on ultrasound both in PsA patients and in healthy volunteers.[8, 9] Studies in healthy volunteers showed that physical activity is also associated with changes in entheses on ultrasound,[10, 11] although this is not confirmed in PsA to our knowledge. We, therefore, aimed to investigate associations between modified MASEI scores and clinical characteristics in an average PsA population. In addition, we aimed to compare the modified MASEI scores of PsA patients and healthy volunteers aged 35 to 60.

METHODS

Patients and Setting

Consecutive patients of all ages with established PsA for at least 2 years attending the rheumatology clinic were eligible to participate, irrespective of disease activity or complaints. Patients were recruited from 3 outpatient clinics in The Netherlands (the academic hospital Erasmus MC, and the general hospitals Vlietland hospital and Albert Schweitzer hospital)

between May and August 2016. Healthy volunteers were invited if they were aged 35 to 60 years, without a history of any of the following: any rheumatic disease, Crohn's disease, uveitis, familial hypercholesterolemia or diabetes. Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study was approved by the local medical research ethics committee of Erasmus MC, University Medical Centre Rotterdam, The Netherlands (MEC-2012-549).

Data collection

In a structured interview, patients answered questions about their disease duration, physical activity and avoidance of activity. Regarding physical activity, patients were asked whether they exercised regularly. With respect to avoidance, patients were specifically asked whether they avoided activities due to complaints or fear of complaints in daily life during exercise, work, household activities and chores. We scored avoidance when patients reported avoiding activities because of pain or fear of pain. Fulfilment of Classification criteria for PsA (CASPAR) criteria[12] and medication use was obtained from chart review.

Data collected during physical examination were height, weight, 66 swollen joint count, 68 tender joint count, enthesitis at clinical examination (Leeds Enthesitis Index, LEI and Maastricht Ankylosing Spondylitis Enthesitis Score, MASES), and Psoriasis Area and Severity Index (PASI).

Ultrasound examination was performed directly after clinical examination by a sonographist trained in enthesis sonography (IH), who was blinded for clinical information. Patients were instructed not to communicate any clinical information to the sonographist by the researchers who conducted the interview and physical examination (MM, KW). The 6 MASEI entheses and the lateral epicondyle were bilaterally examined using an Esaote MyLab60 with linear probes LA435 (6-18 MHz; Doppler frequency of 8.3 MHz, pulse repetition frequency of 750 Hz and a wall filter of 3) and LA532 (4-13 MHz; 6,3 MHz, 750 Hz and a wall filter of 4). The former was used for entheses of the upper limbs and the latter for the entheses of lower limbs. In each site, we scored calcifications, erosions, structural changes, thickness, Power Doppler (PD) signal and bursitis. Only presence of PD signal within 2 mm of the cortex was scored. Patients were positioned according to the MASEI, but with the knee flexed at approximately 30° (rather than 70°) and resting on a pillow to ensure relaxing of the quadriceps muscle. The lateral epicondyle was examined in 90° flexion and a cut off of 4.2 mm was used in this enthesis.[13] If a PD signal was present, images of the severest PD signal were saved and scored by KW and IH, who had an interrater agreement of 93% (intraclass correlation coefficient). Besides the original MASEI score, we calculated the modified MASEI by excluding the knee entheses thickness (i.e. quadriceps and proximal and distal patellar tendon insertion) and grading of PD signal. All abnormalities were recorded during ultrasound evaluation, and PD signal was graded by a second scorer (KW) on the static images. PD signal intensity was scored:

0: absent, 1: 1 spot, 1.5: 2 spots, 2: confluent signal, 3: confluent severe signal (Supplemental Figure 1). Absolute agreement was 93% and weighted Cohen's kappa using linear weights was 0.92. We distinguished an inflammatory component (sum of points for increased thickness, bursitis and PD signal) and structural component (sum of points for structure, calcifications/ enthesophytes and erosions).

Statistical analysis

Within the total PsA population, the association between clinical characteristics, and 1) inflammatory modified MASEI and 2) structural modified MASEI were investigated using multiple linear regression analyses. Using a forward selection ($p<0.30$), the following independent variables were tested: age, BMI, disease duration (square-transformed), current use of disease modifying antirheumatic drugs (DMARDs), current use of nonsteroidal anti-inflammatory drugs (NSAIDs), current use of biologicals, avoidance of activities, exercise and enthesitis at clinical examination. This was done for both inflammatory modified MASEI and structural modified MASEI as dependent variable. The latter was transformed ([y+1]2) because of its skewed distribution. Modified MASEI scores of a subgroup of patients between the age of 35 and 60 and of the healthy volunteers of the same age-range were compared using the Wilcoxon rank-sum test.

RESULTS

In total, 84 consecutive patients with established PsA participated; mean age was 55 years (standard deviation [SD] 11, age range 26 to 76), 45 (54%) were male and mean BMI was 27 (SD 5). Median disease duration was 8 years. Disease activity was mild in our usual care consecutive cohort: median swollen joint count was 0 (interquartile range [IQR] 0-2) and median tender joint count 3 (IQR 0-7). Median LEI score was 0.5 (IQR 0-2). Forty patients (48%) reported to exercise regularly and avoiding activities was reported by 17 (43%) of those patients with regular exercise. Among patients not exercising regularly, avoidance of any physical activity was reported by 28 (64%, Table 1).

Association between ultrasound scores and clinical characteristics

Within patients, a small association was found between a higher inflammatory modified MASEI score and 1) higher age (β 0.07, 95% CI 0-0.13) and 2) current use of biologicals (β 1.56 95% CI 0.16-2.95). Patients that reported to avoid activities had significantly lower inflammatory modified MASEI scores (β -1.71, 95% CI -3.1;-0.32, Table 2). Higher age was also associated with a higher score on structural modified MASEI (β 0.03, 95% CI 0.01-0.05, p=0.001, Table 3). Current use of NSAIDs or DMARDs, regularly exercising, gender and enthesitis at clinical examination

Table 1. Demographic and clinical characteristics of patients

Age, yrs	55 ± 11
Male	45 (54)
BMI	27 ± 5
Disease duration, yrs	8 (5-12)
Fulfilling CASPAR criteria	81 (96)
Swollen joint count (66)	0 (0-2)
Tender joint count (68)	3 (0-7)
LEI	0.5 (0-2)
MASES	1 (0-2)
PASI*	0.6 (0-2.8)
Regularly exercising	40 (48)
Avoidance	45 (55)
Current medication use	
NSAID	31 (37)
DMARD	64 (76)
Prednisone	1 (1)
Biological DMARD	40 (48)

Data presented as mean ± standard deviation, n (%) or median (interquartile range).
*excluding 1 patient without a history of psoriasis
PsA: psoriatic arthritis; BMI: body mass index; CASPAR: Classification criteria for psoriatic arthritis; LEI: Leeds enthesitis index; MASES: Maastricht ankylosing spondylitis enthesitis score; PASI: psoriasis area and severity index; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease modifying anti-rheumatic drug.

Table 2. Association between ultrasound scores (inflammatory modified MASEI) and clinical characteristics

	β	(95% CI)	p-value
Age	0.07	(0;0.13)	0.050
BMI	0.13	(-0.01;0.27)	0.063
Duration^2	0.04	(-0.73;0.82)	0.909
DMARD no vs yes	1.23	(-0.4;2.87)	0.137
Biological no vs yes	1.56	(0.16;2.95)	0.029
Avoidance no vs yes	-1.71	(-3.1;-0.32)	0.017

Linear regression of 84 patients
BMI: body mass index; DMARD: disease modifying antirheumatic drug; CI: confidence interval.

Table 3. Association between ultrasound scores (structural modified MASEI) and clinical characteristics

	β	(95% CI)	p-value
Age	0.03	(0.01;0.05)	0.001
BMI	0.04	(0;0.08)	0.054
Duration^2	0.11	(-0.1;0.32)	0.302

Linear regression of 84 patients. Transformation of structural modified MASEI: $(y+1)^2$.
BMI: body mass index; CI: confidence interval.

were not associated with any of the modified MASEI scores.

Enthesis ultrasound scores

Total ultrasound scores of patients aged 35-60 years were compared with those of 25 healthy volunteers in the same age range. Healthy volunteers had a mean age of 47 (SD 6) years, 12 were male (48%) and average BMI was 25 (SD 4, Supplemental Table 1). The original median (IQR) MASEI scores of 50 PsA patients aged 35-60 years (14 [9-21]) were comparable to those of the 25 healthy volunteers (13 [9-18], Table 4). The prevalence of each abnormality in the total PsA group, in the subgroup aged 35 to 60, and in the healthy volunteer group is shown in Table 5. After excluding knee enthesis thickness and grading PD score, the resulting modified MASEI scores were 11 (IQR 6.5-15) in patients and 7.5 (IQR 5-9, p = 0.01) in healthy volunteers. The inflammatory contribution (i.e. thickness, bursitis and PD signal) to this modified MASEI was similar in patients (5 [IQR 2-7]) and healthy volunteers (3.5 [IQR 2-5.5]). The structural contribution (i.e. calcification, erosion and structural changes) was significantly higher in patients (6 [IQR 3-10]) than in healthy volunteers (2 [IQR 1-6], p = 0.01). Presence of PD signal was similar in patients and healthy volunteers.

Table 4. Comparison of enthesitis ultrasound scores between patients with psoriatic arthritis and healthy volunteers

	Total PsA patients (n=84)	PsA patients aged 35-60 years (n=50)	Healthy volunteers aged 35-60 years (n=25)	p-value PsA vs. HV aged 35-60 years
MASEI	15.5 (11-22)	14 (9-21)	13 (9-18)	0.39
Modified MASEI	12 (7.3-17)	11 (6.5-15)	7.5 (5-9)	0.005
Inflammatory modified MASEI	5 (2.8-7.5)	5 (2-7)	3.5 (2-5.5)	0.16
Structural modified MASEI	7 (3-10)	6 (3-10)	3 (1-6)	0.005
PD				
PD in any enthesis	74 (88)	44 (88)	22 (88)	1.00
PD in two or more enthesis	47 (56)	27 (54)	17 (68)	0.25
Confluent PD in any enthesis	35 (42)	20 (40)	9 (36)	0.74
Severe PD in any enthesis	7 (8)	4 (8)	0 (0)	0.29
Average PD score*	1.5 (1.3-1.8)	1.5 (1.3-1.7)	1.5 (1.3-1.5)	0.44

Data presented as median (interquartile range) or n (%).

*in 74 and 44 patients and 22 healthy volunteers where PD was present

MASEI: Madrid sonographic enthesitis index; modified MASEI: MASEI with lateral epicondyle, excluding knee enthesis thickness and grading of power Doppler; PD: power Doppler, HV: healthy volunteers.

Table 5. Madrid Sonographic Enthesitis Index (MASEI) score per component per enthesis location

	Structure			Thickness			Erosion		
	A	B	C	A	B	C	A	B	C
Lateral epicondyle tendon	1	1		53	50	30	4	3	
Triceps tendon	1	2		13	11		2	3	
Quadriceps tendon				70	64	60			
Proximal patella tendon	1	1		74	72	68	1	1	
Distal patella tendon				96	98		1	1	
Achilles tendon	1	1		10	12	2	2	3	
Plantar fascia				33	23	12			

	Calcification*			PD signal			Bursitis		
	A	B	C	A	B	C	A	B	C
Lateral epicondyle tendon	49	41	16	26	30	18			
Triceps tendon	24	23	2	1	2	2			
Quadriceps tendon	65	66	48	34	32	42			
Proximal patella tendon	8	7	2	11	10	12			
Distal patella tendon	10	8	14	53	30	36			
Achilles tendon	52	55	42	5	4	4			
Plantar fascia	1								

Data are shown as the number of abnormalities (%) per group. A = total PsA group, B = PsA of 35 to 60 years of age, C = healthy volunteers of 35 to 60 years of age. *Calcification is expressed as the number of tendons with a score >0. PD: power Doppler.

DISCUSSION

We found that in a PsA population not selected based on complaints of the entheses, higher age and the current use of biologicals were associated with higher inflammatory scores, while patients reporting avoidance of activity had lower inflammatory scores. More structural changes in PsA was associated with higher age only. No effects of BMI, current NSAIDs use, regular exercise, gender and clinical symptoms of enthesitis on ultrasound were seen, possibly because we did not have the power to detect a small effect. Inflammatory changes of the entheses occurred as often as in healthy volunteers of the same age. The PsA patients did however have twice as many structural changes of the entheses.

The finding that regular exercise was not related to ultrasound changes but avoidance of activity was related seems contradictory. This may relate to the way we recorded avoidance, namely in more domains than only sport activities and patients could both report avoiding activity and exercising regularly. In the statistical analysis ultrasound changes were stronger associated with avoidance than with physical activity. Physical activity is probably both influencing and influenced by pathology of tendons and entheses, which makes the

interpretation of sonographic abnormalities difficult. Some patients avoiding physical activity might have suffered from enthesitis and consequently altered their behaviour. The relation between physical activity and sonographic enthesis changes has not been shown in PsA before, although some work has been done in athletes. Changes of tendons and entheses on ultrasound have been observed in the patellar tendon of athletes immediately after their high-level badminton matches,[10] and after they ran a marathon.[11] Their respective strain on the tendon might be different, but, in both, some reaction after physical exercise was seen on ultrasound. This could be a physiological response or an early sign of a pathological reaction: other studies have shown that abnormalities on ultrasound could precede clinical manifestations of overuse injuries in healthy athletes.[14, 15] In contrast, a study assessing the MASEI scores of 30 athletes (who were running or playing soccer for at least 6 hours per week) and 29 non-athletes (who were playing a sport less than 1 hour per week) were not able to show a difference.[16] These data suggest that in a healthy situation tendons and entheses have adapted to the regular level of physical activity but do respond to a change in physical activity. We found a similar relation in PsA patients, though we did not directly study the modifying effect of PsA by comparing the relation with that in healthy volunteers. Longitudinal studies are needed to investigate whether the response of entheses to physical activity is altered in PsA.

Comparable inflammatory scores of healthy volunteers and PsA patients suggest that ultrasound evaluation of the enthesis is of limited value in screening for inflammation. This was also concluded by Groves et al., who compared MRI and ultrasound evaluation of the elbow in patients with PsA and rheumatoid arthritis who reported elbow pain.[17] In a third of cases, inflammation could be seen on MRI but not on ultrasound. The larger extent in which structural changes were present in PsA patients in our study suggests that patients have been subject to more chronic inflammation of the entheses than healthy volunteers of similar age.

The higher occurrence of inflammatory changes of the entheses in patients using biological DMARDs was an interesting but unexpected finding as biological DMARDs are recommended in the treatment of enthesitis in PsA. One explanation is that patients on biological DMARDs are a selected population with more severe inflammation. Michelsen et al. investigated Achilles enthesitis in PsA patients and found use of biologicals was associated with more structural damage, but not with inflammatory activity.[18] This contradicts our study, as we found an association with inflammatory activity and not with structural damage. A second possible explanation is that tendons and entheses recover at a slow rate and not all patients may have used biological DMARDs for a long enough period. A study in ankylosing spondylitis showed that inflammatory ultrasound lesions did not change after 6 months of tumor necrosis factor blocking therapy.[19] In a similar study, Ayden et al., however, did find a decrease in ultrasound lesions after 2 months of therapy and so did Naredo et al. after 6 months of follow up.[20, 21] Similarly, a study using MRI in axial spondyloarthritis found a decrease

in enthesitis after 2 years of treatment with etanercept.[22] A third explanation is that the effect of biological DMARDs on enthesitis is heterogeneous and depends on the type of treatment (i.e. TNF inhibitors, anti-IL17 or anti-IL12/IL23).

A limitation of our study is its cross-sectional design, which makes the interpretation of the association between clinical symptoms and ultrasound scores difficult. The relation between physical activity and enthesitis might be subject to information bias and the exact impact of physical activity on entheses is better investigated in an experimental setting. For example, the reporting of physical activity and avoiding of physical activity might be influenced by a history of enthesitis and different adaptive behaviour and coping strategies. Second, physical activity and in particular long-term effects of physical activity are difficult to measure and the measurement of self-reported physical activity could be biased. Third, this study has an exploratory nature, in which multiple factors of influence were tested. The models were fitted to this established usual care population with relatively low disease activity and use of NSAIDs and biologicals by the majority. For these reasons, future studies – preferably longitudinal studies – are needed to confirm these results.

In conclusion, in this cross-sectional study, avoiding physical activity, younger age and not using biological DMARDs were associated with less inflammation of the entheses. PsA patients and healthy volunteers aged 35 to 60 years display similar levels of inflammatory changes of the entheses, but PsA patients had more structural damage. The only way to understand these associations is to investigate changes of entheses on ultrasound in prospective longitudinal studies.

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SUPPLEMENTAL DATA

Supplemental Figure 1. Recoding of power Doppler score within 2 mm of the cortex, Figure shown as Supplemental Figure 1 in Chapter 2.

Supplemental Table 1. Participant characteristics

	PsA patients age 35-60 (n=50)	Healthy volunteers age 35-60 (n=25)
Age, yrs	50 ± 6	47 ± 6
Male	23 (46)	12 (48)
BMI	28 ± 5	25 ± 4**
Disease duration, yrs	7 (4-12)	
Fulfilling CASPAR criteria	48 (96)	
Swollen joint count (66)	0 (0-2)	
Tender joint count (68)	3 (0-8)	
LEI	0 (0-2)	0 (0-0)**
MASES	1 (0-2)	0 (0-0)**
PASI*	0.5 (0-1.8)	
Regularly exercising	25 (50)	25 (100)**
Avoidance	29 (58)	4 (16)**
Current medication use		
NSAID	22 (44)	1 (4)**
DMARD	33 (66)	0 (0)**
Prednisone	24 (48)	0 (0)**
Biological DMARD	40 (48)	

Data presented as mean ± standard deviation, n (%) or median (interquartile range).
*excluding 1 patient without a history of psoriasis.
**PsA vs. Healthy volunteers $p < 0.01$
PsA: psoriatic arthritis; BMI: body mass index; CASPAR: Classification criteria for psoriatic arthritis; LEI: Leeds enthesitis index; MASES: Maastricht ankylosing spondylitis enthesitis score; PASI: psoriasis area and severity index; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease modifying anti-rheumatic drug.

CHAPTER 4

Influence of disease manifestations on health related quality of life in early psoriatic arthritis

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ABSTRACT

Objective: Psoriatic arthritis (PsA) is a multifaceted disease. Affecting joints, skin, entheses and dactylitis, its impact on health-related quality of life (HRQOL) could be substantial. We aim to assess HRQOL in patients with newly diagnosed PsA and analyze its associations with disease manifestations.

Methods: Data collected at time of diagnosis from patients with PsA included in the Dutch southwest Early Psoriatic Arthritis cohoRt (DEPAR) study were used. HRQOL was assessed using eight domains of the Short Form-36 (SF-36) questionnaire. Patients were classified based on primary manifestation in arthritis subtypes (i.e., mono-, oligo-, or polyarthritis) and other subtypes (i.e., enthesitis, dactylitis, and axial disease). In all patients, presence of arthritis, enthesitis, dactylitis, psoriasis and chronic inflammatory back pain was determined. Multivariable linear regression was used to determine associations of PsA manifestations with HRQOL.

Results: Of 405 patients, primary manifestation was peripheral arthritis in 320 (78 monoarthritis, 151 oligoarthritis, and 91 polyarthritis), enthesitis in 37, axial disease in 9 and dactylitis in 39. Mean scores of SF-36 domains were lower than the Dutch reference population and similar across arthritis subtypes. A higher number of enthesitis locations and tender joints, and presence of chronic back pain, were independently associated with worse SF-36 scores. Psoriasis and dactylitis were not associated with worse scores.

Conclusion: HRQOL was diminished in PsA at time of diagnosis compared to the Dutch reference population, and tender joints, enthesitis at clinical examination, and back pain as indicators of pain impacted HRQOL.

INTRODUCTION

Psoriatic arthritis (PsA) is a spondyloarthropathy that can present with arthritis, enthesitis, psoriasis, spondylitis and dactylitis.[1] PsA patients report lower health-related quality of life (HRQOL) than the general population and patients with psoriasis.[2-6] The reported burden of disease is substantial; however, HRQOL in PsA is studied only in patients with longstanding disease. It is unknown to what extent this burden of disease is already present at time of diagnosis before starting treatment. Also, very little is known about how much each disease manifestation impacts HRQOL.

One of the challenges in treating PsA is the heterogeneity of manifestations. In studies analyzing the effect of clinical variables on HRQOL in PsA patients, arthritis has been the only musculoskeletal manifestation investigated.[7, 8] Within PsA patients, arthritis was found to impair HRQOL. A study in PsA showed that psoriasis, which is known to affect HRQOL, had no additional effect on HRQOL in patients who already had PsA.[8] The Corrona registry, however, showed that patients with more skin involvement report more pain and disability than patients with less skin involvement. In all studies evaluating the effect of PsA manifestations on HRQOL, other PsA specific disease features such as dactylitis or enthesitis were not specifically evaluated. In making treatment decision, it is very important to know how all PsA manifestations affect HRQOL.

The main objectives of this real-life cohort study are (1) to describe the quality of life in newly diagnosed patients with PsA, and (2) to analyze the influence of swollen and tender joints, enthesitis, dactylitis, back complaints and skin involvement on HRQOL.

MATERIALS AND METHODS

Patients and Setting

Newly diagnosed patients with PsA were invited to participate in the Dutch southwest Early Psoriatic Arthritis cohoRt (DEPAR). The diagnosis was made by rheumatologists and based on expert opinion; no classification criteria were applied, to ensure enrolment of a population representative of daily clinical practice. All eligible patients with newly diagnosed PsA (aged ≥18 years, no current treatment with disease-modifying antirheumatic drugs [DMARDs] for joint complaints, and sufficient knowledge of the Dutch language) were asked to participate. Use of DMARDs for psoriasis and use of non-steroidal anti-inflammatory drugs were allowed. Patients were recruited in centers in the southwest of the Netherlands (1 academic hospital, 10 general hospitals, and 1 treatment center specialized in rheumatic care). For this analysis, baseline data from patients included between August 2013 and November 2016 was used. Written informed consent was obtained from all participants according to the Declaration of

Helsinki. The study was approved by the local medical research ethics committee of Erasmus MC, University Medical Center Rotterdam, the Netherlands (MEC-2012-549).

Patient and disease characteristics

Trained research nurses collected clinical data, including swollen and tender joint count (66 and 68 joints, respectively), enthesitis at clinical examination (Leeds Enthesitis Index [LEI][9] and Maastricht Ankylosing Spondylitis Enthesitis Score [MASES][10]), dactylitis (Leeds Dactylitis Index [LDI][11]), psoriasis (Psoriasis Area and Severity Index [PASI][12]), and a standardized history of complaints (including duration, musculoskeletal complaints, and back complaints). Psoriasis severity was categorized as absent (PASI = 0), mild (PASI > 0 and PASI ≤ 7), and moderate to severe (PASI > 7).[13] Patients were classified as having chronic back pain (CBP) if they reported chronic complaints of back pain for a duration of longer than 3 months at present or in the past 12 months, and with onset < 45 years of age. In these patients, fulfilment of Assessment of SpondyloArthritis international Society (ASAS) classification criteria for inflammatory back pain (IBP) was determined.[14] Disease subtype at time of diagnosis was determined by the rheumatologist and defined by primary presentation as monoarthritis (1 joint), oligoarthritis (2-4 joints) and polyarthritis (≥ 5 joints), and in case of absence of peripheral arthritis defined as enthesitis, dactylitis, or with axial involvement. A diagnosis of enthesitis was made based on patient-reported complaints of enthesitis and entheseal pain at subsequent clinical assessment by the physician. The subtyping was based on the most prominent musculoskeletal feature at presentation as assessed by the rheumatologist. Fulfillment of ClASsification criteria for Psoriatic ARthritis (CASPAR) was determined.[15]

Primary outcome of interest - HRQOL

HRQOL was assessed using the Short Form-36 (SF-36). This generic measure covers 8 domains: physical functioning (PF), physical role functioning (PR), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF), emotional role functioning (ER), and mental health (MH). With these separate domains, the physical component summary (PCS) and mental component summary (MCS) were calculated to provide a global score.[16] The domains have a range of 0 to 100 with a higher score representing a better state and were compared to domain scores of the Dutch reference population.[17] This reference population (n=1742) had a mean age of 47.6 years and 56% was male. The component summary scores were adjusted by the general Dutch population, resulting in norm-based scores with mean 50 (standard deviation [SD] 10). Patients filled out their questionnaires either online (92%) or on paper, shortly before or after their visit to the research nurse.

Statistical analysis

Patient characteristics were described using simple descriptive analysis techniques. To

evaluate the impact of each disease manifestation, domain scores in subgroups of arthritis (monoarthritis, oligoarthritis, and polyarthritis), enthesitis (present and absent), psoriasis (absent, mild, moderate-severe), dactylitis (present and absent) and back pain (no CBP, CBP-IBP+, and CBP-IBP-) were compared and differences were tested with Wilcoxon rank tests in case of 2 subgroups and Kruskal-Wallis tests in case of more subgroups. In subsequent univariable and multivariable linear regression analyses, we tested whether these associations were also present when adjusting the scores for the other disease manifestations. The dependent variables were the SF-36 PCS and SF-36 MCS. The SF-36 MCS was square-transformed to improve model fitting. Independent variables included in both models were age, sex, swollen joint count (66), tender joint count (68), number of enthesitis at clinical examination (LEI + MASES), presence of dactylitis (LDI>0), PASI, and presence of IBP. Interaction terms of enthesitis at clinical examination, tender joint count, and chronic back pain were tested. Complete cases were used in these analyses and with a sensitivity analysis the effects of patients with missing variables were tested. The variance inflation factor (VIF) was calculated in each model to test for multicollinearity. STATA 14.0 was used.

RESULTS

In November 2016, 405 patients with newly diagnosed PsA had been included. Table 1 shows patient characteristics at baseline. Mean age was 50 years (SD 13.8) and 49% was male. Median self-reported duration of complaints at time of diagnosis was 11.6 months (interquartile range [IQR] 3.9-32 months). The primary manifestation at time of diagnosis was monoarthritis in 78 patients (19%), oligoarthritis in 151 (37%), and polyarthritis in 91 (22%). Primary manifestation was in 37 (9%) enthesitis, 9 (2%) axial disease, and 39 (10%) dactylitis among patients without peripheral arthritis. Most patients had more than 1 feature present. In 186 of 404 patients (46%) enthesitis at clinical examination was present according to the LEI and/or MASES. Dactylitis was present in 51 patients (13%), 344 patients had active psoriasis (85%, median PASI score 2.6, IQR 1-4.7) and 57 (15%) fulfilled ASAS IBP criteria. The CASPAR criteria were fulfilled by 328 (81%) patients. Of the 77 that did not fulfill CASPAR criteria, 31 (8%) had a missing rheumatoid factor (RF) status, 24 (6%) only had a history or family history of psoriasis combined with negative RF, and 9 patients had a moderately positive RF and were negative for anti-cyclic citrullinated protein antibody.

The 62 (16%) patients with missing baseline questionnaires were not significantly different from the other patients (Supplemental Table 1). Overall, HRQOL was lower in patients with early PsA than in the Dutch reference population. The differences were greater in the physical domains (i.e. PF, PR, BP, and GH) while psychosocial domains (i.e. VI, SF, ER, and MH) were close to the healthy population (Figure 1A). SF-36 scores did not differ significantly among

Table 1. Patient characteristics of DEPAR cohort (n=405)

Characteristics	Values
Demographic characteristics	
Age, mean (SD)	50.1 (13.8)
Male, n (%)	200 (49)
Duration of complaints, months, median (IQR)	11.6 (3.9-32)
Paid employment, n (%)	216 (63)
CASPAR criteria[$], n (%)	328 (81)
Clinical characteristics	
BMI, mean (SD)	28.1 (5.2)
Tender joint count (68), median (IQR)	3 (1-7)
Swollen joint count (66), median (IQR)	2 (1-4)
Disease subtype, n (%)	
Monoarthritis	78 (19)
Oligoarthritis	151 (37)
Polyarthritis	91 (22)
Enthesitis	37 (9)
Axial Disease	9 (2)
Dactylitis	39 (10)
Enthesitis at clinical examination	
LEI > 0, n (%)	162 (40)
LEI in case of enthesitis, median (IQR)	2 (1-3)
MASES > 0, n (%)	136 (34)
MASES in case of enthesitis, median (IQR)	2 (1-3)
Dactylitis present, n (%)	51 (13)
Psoriasis	
PASI > 0, n (%)	344 (85)
PASI in case of psoriasis, median (IQR)	2.6 (1-4.7)
Family history of psoriasis in case of no active psoriasis, n (%)	36 (60)
CBP onset < 45 years of age*	147 (39)
Fulfillment of IBP criteria in CBP*	57 (15)

[$]Rheumatoid Factor status missing in 31 (8%), and 24 (6%) only history or family history of psoriasis with negative rheumatoid factor.

*Data on CBP in 380 patients.

DEPAR: Dutch southwest Early Psoriatic Arthritis cohoRt; SD: Standard Deviation; IQR: interquartile range; CASPAR: Classification criteria for Psoriatic Arthritis; BMI: body mass index; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Index; PASI: Psoriasis Area and Severity Index; CBP: chronic back pain, defined as presence of back pain complaints for more than 3 months at present or in the past 12 months; IBP: inflammatory back pain (criteria: ASAS criteria for IBP); ASAS: Assessment of SpondyloArthritis international Society.

Figure 1. SF-36 domain scores in subgroups

Health-related quality of life measured these domains of the SF-36: physical functioning (PF), physical role functioning (PR), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF), emotional role functioning (ER), and mental health (MH) (SF-36).

A: All patients

B: Arthritis subgroups

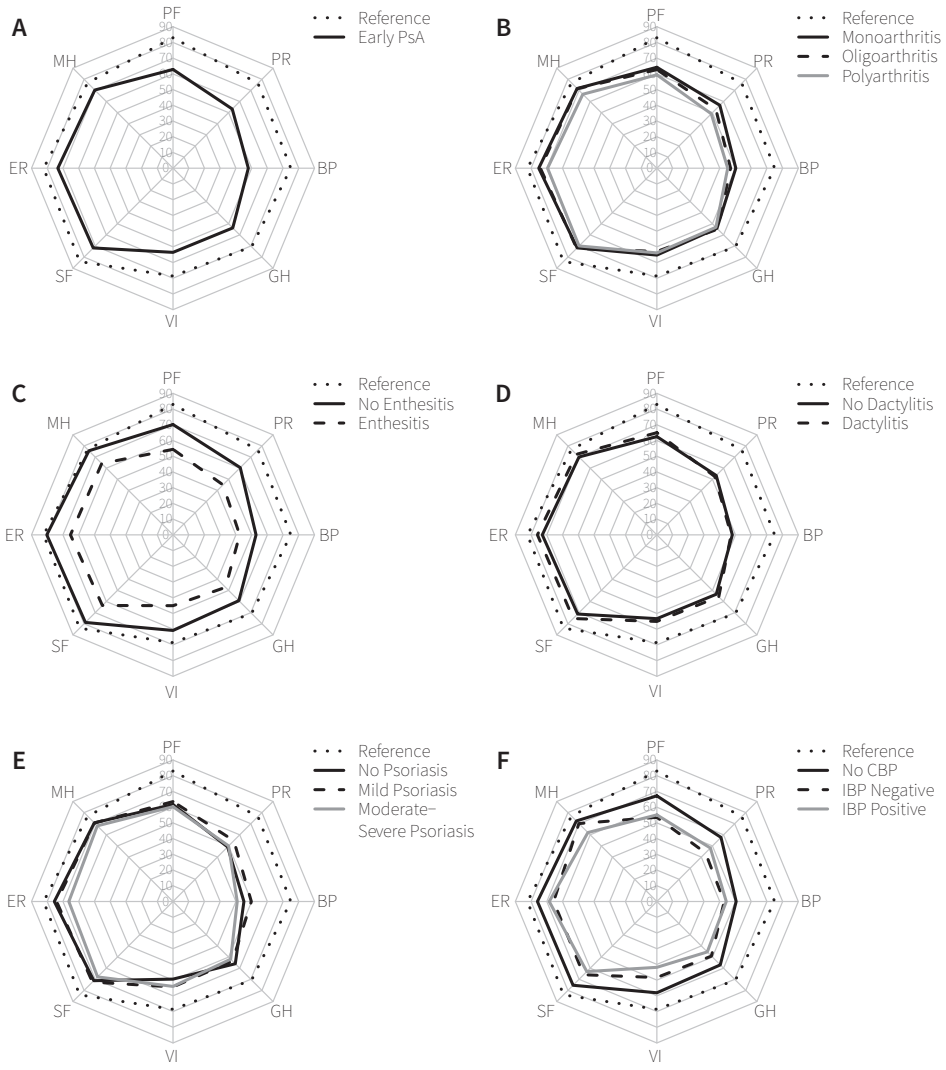
C: Enthesitis subgroups (LEI and/or MASES ≥ 0)

D: Dactylitis subgroups (LDI ≥ 0)

E: Psoriasis subgroups (PASI: none 0, mild 0-7, moderate/severe >7)

F: Back pain (no CBP with onset before 45 yrs, or CBP with or without IBP)

PsA: psoriatic arthritis; SF-36: Short Form-36; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; LDI: Leeds Dactylitis Index; PASI: Psoriasis Area and Severity Index; CBP: chronic back pain; IBP: inflammatory back pain.



patients with monoarthritis, oligoarthritis, or polyarthritis (Figure 1B, and Supplemental Table 2). Patients with enthesitis at clinical examination had significantly lower scores on all SF-36 domains than patients without enthesitis at clinical examination (Figure 1C, and Supplemental Table 3). Severity of psoriasis and presence of dactylitis did not significantly influence SF-36 scores (Figure 1D and Figure 1E, and Supplemental Table 4 and 5). Patients reporting CBP with onset before 45 years of age had significantly worse HRQOL in all domains of the SF-36 than those without. There was no significant difference in HRQOL between patients with CBP fulfilling ASAS IBP criteria and those not fulfilling ASAS IBP criteria, except for the MH domain, which is worse in patients fulfilling ASAS IBP criteria (Figure 1 F, Supplemental Table 6). Patients with enthesitis at clinical examination also reported IBP more often.

Table 2. Univariable and multivariable linear regression analysis of SF-36 PCS

	Univariable		Multivariable	
Variables	β	(95% CI)	β	(95% CI)
Age, yrs	-0.06	(-0.13;0.01)	-0.05	(-0.12;0.01)
Sex (male vs female)	-3.69	**(-5.51;-1.86)**	-2.39	**(-4.24;-0.55)**
Swollen joint count (66)	-0.28	**(-0.55;-0.01)**	-0.07	(-0.37;0.23)
Tender joint count (68)	-0.43	**(-0.59;-0.26)**	-0.25	**(-0.44;-0.05)**
No. enthesitis locations	-1.11	**(-1.47;-0.74)**	-0.84	**(-1.25;-0.43)**
Dactylitis (no vs yes)	-0.37	(-3.22;2.49)	-0.97	(-3.63;1.69)
PASI	-0.13	(-0.39;0.12)	-0.12	(-0.36;0.11)
Chronic back pain (no vs yes)	-2.71	(-5.31;-0.11)	-5.33	**(-9.56;-1.1)**
Enthesitis x chronic back pain	-2.45	(-5.48;0.58)	5.43	(0.38;10.48)

Analysis of complete cases (n=311), significant coefficients in bold face.
SF-36 PCS: Short Form-36 physical component summary; PASI: Psoriasis Area and Severity Index; CI: confidence interval.

Table 3. Univariable and Multivariable linear regression analysis of SF36-MCS (square transformation)

	Univariable		Multivariable	
Variables	β	(95% CI)	β	(95% CI)
Age, yrs	1.97	(-5.50;9.44)	1.3	(-6.03;8.63)
Sex (male vs female)	**-432**	**(-632;-231)**	**-292**	**(-499;-85)**
Swollen joint count (66)	5	(-25;35)	27	(-6;61)
Tender joint count (68)	**-40**	**(-59;-22)**	**-38**	**(-59;-16)**
No. enthesitis locations	**-93**	**(-134;-52)**	-38	(-83;7)
Dactylitis (no vs yes)	118	(-197;433)	104	(-195;402)
PASI	-15	(-43;13)	-16	(-43;10)
Chronic back pain (no vs yes)	**-660**	**(-987;-333)**	**-298**	**(-580;-16)**

Analysis of complete cases (n=317), significant coefficients in bold face.
MCS square-transformed for a better distribution. SF-36 MCS: Short Form-36 mental component summary; PASI: Psoriasis Area and Severity Index; CI: confidence interval.

To test the independent association between disease manifestations and HRQOL, univariable and multivariable linear regression analyses of the PCS and MCS were conducted (Table 2 and Table 3). In the univariable analysis, female sex, more tender joints, more enthesitis at clinical examination, and chronic back pain were associated with worse PCS and MCS scores. These factors remained significant in the multivariable analysis of the PCS. In the analysis of the MCS, the interaction term of enthesitis and CBP was not significant and removed from the final model. In the final multivariable model of the MCS, female sex and tender joint count were independently associated with worse MCS scores. In the sensitivity analysis of missing data, no relevant changes of βs and p-values occurred.

DISCUSSION

The main objective of this study was to describe HRQOL in PsA at time of diagnosis. Compared to the Dutch reference population, HRQOL was lower in patients with PsA and especially lower in the physical domains of the SF-36. Lower levels of HRQOL were observed in patients with more tender joints, more locations of enthesitis at clinical examinations, and patients with CBP. Because patients often presented with more than 1 disease manifestation, the contribution of each manifestation was evaluated in a multivariable analysis. Tender joints, enthesitis at clinical examination, and CBP were all independently associated with worse HRQOL. Psoriasis and presence of dactylitis did not result in loss of HRQOL as measured by the SF-36.

To our knowledge, no other studies have assessed HRQOL in a stage of disease this early. Husted et al. reported HRQOL of 631 established PsA patients with moderate to severe disease activity, and also showed that PsA lowers HRQOL.[7] Similar results were seen in a study of 551 veterans with PsA.[18] Many clinical trials, however, report a higher disease activity and a lower HRQOL before starting treatment than we found.[19-22] These data cannot directly be compared to our data, because the populations probably differ in terms of disease severity and selection of patients. It does, however, indicate that PsA is a severe chronic disease that already affects HRQOL at time of diagnosis, though the effect of disease in this usual-care population is not as great as in patients in which the first disease-modifying treatment did not suffice.

Within the PsA population, presence of tender joints, enthesitis at clinical examination, and CBP were associated with worse HRQOL, which shows that pain as a consequence of inflammation is an important determinant of HRQOL. Entheseal tenderness at clinical examination reflecting enthesitis is 1 of the sources of pain identified. It worsens HRQOL, even in patients who already have a polyarthritis. The relationship between enthesitis and HRQOL has not been investigated in PsA specifically, but some work has been done in other patients with spondyloarthritis (SpA). A study of 1505 patients with SpA, of whom 18% had PsA, showed

that patients with enthesitis at clinical examination reported lower disease-specific HRQOL.[23] Other studies in axial SpA found strong correlations between the total enthesitis score and lower scores on physical subscales of the SF-36.[24-26] No specific analysis in PsA was done. These and our findings suggest specific attention for enthesitis is needed in the treatment for PsA.

The validity of measuring enthesitis at clinical examination could be debated. Although joints are assessed for the presence of swelling and pain to detect arthritis, enthesitis does often not present with clearly visible signs of inflammation but with pain only. However, entheseal pain does not necessarily equal enthesitis; it could be caused by other enthesiopathies such as degenerative or metabolic processes.[27] Most cases of entheseal pain in PsA do seem to have an inflammatory origin, as it is known to resolve after biological treatment.[28,29] But in a small part of the patients, it may indicate a more general pain syndrome. In our study, patient generally reported enthesitis at only 1 to 3 locations, which is less likely in case of a general pain syndrome.

Psoriasis, present in 85% of patients, was usually mild and its influence on HRQOL was not detected with the SF-36. This may suggest psoriasis does not affect HRQOL in PsA. In studies comparing HRQOL in PsA and rheumatoid arthritis, emotional and mental health were more affected in PsA than in rheumatoid arthritis[2,30,31] and this difference was attributed to the presence of psoriasis in PsA patients. In patients with PsA, we did not see an effect of psoriasis on HRQOL, possibly because at time of diagnosis pain overshadowed skin involvement in its association with HRQOL. In addition, the effect of psoriasis symptoms such as itching and skin pain might not be detected in a general health questionnaire and may require Dermatology Life Quality Index or Skindex.

There are several strengths and limitations to this study. One of the strengths is that this study has a large population of patients with PsA, which makes it possible to analyze the disease in different subgroups of patients. In addition, patients with a new PsA diagnosis made by the rheumatologist were all eligible to participate if they had not yet received treatment for PsA. Our incident PsA cohort therefore reflects the population as seen in usual clinical practice, not influenced by classification criteria or criteria from trials. We were able to relate the burden of disease to the general population and compare patients with different manifestations by using the SF-36. However, by using this general questionnaire we possibly missed the disease-specific impact on HRQOL. With the data available, we were not able to distinguish CBP with inflammatory origin from lower back complaints commonly occurring in the general population.[32] Nevertheless, because the presence of CBP affects functioning, it is a sign that pain warrants attention in the treatment of PsA. Last, we only performed a cross-sectional analysis of HRQOL. Further evaluation is needed of the evolvement of manifestations and subsequent change in HRQOL over time.

We found that HRQOL was diminished in PsA at time of diagnosis compared with the

Dutch reference population and showed that tender joints, enthesitis at clinical examination, and presence of CBP impacted HRQOL. Pain is an important determinant of functioning in early disease, which warrants attention in the treatment of PsA.

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SUPPLEMENTAL DATA

In order to provide extra insight in the data besides visual representation from the figures in the manuscript, we added Supplemental Table 2-6 and performed non-parametric tests on all groups.

Supplemental Table 1. Demographic characteristics of patients with non-missing and missing questionnaires

	Non-missing questionnaires (n=341)	Missing questionnaires (n=64)	p-value
Demographic characteristics			
Age, mean (SD)	50 (14)	48 (14)	0.24
Male, n (%)	173 (51)	27 (42)	0.21
Duration of complaints, median months (IQR)	11.7 (4-34)	11.1 (3.5-26)	0.93
Clinical characteristics			
BMI, mean (SD)	28 (5)	28 (5)	0.37
Tender joint count (68), median (IQR)	3 (1-7)	3 (2-8.5)	0.05
Swollen joint count (66), median (IQR)	2 (1-4)	2 (1-4.5)	0.28
Disease subtype, n (%)			
Monoarthritis	65 (19)	14 (22)	
Oligoarthritis	128 (38)	23 (36)	
Polyarthritis	76 (22)	15 (23)	
Enthesitis	31 (9)	6 (9)	
Axial Disease	8 (2)	1 (2)	
Dactylitis	34 (10)	5 (8)	
Enthesitis			
LEI > 0, n (%)	119 (35)	17 (27)	0.19
LEI in case of enthesitis, median (IQR)	2 (1-3)	2 (1-3)	0.82
MASES > 0, n (%)	119 (35)	17 (27)	0.19
MASES in case of enthesitis, median (IQR)	2 (1-3)	2 (1-3)	0.27
Dactylitis present, n (%)	43 (13)	8 (13)	0.98
Psoriasis			
PASI > 0, n (%)	291 (86)	53 (83)	0.57
PASI in case of psoriasis, median (IQR)	2.6 (1-4.7)	2.5 (1-4.5)	0.85
CBP onset < 45 years of age	118 (37)	29 (47)	0.15
Fulfillment of IBP criteria in CBP	47 (42)	10 (36)	0.54

SD: Standard Deviation; IQR: interquartile range; BMI: body mass index; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Index; PASI: Psoriasis Area and Severity Index; CBP: chronic back pain, defined as presence of back pain complaints for more than 3 months at present or in the past 12 months; IBP: inflammatory back pain (criteria: ASAS criteria for IBP); ASAS: Assessment of SpondyloArthritis international Society.

Supplemental Table 2. SF-36 Domain scores in arthritis subgroups

	Monoarthritis (n=64)	Oligoarthritis (n=128)	Polyarthritis (n=77)
Physical Functioning (PF)	70 (45-85)	65 (45-80)	65 (40-80)
Physical Role Functioning (PR)	56 (38-75)	50 (25-75)	50 (25-63)
Bodily Pain (BP)	51 (41-62)	51 (32-62)	41 (31-62)
General Health (GH)	52 (44-67)	57 (40-72)	52 (37-67)
Vitality (VI)	56 (44-72)	56 (38-69)	50 (38-69)
Social Functioning (SF)	75 (56-88)	75 (50-100)	75 (50-88)
Emotional Role Functioning (ER)	83 (50-100)	75 (50-100)	75 (50-100)
Mental Health (MH)	75 (60-85)	75 (60-85)	70 (55-80)

Data shown as median (interquartile range).
Kruskal-Wallis tests comparing overall scores between subgroups, none significant.

Supplemental Table 3. SF-36 Domain scores in enthesitis subgroups

	Enthesitis - (n=184)	Enthesitis + (n=157)
Physical Functioning (PF)	75 (55-90)	58 (35-75)*
Physical Role Functioning (PR)	63 (38-84)	50 (25-63)*
Bodily Pain (BP)	51 (41-62)	41 (31-51)*
General Health (GH)	62 (45-72)	47 (35-57)*
Vitality (VI)	63 (44-75)	44 (31-56)*
Social Functioning (SF)	88 (63-100)	63 (50-88)*
Emotional Role Functioning (ER)	100 (58-100)	67 (50-100)*
Mental Health (MH)	80 (65-90)	65 (50-75)*

Data shown as median (interquartile range).
*$p < 0.05$ Wilcoxon rank tests.

Supplemental Table 4. SF-36 Domain scores in psoriasis subgroups

	No Psoriasis (n=50)	Mild Psoriasis (n=250)	Moderate/Severe Psoriasis (n=42)
Physical Functioning (PF)	65 (45-75)	68 (45-85)	63 (40-80)
Physical Role Functioning (PR)	50 (25-63)	50 (31-75)	50 (25-63)
Bodily Pain (BP)	51 (31-62)	51 (41-62)	41 (31-62)*
General Health (GH)	55 (42-67)	55 (40-67)	52 (35-67)
Vitality (VI)	47 (38-63)	56 (38-69)	56 (38-63)
Social Functioning (SF)	75 (50-100)	75 (50-100)	75 (50-88)
Emotional Role Functioning (ER)	83 (50-100)	75 (50-100)	75 (50-83)
Mental Health (MH)	73 (60-85)	75 (60-85)	73 (55-80)

Data shown as median (interquartile range).
*$p < 0.05$ Kruskal-Wallis tests comparing overall scores between subgroups.

Supplemental Table 5. SF-36 Domain scores in dactylitis subgroups

	Dactylitis - (n=278)	Dactylitis + (n=31)
Physical Functioning (PF)	65 (45-80)	70 (50-85)
Physical Role Functioning (PR)	50 (31-75)	56 (25-69)
Bodily Pain (BP)	51 (32-62)	41 (41-62)
General Health (GH)	52 (40-67)	62 (40-67)
Vitality (VI)	56 (38-69)	56 (44-69)
Social Functioning (SF)	75 (50-100)	75 (63-100)
Emotional Role Functioning (ER)	75 (50-100)	75 (58-100)
Mental Health (MH)	75 (56-85)	75 (65-90)

Data shown as median (interquartile range).
Wilcoxon rank test, none significant.

Supplemental Table 6. SF-36 Domain scores in chronic back pain subgroups

	no CBP (n=200)	CBP, IBP negative (n=66)	CBP, IBP positive (n=47)
Physical Functioning (PF)	70 (50-85)*	58 (30-75)	55 (40-75)
Physical Role Functioning (PR)	56 (41-81)*	44 (25-63)	50 (31-63)
Bodily Pain (BP)	51 (41-62)*	41 (31-61)	41 (31-62)
General Health (GH)	57 (44-72)*	47 (35-62)	45 (35-62)
Vitality (VI)	56 (44-75)*	50 (38-63)	38 (25-56)
Social Functioning (SF)	75 (63-100)*	63 (50-88)	63 (50-88)
Emotional Role Functioning (ER)	75 (58-100)*	67 (42-100)	75 (50-100)
Mental Health (MH)	75 (60-85)*	75 (55-85)	65 (50-80)#

Data shown as median (interquartile range).
*$p < 0.05$ Wilcoxon rank test comparing domain scores in no CBP onset < 45 yrs vs CBP onset < 45 yrs
#$p < 0.05$ Wilcoxon rank test comparing scores on domains within CBP, IBP fulfillment vs no IBP fulfillment
CBP: chronic back pain; IBP: inflammatory back pain (criteria: ASAS criteria for IBP); ASAS: Assessment of SpondyloArthritis international Society.

CHAPTER 5

Time to minimal disease activity in relation to quality of life, productivity and radiographic damage 1 year after diagnosis in psoriatic arthritis

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ABSTRACT

Background: In a cohort of patients with newly diagnosed psoriatic arthritis (PsA) who received usual care, we investigated the impact of time elapsed to minimal disease activity (MDA) on health-related quality of life (HRQOL), work productivity, and radiographic damage throughout the first year after diagnosis.

Methods: Data collected in the Dutch southwest early PsA cohort (DEPAR) study were analyzed. These 3-monthly data encompassed disease activity, HRQOL measured with the Short Form-36 (SF-36) Physical Component Summary (PCS) and Mental Component Summary; and productivity with the Productivity Cost Questionnaire. Radiographic damage was scored at baseline and at 12 months with the PsA-modified Sharp/van der Heijde score. Patients were classified by time to MDA as in early (within 3 months), late (at 6-12 months), and never MDA in the first year.

Results: We included 296 patients who had had their 1-year outpatient visit (mean age 51 years, 53% male). Ninety-six (32%) were classified as early MDA, 78 (26%) as late MDA, and 98 (33%) as never MDA. Data of 24 patients (8%) were missing. SF-36 PCS and productivity scores improved after gaining MDA, but remained low in never MDA patients. At 1 year, SF-36 PCS and productivity scores were similar in early and late MDA patients. Radiographic progression rate was low and similar in all groups.

Conclusion: Gaining MDA was associated with considerable improvement in HRQoL and functioning, irrespective of time to first MDA. In the one third of patients not in MDA in the first year, the disease had a substantial health impact.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease presenting with arthritis, enthesitis, spondylitis, dactylitis, and psoriasis.[1] As in other rheumatic diseases, chronic inflammation leads to progressive joint damage, increased disability and reduced life expectancy.[2-4] Treatment with disease-modifying antirheumatic drugs (DMARDs) can alleviate this inflammation and prevent these complications.[5, 6] Better clinical, functional, and structural outcomes have been achieved with the use of treat-to-target strategies in patients with rheumatoid arthritis.[7] This implies that treatment is intensified until a target of low disease activity is reached. This strategy has been recommended in the treatment of PsA as well,[8] although as yet there is no consensus of which target to use. Minimal disease activity (MDA) is one of the proposed treatment targets in PsA.

MDA is assumed to have been reached when at least 5 out of 7 PsA remission criteria are met.[9] In previous cross-sectional studies, a state of MDA was strongly related with better functioning and health-related quality of life (HRQOL).[10-12] Longitudinal studies confirming these findings are lacking. We need more information on how the state of MDA is related to long-term improvement in disability and whether achieving MDA early after the diagnosis results in better outcomes than achieving MDA at a later stage. We investigated the impact of time elapsed from diagnosis to MDA on HRQOL, productivity and radiographic damage at 1-year follow up in a cohort of patients newly diagnosed with PsA and receiving usual care. We established if patients had reached MDA early, late or never in the first year after diagnosis and how their HRQOL, work productivity and radiographic damage was throughout the first year after diagnosis.

METHODS

Patients and setting

We used data collected in the Dutch southwest Early Psoriatic Arthritis cohoRt (DEPAR) study, of which details are described elsewhere.[11] Patients with a new diagnosis of PsA are eligible to participate if they have not yet received treatment with DMARDs for PsA. Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study was approved by the medical research ethics committee of the Erasmus University Medical Center Rotterdam, the Netherlands (MEC-2012-549). We analyzed data collected between August 2013 and June 2017 and excluded patients with baseline visits after June 2016.

Data collection

In the first year, data are collected every 3 months. During the study visits, trained research

nurses collect clinical data, including swollen and tender joint count (resp. SJC 66 and TJC 68 joints), enthesitis at clinical examination (Leeds Enthesitis Index [LEI][13]), and psoriasis (Psoriasis Area and Severity Index [PASI][14]). Patients complete multiple questionnaires shortly before or after their visits. For this analysis we used data on the Short Form-36 (SF-36[15]); the Health Assessment Questionnaire (HAQ[16]); the Productivity Cost Questionnaire(PCQ[17]), and patient-reported Visual Analogue Scale (VAS) scores for global and pain.

Minimal Disease Activity

MDA state was determined at each visit within the first year. A state of MDA was assumed to have been reached if 5 of 7 MDA criteria were met: SJC ≤ 1, TJC ≤ 1, LEI ≤ 1, PASI ≤ 1, global VAS ≤ 20 mm, pain VAS ≤ 15 mm, HAQ ≤ 0.5.[9] In case of missing data of some criteria, MDA status was ascertained irrespective of the missing information (e.g. fulfilling 5 criteria and missing 2 criteria). If missing information could alter the MDA status (e.g. fulfilling 4 criteria and missing 2) we considered MDA status missing. If MDA status before and after a missing visit was equal (i.e. both MDA or both no MDA), we assumed that MDA status at the missing visit was equal to that state. Achieving MDA was classified as early if it had been achieved at baseline or at 3 months; as late if it was first achieved after 3 months but within the first year; and as never if it was not achieved in the first year. In addition, achieving MDA was classified as sustained if patients remained in MDA until their 1-year follow up visit.

Outcomes

Patients self-reported HRQOL with the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS). Work productivity was assessed with the PCQ, relating to work and productivity in the 4 weeks preceding the study visit. We determined employment status, absence, working hours, and productivity loss at work and at home throughout the first year. The actual number of productivity hours per week was calculated by subtracting hours of absence and productivity loss at work in hours from the total number of self-reported working hours.

Radiographs of the hand and feet obtained at baseline and after 1 year were scored twice, by 3 trained assessors separately. The assessors were blinded to the patient's identity and clinical data and scored the images in chronological order. According to the PsA-modified Sharp/Van der Heijde score (PsA-SHS), erosions and narrowing of hand and feet joints were scored with a maximum of 320 for erosions and 208 for joint space narrowing.[18] Differences in absolute score above 2 and differences in progression were discussed by the 2 assessors. Regarding the inter-rater reliability, the kappa statistics was 0.79 with absolute agreement of 99%. For each patient the mean of 2 scores was calculated. The smallest detectable difference (SDD) was 0.27. Progression was defined as an mean increase in PsA-SHS in the first year exceeding the SDD.

Statistical analysis

Differences in characteristics between MDA groups were tested with ANOVA tests and subsequent t-tests for continuous data and chi-squared tests for categorical data. The effect of time to MDA on outcomes after 1 year was analyzed with multiple linear regression analysis with outcomes SF-36 PCS, SF-36 MCS and productivity. The association of time to MDA (early vs. late, early vs. never and late vs. never) with the outcome was corrected for baseline SF-36 or productivity score, age, gender, symptom duration, DMARDs use, erosive disease at baseline, and baseline disease activity (baseline SJC, TJC, LEI, PASI, VAS global, VAS pain and HAQ). In the subset of patients using DMARDs in the first year, the same analysis was performed with the added variables time to start and duration of DMARD therapy. Linear mixed effects models were used to compare progression of outcomes between the 3 groups and to account for missing data. Baseline outcome score, baseline disease activity and erosive disease, age, gender, symptom duration, DMARD use, time, MDA group and interaction between time and MDA group were included in the fixed-effects part. Random intercepts were included in the random-effects part; an optimal random-effects structure was chosen based on the Akaike information criterion. Analyses were performed in STATA 15.1 and R-3.4.2.

RESULTS

In July 2017, 296 patients had had their 1-year visit and 268 (92%) could be assigned an MDA category. The mean age of the latter was 51.2 years (standard deviation (SD) 14), 142 were male (53%) and the median self-reported symptom duration was 1.0 years (interquartile range (IQR) 0.4-2.7, Table 1). Ninety-four (35%) had achieved MDA within 3 months (early MDA; 40 already in MDA at baseline), 77 (29%) between 6 and 12 months (late MDA), and 97 (36%) were never in MDA during the first year (never MDA). MDA state was sustained until 1 year by 43 (48%) early MDA patients and 46 (52%) late MDA patients. Patients early in MDA were significantly more often in MDA than patients late in MDA (of 5 visits: mean 3.6 vs. 1.8, $p < 0.01$).

Age, gender and symptom duration did not differ significantly between groups (Table 1). Patients never in MDA had significantly higher SJC, TJC, LEI, HAQ, PASI and VAS scores at baseline than patients in MDA (both early and late). Patients late in MDA had significantly higher disease activity than patients early in MDA on all domains but SJC and PASI. In the first year, DMARDs were prescribed to 210 patients (78%): methotrexate to 197 patients (74%) and biological therapy to 33 patients (12%).

Table 1. Patient characteristics of MDA groups and of total study population

	Early MDA (n= 94)	Late MDA (n=77)	Never MDA (n=97)
Age	50.1 ± 14	50.4 ± 13	52.8 ± 14
Male	57 (61)	41 (53)	44 (45)
Symptom duration in years	0.9 (0.2-2.4)	0.8 (0.3-1.5)	1.6 (0.4-4.1)
Disease Activity at baseline			
Swollen joint count (66)	1 (1-3)	3 (1-4)	2 (0-6)$
Tender joint count (68)	1 (0-3)	3 (2-7)*	5 (3-12)$
LEI	0 (0-0)	0 (0-1)*	1 (0-2)$
HAQ	0.13 (0.00-0.63)	0.63 (0.38-0.89)*	0.88 (0.63-1.38)$
PASI	1.5 (0.4-3.8)	2.3 (0.3-4.1)	3 (1.2-6.1)$
VAS Global	21 (9-37)	46 (24-66)*	55 (40-70)$
VAS Pain	17 (9-44)	47 (30-63)*	56 (44-74)$
Medication in first year			
Any DMARD	62 (66)	63 (82)*	85 (88)$
Methotrexate	57 (61)	61 (79)*	79 (81)$
Sulfasalazine	8 (9)	14 (18)	23 (24)$
Hydroxychloroquine	4 (4)	11 (14)	8 (8)
Leflunomide	8 (9)	8 (10)	17 (18)
Prednisone (oral)	13 (14)	14 (18)	18 (19)
Prednisone (intramuscular injection)	11 (12)	21 (27)*	34 (35)$
Prednisone (intra-articular injection)	29 (31)	27 (35)	15 (15)$
Biological	5 (5)	12 (16)*	16 (16)

Results shown as mean ± standard deviation, n (%) or median (interquartile range).

*Early vs Late MDA

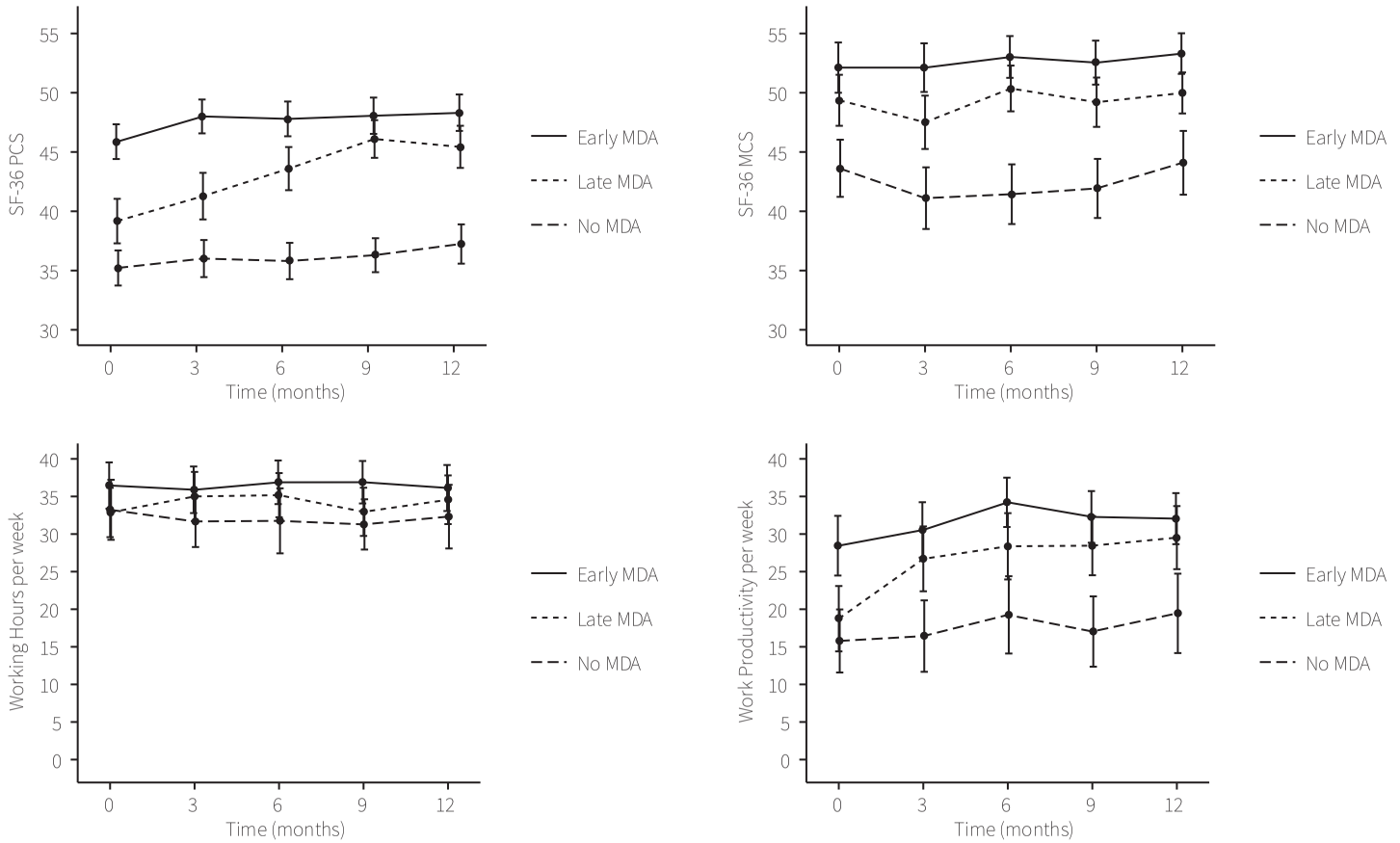
$MDA vs Never MDA $p < 0.05$ of t-test (continuous data) or chi-squared test (categorical data).

MDA: Minimal Disease Activity; Early MDA: MDA within 3 months; Late MDA: MDA between 3 and 12 months; Never MDA: no MDA within the first year. LEI: Leeds Enthesitis Index; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area and Severity Index; VAS: Visual Analogue Scale; DMARD: disease-modifying antirheumatic drug.

Quality of Life

The evolvement of the mean SF-36 PCS and SF-36 MCS scores per group is shown in Figure 1. The mean SF36-PSC score at 1 year was similar in the early and late MDA groups and was better than that in the never MDA group. Linear regression analysis of the SF-36 PCS score at 1 year, correcting for baseline score, gender, age, symptom duration, DMARD use, erosive disease at baseline, and baseline disease activity, showed that SF-36 PSC scores were significantly lower in the never MDA group than in the early MDA group (β -6.22, 95% CI -9.92, -2.51) and the late MDA group (β-7.86, 95% CI -11.52, -4.21, Table 2). At baseline, SF-36 PCS scores in the early MDA group were higher than those in the late MDA group and the never MDA group and had increased earlier than in the late MDA group. Linear mixed model analysis confirmed a difference in evolution over time between the 3 groups (likelihood ratio test (LRT) of interaction

Figure 1. HRQOL and productivity outcomes in the first year per MDA group
Results shown as mean and 95% confidence interval
SF-36: Short Form-36, PCS: Physical Component Summary, MCS: Mental Component Summary, MDA: Minimal Disease Activity.



between time and group: 34.5, p < 0.0001). Results in the subgroup of patients using DMARDs were similar in analyses correcting for duration of DMARD therapy and time to start DMARD therapy. The SF-36 MCS scores significantly differed between the 3 groups at baseline and remained fairly stable over time, which was confirmed by a non-significant interaction term of time and MDA in the linear mixed model analysis (LRT 1.73, p=0.42). At 1 year, the SF-36 MCS scores were significantly higher in the early MDA group than in the never MDA group (β -6.11, 95% CI -9.51, -2.70, Table 2).

Table 2. Linear regression models outcomes after 1 year of MDA groups

	β	(95% CI)
SF-36 PCS		
Early vs Late MDA	1.64	(-1.63; 4.91)
Early vs Never MDA	-6.22	(-9.92; -2.51)
Late vs Never MDA	-7.86	(-11.52; -4.21)
SF-36 MCS		
Early vs Late MDA	-2.83	(-6.14; 0.06)
Early vs Never MDA	-6.11	(-9.51; -2.70)
Late vs Never MDA	-3.07	(-6.16; 0.02)
Hours productivity loss		
Early vs Late MDA	0.78	(-5.63; 7.20)
Early vs Never MDA	-6.59	(-14.55; 1.37)
Late vs Never MDA	-7.38	(-14.38; -0.38)

All analyses corrected for baseline score, gender, age, symptom duration, use of disease-modifying antirheumatic drugs, erosive disease at baseline, and baseline disease activity (SJC66, TJC68, LEI, PASI, VAS global, VAS pain and HAQ).

Early MDA: MDA within 3 months; Late MDA: MDA between 3 and 12 months; Never MDA: no MDA within the first year. SF-36: Short Form-36; PCS: Physical Component Summary; MCS: Mental Component Summary.

Productivity

At 1 year, 207 of the 250 patients who had completed productivity questionnaires (83%) were in the employable age. Of those, 153 (74%) were actually employed: 64 (87%) early MDA, 48 (76%) late MDA and 41 (60%) never MDA patients (Table 3). Of the 53 unemployed subjects, 7 patients had become unemployed since diagnosis (1 early MDA, 3 late MDA and 3 never MDA), and 46 were already unemployed at baseline. At 1 year, 8 reported long-term sick leave (1 late MDA [2%] and 7 never MDA [17%]) and 21 short-term sick leave in the past 4 weeks (10 early MDA [16%], 5 late MDA [11%] and 6 never MDA [18%]). Work productivity loss in the past 4 weeks was reported most often by never MDA patients (71%, vs early MDA 27% and late MDA 30%). The mean productivity loss in patients with productivity loss did not differ significantly between the groups. Mean productivity at work of employed patients during the first year is shown in Figure 1. Productivity increased in the late MDA group from a baseline level similar

to that in the never MDA group, to a level similar to that in the early MDA group at 1-year follow up. This was confirmed in the linear regression analysis (Table 2): total productivity at work was significantly lower at 1 year in the never MDA group than in the late MDA group (β -7.38 , 95% CI -14.38, -0.38). The difference in evolution over time between the 3 groups was confirmed in a linear mixed model analysis (LRT of interaction between time and group 6.93, p = 0.032).

Table 3. Productivity outcomes after 1 year in MDA groups and in total study population

	Early MDA (n= 91)	Late MDA (n=73)	Never MDA (n=86)
Employable age	74 (81)	64 (88)	69 (80)
Employed	64 (87)	48 (76)	41 (60)
Working hours per week	36 (33-39)	35 (31-38)	32 (28-37)
Long-term absence	0 (0)	1 (2)	7 (17)
Short-term absence	10 (16)	5 (11)	6 (18)
Productivity loss at work	17 (27)	14 (30)	24 (71)
Hours per week productivity loss at work in patients with productivity loss	6.7 (4-10.5)	7.6 (4.8-16.8)	7.9 (4.5-18.9)
Total productivity at work	32 (29-35)	29 (25-34)	19 (14-25)

Results shown as mean (95% confidence interval) or n (%).
Early MDA: MDA within 3 months; Late MDA: MDA between 3 and 12; Never MDA: no MDA within first year. Total productivity = hours per week - absence - productivity loss at work, calculated in average per week over past 4 weeks.

Radiological damage

Mean PsA-SHS was 3.5 (SD 10; 16 missing) at baseline: the erosion score was 1.4 (SD 4.6) and the narrowing score was 2.2 (SD 5.9). Mean progression in 1 year was 0.38 (SD 1.4; 31 missing). Both baseline and progression scores did not differ significantly between the groups. The PsA-SHS score had progressed in 34 patients (14%): 8 in the early MDA group (10%), 11 in the late MDA group (17%) and 15 in the never MDA group (17%). Twenty-seven of the 34 patients with progression in the first year had already radiological damage at baseline.

DISCUSSION

In this cohort of newly diagnosed PsA patients receiving usual care, HRQOL and productivity throughout the first year after diagnosis were best in those who reached MDA early. At 1 year, however, patients late in MDA had achieved similar levels of HRQOL and work productivity as patients in the early MDA group, even though they were significantly shorter in MDA. Patients never in MDA had significantly lower scores throughout the first year and this remained so at their 1-year visit. Radiological progression did not differ in the first year between the 3 groups.

In a previous cross-sectional analysis in our cohort, having reached a state of MDA was

related to better HRQOL and functioning.[11] Other studies found similar results.[10, 12] The present study, however, is the first to address associations between gaining MDA and improvement of HRQOL and functioning over time. We found that gaining MDA, irrespective of the time elapsed since diagnosis, was associated with subsequent improvements of HRQOL and functioning over time. A slightly longer period of high disease activity was not associated with irreversible effects on HRQOL, functioning or radiology after 1 year.

Still, one third of all patients was not able to achieve MDA in the first year, and also did not show improvement in HRQOL and functioning. Even after correcting for baseline differences in disease activity and HRQOL scores, these patients' SF-36 PCS scores were 8 points lower than in the rest of the population. While patients in the late MDA group showed a clinically important improvement,[19] patients in the never MDA group did not. Furthermore, almost all patients in the latter group reported some form of impact on their work: becoming unemployed, sick leave or significant productivity loss at work. Thus, the impact of disease is severe and widespread in patients who do not achieve MDA. Interestingly, the baseline values of patients in the never MDA group did not differ much from those of patients in the late MDA group. If it were possible to predict achievement of MDA, patients at risk of not achieving MDA could be offered more intensive monitoring and earlier escalation of therapy.

Although analysis revealed a relation between time to MDA and HRQOL and productivity throughout the first year, a difference in radiological progression between the 3 groups was not shown. We assume that this is the consequence of a lack of power resulting from the strong association with damage present at baseline and the low prevalence of progression of 14%. Several causes for this low prevalence can be proposed. First, the 1-year follow up was too short to demonstrate differences in this population. Second, radiological evaluation comprised assessment of hand and feet joints only, which are not necessarily the joints most often affected in for example oligoarthritis or monoarthritis patients. Third, disease activity in this usual care population at time of inclusion was lower than that in, for example, trial populations, for which higher progression rates have been reported.[20, 21]

In this observational cohort, all patients with a new diagnosis of PsA were eligible to participate. They all received usual clinical care and their outcomes are therefore reflective of current clinical care. Their treatment differed, however, as treatment was not protocolized. This heterogeneity of treatment could be a confounder of the relation between time to MDA and outcomes. However, as choice of treatment was associated with disease activity, correcting for baseline disease activity and use of DMARDs in the analyses reduced a substantial part of the confounding. Further, correcting for time to starting DMARD therapy and time on DMARD therapy did not alter the effects of MDA group on the outcomes. Unmeasured confounding by treatment could be present but likely has not affected our conclusion, given the small differences in treatment between the three groups.

This study has several strengths and limitations. First, the population studied

reflects the population of PsA patients receiving usual care. Thus, our conclusions are better generalizable than those from trials or biological registries, where patient selection bias might have occurred. Second, reliability of the clinical data collection is ensured because data were collected by research nurses in a standardized manner during dedicated study visits. As a limitation, this could however introduce discrepancies between disease activity and treatment strategy, as the latter is determined by physicians based on their own assessment of disease activity, unaware of the nurse's assessment. We, therefore, cannot exclude incomplete correction for confounding by disease activity, although we also corrected for DMARD therapy. Another limitation is the heterogeneity of treatment strategies, as discussed above. There is a possibility of selective drop-out of patients. It could well be that patients with early MDA are discharged from clinical care and are less likely to complete follow up and be included in our 1-year analysis. As a consequence, the rates of MDA and productivity may be underestimated, in which case the true effect of MDA on productivity is even larger. Last, in our analysis of data after 1 year, we were not able to show a difference between groups in MDA within 1 year on outcomes at 1 year, but we might see a difference in future analyses of patients later in MDA and with longer follow up.

CONCLUSION

In conclusion, gaining MDA in the first year after diagnosis was associated with considerable improvement in HRQOL and functioning, irrespective of time to first MDA. This improvement was not seen in a third of early PsA patients not in MDA in their first year after diagnosis, whose impact of disease remained as substantial as at the time of diagnosis.

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CHAPTER 6

Burden of Psoriatic Arthritis according to different definitions of disease activity: comparing Minimal Disease Activity and the Disease Activity index for Psoriatic Arthritis

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ABSTRACT

Objective: Treat-to-target strategies have improved outcomes in rheumatic diseases. In psoriatic arthritis (PsA), the proposed targets are the multidimensional target Minimal Disease Activity (MDA) and the articular target Disease Activity index for PsA (DAPSA). The aim of this study was to compare the disease burden of PsA in patients with low disease activity according to the two definitions, MDA and DAPSA-low disease activity (DAPSA-LDA), 1 year after diagnosis.

Methods: We obtained data on MDA, DAPSA-LDA and disease burden 1 year after diagnosis for patients included in the Dutch southwest early PsA cohort. Disease burden was assessed in 2 domains: "Body functions", including the Short Form 36 Bodily Pain (SF36-BP) measure, and "Activity", including the Health Assessment Questionnaire (HAQ).

Results: Among the 292 patients included, 48% achieved MDA and 74% achieved DAPSA-LDA. Average scores for Body functions and Activity were better in patients who achieved MDA and those who achieved DAPSA-LDA. The scores were significantly better in the 46% of patients who achieved both MDA and DAPSA-LDA than in the 29% of patients who achieved only DAPSA-LDA. The average SF-36 BP score was higher in patients achieving both targets (73.8, 95% confidence interval [95% CI] 71.1-76.5) than in patients achieving only DAPSA-LDA (57.6, 95% CI 54.5-60.8). Similarly, mean HAQ scores measuring Activity were 0.21 (95% CI 0.15-0.26) and 0.63 (95% CI 0.53-0.72), respectively.

Conclusion: Among patients with newly diagnosed PsA, 48% achieved MDA and 74% achieved DAPSA-LDA after 1 year of receiving usual care. The average disease burden was better in patients who achieved MDA than those who achieved DAPSA-LDA. Also, patients who achieved only DAPSA-LDA reported worse outcomes than those who also achieved MDA.

INTRODUCTION

Psoriatic arthritis (PsA) belongs to the group of spondyloarthritides and is a heterogenic disease that involves both the skin (skin and nail psoriasis) and musculoskeletal features (arthritis, enthesitis spondylitis and dactylitis).[1, 2] Without treatment, most patients with PsA experience progressive joint damage and increasing disability and have a reduced life expectancy.[3-5]

Outcomes in rheumatic diseases have improved substantially over the last decades, largely due to the introduction of new therapies[6] and their use in treat-to-target strategies.[7] The objective of treat-to-target strategies is to achieve remission or a low or minimal disease activity state. Such a state of disease signifies that the disease burden at that time is low and long term worsening of functioning, quality of life and joint erosion are prevented. The TICOPA study has shown that a treat-to-target strategy is also effective in PsA cases.[8] In clinical practice however, treat-to-target has not been implemented in PsA as successfully as in rheumatoid arthritis. One of the main reasons is the lack of consensus on what the target should be in PsA. This is among other things related to the heterogenic nature of PsA. In the first trials in PsA, treatment effect was measured with targets used in rheumatoid arthritis and consequently mainly effects on arthritis were measured.[9] However, other disease manifestations, such as psoriasis, enthesitis and dactylitis, are considered important as well.[10] It is unknown whether inclusion of manifestations other than arthritis in a treatment target is associated with better patient outcomes.

Different disease activity measures have been proposed as treatment targets, such as the Psoriatic Arthritis Disease Activity Score, the Composite Psoriatic arthritis Disease Activity Index, the Disease activity index for Psoriatic Arthritis (DAPSA) and Minimal Disease Activity (MDA).[11-14] Of these measures, MDA and the DAPSA have recently both been recommended by international experts as the main targets.[15] A patient is considered to be in MDA if at least 5 out of 7 remission criteria are met. Remission is assessed by tender joint count in 68 joints (TJC68) and the swollen joint count in 66 joints (SJC66), psoriasis, enthesitis, patient's global and pain assessment as measured on a Visual Analogue Scale (VAS), and the Health Assessment Questionnaire (HAQ).[16] The DAPSA score is calculated using scores in TJC68 and SJC66 scores, patient's global and pain scores on a VAS, and the C-reactive protein (CRP) level.[11] DAPSA ≤ 14 represents a state of low disease activity (DAPSA-LDA), and a score of ≤ 4 represents remission (DAPSA-REM).[17] In contrast with MDA, DAPSA is a unidimensional target that mainly measures articular involvement.[15] Before choosing either one of the targets, more information is needed regarding how they relate to outcomes relevant to patients. Therefore, the aim of our study was to compare the PsA disease burden in patients with LDA according to the 2 different definitions, MDA and DAPSA-LDA, 1 year after diagnosis. In addition, we sought to determine which aspect of disease activity prevented patients from achieving MDA or DAPSA-LDA. Disease burden was assessed using the International Classification of Functioning, Disability and Health (ICF)

domains 'Body functions' and 'Activity'.[18]

PATIENTS AND METHODS

Patients and Setting

We used data collected from the Dutch southwest Early Psoriatic Arthritis cohoRt (DEPAR). Patients with newly diagnosed PsA were invited to participate in DEPAR. The diagnosis of PsA was made according to the expert opinion of the participating rheumatologists. All eligible patients with newly diagnosed PsA (ages ≥ 18 years and with no current treatment with disease-modifying antirheumatic drugs [DMARDs] for joint symptoms) were asked to participate. Use of DMARDs for psoriasis and use of nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed. Patients were recruited in centers in the south-west region of the Netherlands (1 academic hospital, 10 general hospitals and 1 treatment center specializing in rheumatic disease care). Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study was approved by the local medical research ethics committee at Erasmus Medical Center Rotterdam, the Netherlands (approval no. MEC-2012-549). Data from patients who were included between August 2013 and June 2017 were used. For this analysis, we used data 1 year after diagnosis and inclusion in DEPAR.

Patient and disease characteristics

Trained research nurses collected clinical data, including the SJC66 and TJC68, enthesitis at time of clinical examination (Leeds Enthesitis Index [LEI][19]), dactylitis (Leeds Dactylitis Index [LDI][20]) and psoriasis (Psoriasis Area and Severity Index [PASI][21]). Patients filled out questionnaires shortly before or after their visit to the research nurse. Multiple questionnaires are used to measure patient-reported disease activity and different outcomes, such as health-related quality of life. For this analysis we used the Short Form-36 (SF-36[22]), the HAQ[23], patient's global and pain scores on a VAS and the Bristol Rheumatoid Arthritis Fatigue (BRAF[24]) questionnaire.

Primary outcome

The impact of disease activity status as measured by MDA and DAPSA on the burden of disease was assessed in 2 domains of the World Health Organization (WHO) ICF.[18] The primary outcomes in the 'Body functions' domain were Bodily Pain (BP) as measured with the SF-36 and fatigue measured by the BRAF. In the 'Activity' domain the primary outcomes were Physical Functioning (PF) as measured by the SF-36 and HAQ scores. The range of scores for both SF-36 BP and SF-36 PF is 0-100, with a higher score representing better health status. For BRAF scores (range 0-70) and HAQ scores (range 0-3), a lower score represents better health status.

Disease activity status

Disease activity status was assessed using MDA and DAPSA. MDA is defined as having met at least 5 out of 7 remission criteria (SJC66 ≤ 1, TJC68 ≤ 1, LEI ≤ 1, PASI ≤ 1, patient's global score ≤ 2.0 cm [VAS], patient's pain score ≤ 1.5 cm [VAS], HAQ score ≤ 0.5). In addition, we determined which patients had achieved Very Low Disease Activity (VLDA), which is a stricter form of MDA in which all remission criteria for the MDA must be met.[25] The DAPSA was calculated as TJC68 + SJC66 + patient's global assessment score (VAS, cm) + pain's pain assessment score (VAS, cm) + CRP. Categories of DAPSA were DAPSA-LDA (DAPSA score ≤ 14) and DAPSA-REM (DAPSA score ≤ 4).[11, 17] Residual disease activity in the SJC66, TJC68, LEI, PASI, patient's global assessment score, patient's pain score, HAQ, dactylitis and CRP level was determined.

Statistics

Patient characteristics and fulfillment of targets were described using simple descriptive analysis techniques. First, the average disease burden in patients who had achieved MDA, DAPSA-LDA, VLDA or DAPSA-MDA was compared. Second, we tested whether patients with MDA had also achieved DAPSA-LDA and vice versa, or whether patients had a different disease status according to the 2 definitions. We compared disease burden in these categories as well, using ANOVA and t-tests. STATA 14.0 was used.

RESULTS

Achieving low disease activity

292 (58%) of 504 patients had attended their 12-months follow-up visit at time of the analysis. Their mean ± SD age was 51 ± 14 years, 150 were male (51%) and median symptom duration before diagnosis was 12 months (interquartile range 4-32) (Table 1). At the 12-month follow-up visit, 48% of patients had achieved in MDA and 74% had achieved DAPSA-LDA. According to stricter criteria, 13% of patients had achieved VLDA, and 32% had achieved DAPSA-REM (Figure 1). In 234 of the 292 patients, both DAPSA and MDA status were known. Reasons for missing data included incomplete questionnaires (40 patients) and missing CRP values (18 patients). Of these 234 patients, 58 (25%) had achieved neither DAPSA nor MDA, 67 (29%) had achieved DAPSA-LDA but not MDA, 2 (1%) had achieved MDA but not DAPSA-LDA, and 107 (46%) had achieved both MDA and DAPSA-LDA.

Disease burden according to different definitions of low disease activity

Disease burden was assessed using the WHO ICF domains 'Body functions' and 'Activity' and the average scores of patients with a low disease status according to different definitions were compared. Body functions were better in patients with MDA than in patients with DAPSA-

Table 1. Characteristics of the 292 patients at time of diagnosis

Age, mean ± SD years	51 (14)
Male sex, n (%)	150 (51)
Duration of symptoms, median (IQR) months	12 (4 - 32)
TJC68, median (IQR)	3 (1 - 8)
SJC66, median (IQR)	2 (1 - 5)
HAQ score, median (IQR)*	0.63 (0.25 - 1.00)
Elevated CRP level, n (%)#	71 (29)

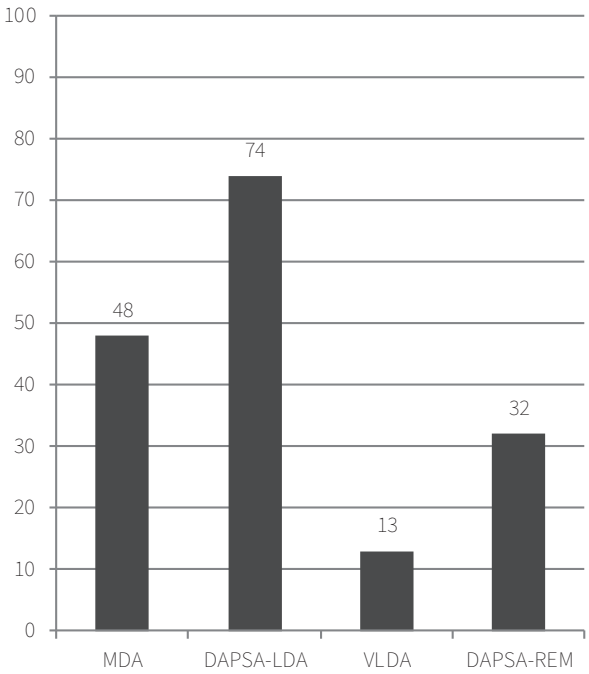
*41 missing questionnaires

#103 missing values.

SD: standard deviation; IQR: interquartile range; TJC68: tender joint count in 68 joints; SJC66: swollen joint count in 66 joints; HAQ: Health Assessment Questionnairre; CRP: C-reactive Protein.

Figure 1. Percentages of patients fulfilling definitions of low disease activity

MDA: Minimal Disease Activity; DAPSA-LDA: Disease Activity index for Psoriatic Arthritis – Low Disease Activity (DAPSA ≤ 14); VLDA: Very Low Disease Activity; DAPSA-REM: DAPSA Remission (DAPSA ≤ 4).



LDA as measured with SF-36 BP and BRAF. These scores were again slightly better in patients fulfilling the stricter VLDA and DAPSA-REM criteria. The mean SF-36 BP score was 73.6 (95% CI 70.9-76.3) in patients who achieved MDA, 67.6 (95% CI 65.2-69.9) in those with DAPSA-LDA, 83.0 (95% CI 78.5-87.4) in those with VLDA, and 77.3 (95% CI 74.1-80.6) in those who achieved DAPSA-REM (Figure 2). Similarly, impact on the domain Activity was significantly better in patients in MDA than those who achieved DAPSA-LDA, and was even better in those with VLDA

and those with DAPSA-REM (Figure 3). The mean SF-36 PF scores were 85.8 (95% CI 83.1-88.4) in patients who achieved MDA, 79.7 (95% CI 77.1-82.3) in those with DAPSA-LDA, 92.8 (95% CI 89.6-96.0) in those with VLDA, and 88.5 (95% CI 85.3-91.8) in those who achieved DAPSA-REM. The mean HAQ score were 0.22 (95% CI 0.17-0.27) in the MDA group, 0.37 (95% CI 0.31-0.43) in the DAPSA-LDA group, 0.06 (95% CI 0.02-0.10) in the VLDA group, and 0.16 (95% CI 0.10-0.22) in the DAPSA-REM group.

Measures of Body functions were significantly better in patients with both MDA and DAPSA-LDA than in patients with only DAPSA-LDA; mean SF-36 BP scores 73.8 (95% CI 71.1-76.5) and 57.6 (95% CI 54.5-60.8), respectively, and mean BRAF scores 11.8 (95% CI 9.8-13.9) and 20.8 (95% CI 17.7-23.9), respectively. A similar outcome was observed for measures of Activity; mean SF-36 PF scores 86.0 (95% CI 83.2-88.9) and 69.6 (95% CI 65.6-73.7), respectively, and mean HAQ scores 0.21 (95% CI 0.15-0.26) and 0.63 (95% CI 0.53-0.72), respectively. There was no statistically significant difference in Body functions and Activity between patients who achieved both MDA and DAPSA and those who achieved only MDA (Supplemental Figure 1 and Supplemental Figure 2, patients who achieved MDA but not DAPSA-LDA not shown because of small sample size).

Figure 2. 'Body functions' within different definitions of low disease activity
Data shown as mean with 95% confidence intervals.
SF-36: Short Form-36; BP: Bodily Pain; BRAF: Bristol Rheumatoid Arthritis Fatigue; MDA: Minimal Disease Activity; DAPSA-LDA: Disease Activity index for Psoriatic Arthritis – Low Disease Activity (DAPSA ≤ 14); VLDA: Very Low Disease Activity; DAPSA-REM: DAPSA Remission (DAPSA ≤ 4).

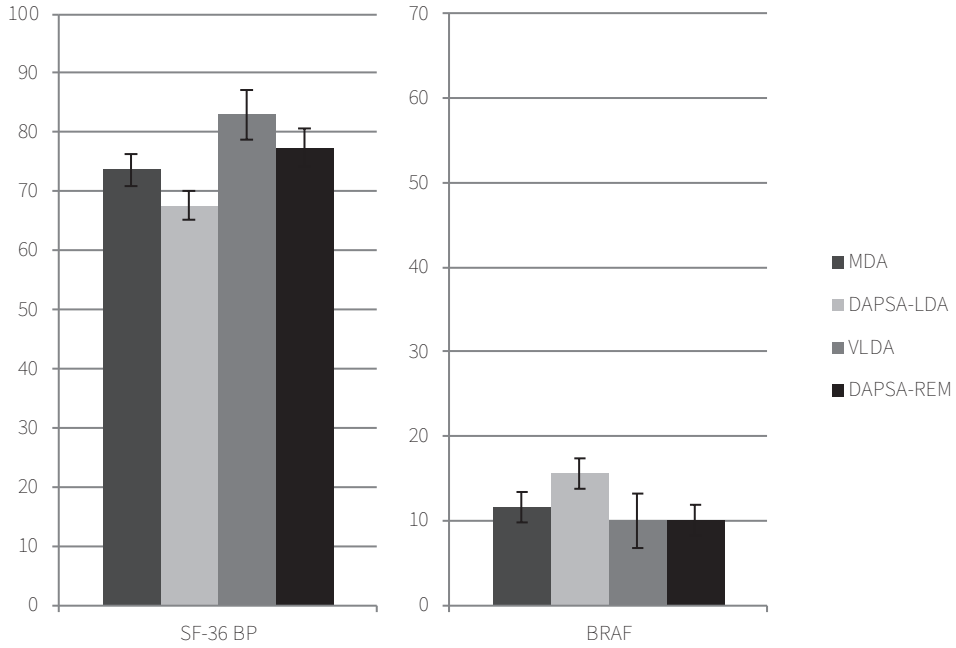
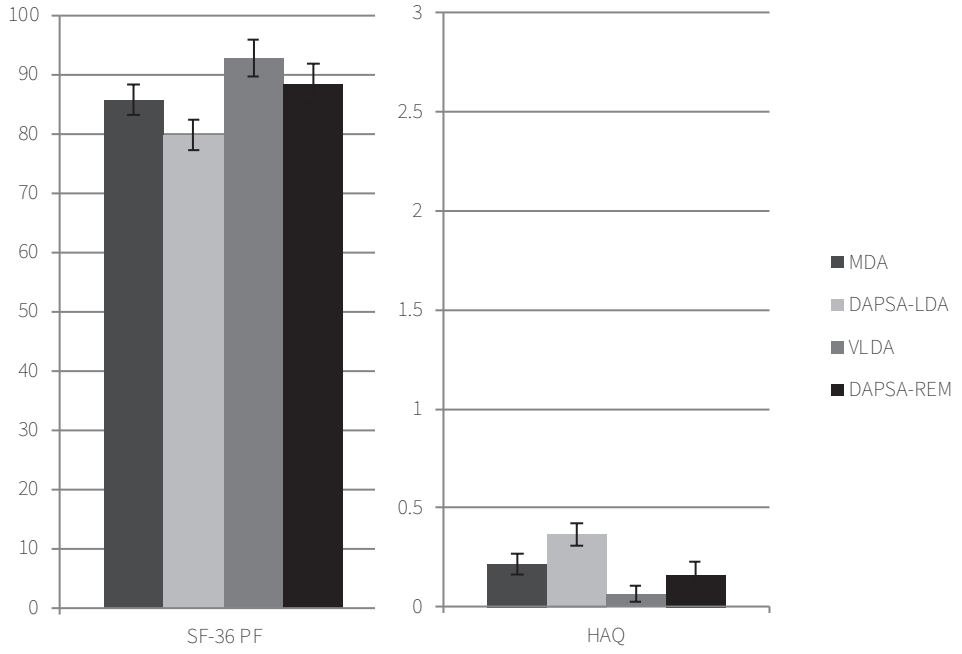


Figure 3. 'Activity' within different definitions of low disease activity
Data shown as mean with 95% confidence intervals.
SF-36: Short Form-36; PF: Physical Functioning; HAQ: Health Assessment Questionnaire; MDA: Minimal Disease Activity; DAPSA-LDA: Disease Activity index for Psoriatic Arthritis – Low Disease Activity (DAPSA ≤ 14); VLDA: Very Low Disease Activity; DAPSA-REM: DAPSA Remission (DAPSA ≤ 4).



Residual disease activity

In patients with low disease activity according to criteria for MDA or DAPSA, main areas of residual disease activity were the tender joints, psoriasis, patient's global assessment and pain assessment scores, and HAQ scores. These percentages were slightly higher in patients who achieved DAPSA-LDA than in those who achieved only MDA. None of the patients in VLDA had any residual disease activity. Clinical enthesitis, dactylitis and an elevated CRP level were rarely observed in all definitions of low disease activity (Table 2). In patients who had not achieved MDA, the domains with the highest residual activity were patient's pain score (91%), patient's global score (86%), HAQ score (67%), TJC68 (61%), and psoriasis (59%) (Table 3). More than 1 joint was swollen in 27%, and more than 1 clinical manifestation of enthesitis was present in 24% (LEI score > 1). Residual activity in patients who did not fulfill DAPSA-LDA criteria was similar to that in patients who did not fulfill the MDA criteria, except more patients in the former group had more than one tender joint (85%). Dactylitis in more than one digit was rarely observed. The patients who achieved only DAPSA-LDA most often had residual disease activity in patient's pain score (88%) and patient's global assessment score (78%), which prevented them from achieving MDA (Supplemental table 1).

Table 2. Residual disease activity in patients with low disease activity

	MDA (n=127)	DAPSA ≤ 14 (n=174)	VLDA (n=34)	DAPSA ≤ 4 (n=75)
TJC68 > 1	9	21	0	3
SJC66 > 1	6	13	0	3
PASI score > 1	34	45	0	41
Pain score > 1.5 (0-10 cm VAS)	26	48	0	17
Global score >2.0 (0-10 cm VAS)	18	41	0	4
HAQ score > 0.5	7	25	0	9
LEI score >1	1	6	0	3
Dactylitis	2	2	0	1
Elevated CRP level	6	10	0	3

Data shown as percentage of patients with residual disease activity.
TJC68: tender joint count in 68 joints; SJC66: swollen joint count in 66 joints; PASI: Psoriasis Area and Severity Index; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire; LEI: Leeds Enthesitis Index; CRP: C-reactive protein; MDA: Minimal Disease Activity; DAPSA: Disease Activity index for Psoriatic Arthritis; VDLA: Very Low Disease Activity.

Table 3. Residual Disease Activity in patients with high disease activity

	No MDA (n=137)	DAPSA > 14 (n=60)	no VLDA (n=218)	DAPSA > 4 (n=159)
TJC68 > 1	61	85	42	54
SJC66 > 1	27	33	20	25
PASI score > 1	59	53	54	50
Pain score > 1.5 (0-10 cm VAS)	91	98	70	82
Global score >2.0 (0-10 cm VAS)	86	95	63	79
HAQ score > 0.5	67	82	45	54
LEI score >1	24	32	31	17
Dactylitis	3	3	3	3
Elevated CRP level	16	17	14	16

Data shown as percentage of patients with residual disease activity.
TJC68: tender joint count in 68 joints; SJC66: swollen joint count in 66 joints; PASI: Psoriasis Area and Severity Index; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire; LEI: Leeds Enthesitis Index; CRP: C-reactive protein; MDA: Minimal Disease Activity; DAPSA: Disease Activity index for Psoriatic Arthritis; VDLA: Very Low Disease Activity.

DISCUSSION

In patients receiving usual care, in which treatment is not directed at achieving a specific PsA target, we did not observe large differences in average disease burden between PsA patients who achieved either MDA or DAPSA-LDA. In addition, we showed that patients with MDA usually also were had DAPSA-LDA. In contrast, not all patients with DAPSA-LDA had achieved

MDA. In a subsequent analysis of the burden of disease in these patients, we showed that patients achieving both targets reported better Body functions and Activity compared with those achieving only DAPSA-LDA. It seems that this subgroup of patients warranted more attention but were regarded as having low disease activity as determined using the DAPSA score. No or very little residual disease activity was measured in patients achieving VLDA or DAPSA-REM. However, only 13% of patient receiving usual care reached that target.

Our study is unique in the sense that we compared different targets and their relationship to the disease burden in patients with early PsA. Previous studies have shown high agreement between MDA and DAPSA; however the investigators in those studies were not able to determine whether these groups differed in terms of disease burden.[26, 27] Investigators in other studies did assess the burden of disease in patients fulfilling only 1 of the targets compared with those not fulfilling that target. It was shown in those studies that patients achieving the target had better scores for patient-reported outcomes compared with patients in whom the target as not achieved.[28-31]

Besides the target being related to better outcomes, it should also be feasible to use in clinical practice. In patients with MDA, the presence of enthesitis, dactylitis, and psoriasis must be assessed additionally, although such an assessment probably was done during routine care, because the recommended treatment depends on the domain involved.[32, 33] In contrast, a high DAPSA score indicates that treatment should be intensified, but it is less informative for determining how it should be intensified, because the choice of treatment depends on the domains involved. One of the reasons why patients who achieve both MDA and DAPSA report better outcomes than patients who achieve only DAPSA-LDA, is that the HAQ is also included in the criteria for MDA. A higher HAQ score in the patients who achieved DAPSA only could be the result of these patients not achieving MDA because of a high HAQ score. However, patients with only DAPSA-LDA also had higher PASI scores, global and pain scores, and higher SJC66 and TJC68 scores. The impact of psoriasis was recently demonstrated by Mease et al.,[29] in which patients enrolled in the Consortium of Rheumatology Researchers of North America Registry who had greater skin involvement more often had not achieved MDA and also had poorer functional status. Furthermore, the overall burden of disease in patients with MDA did not change when we excluded the HAQ score as a remission criterion for MDA.

Studying the true value of different targets in the treatment of PsA ideally would be investigated in a large randomized clinical trial, studying treat-to-target strategies, and randomizing patients to treat-to-target care with different targets. Such data are currently not available. Therefore, we used the second-best alternative, a large observational cohort of patients with early PsA. Use of this approach causes some challenges in interpreting the results. Rheumatologists were not instructed to treat patients according to a certain target. We do not know whether treatment would have differed between patients treated to target with either MDA or DAPSA, if they would have been randomized. In the current study, after

12 months of treatment, patients achieving only DAPSA-LDA had a higher burden of disease compared with patients who achieved both targets. Whether this gap would have been resolved with treatment remains to be determined. For example, comorbidities could influence the subjective elements of disease activity.[34, 35] Irrespective of the disease activity measure that is used, in daily clinical care disease activity always needs to be interpreted by the treating physician. A second challenge in the interpretation of our results is that in this real life cohort study, selection bias may have occurred. Some patients were lost to follow up and did not have a 12-month assessment. This occurrence could be related to disease activity as well, because some patients were discharged from care by the rheumatologist and subsequently did not visit the research nurse when invited. The data we present are representative of the population visiting the rheumatologist 1 year after diagnosis, instead of all patients 1 year after diagnosis.

In conclusion, in our study of early PsA, no large differences were observed in the disease burden between patients achieving MDA or DAPSA-LDA while receiving current usual care, because most patients who achieved MDA also achieved DAPSA-LDA. However, patients who reached both targets reported better Body functions and Activity compared with those who achieved only DAPSA-LDA. It appears that MDA is more difficult to achieve, but aiming for MDA even after DAPSA-LDA is achieved potentially results in better outcomes for patients.

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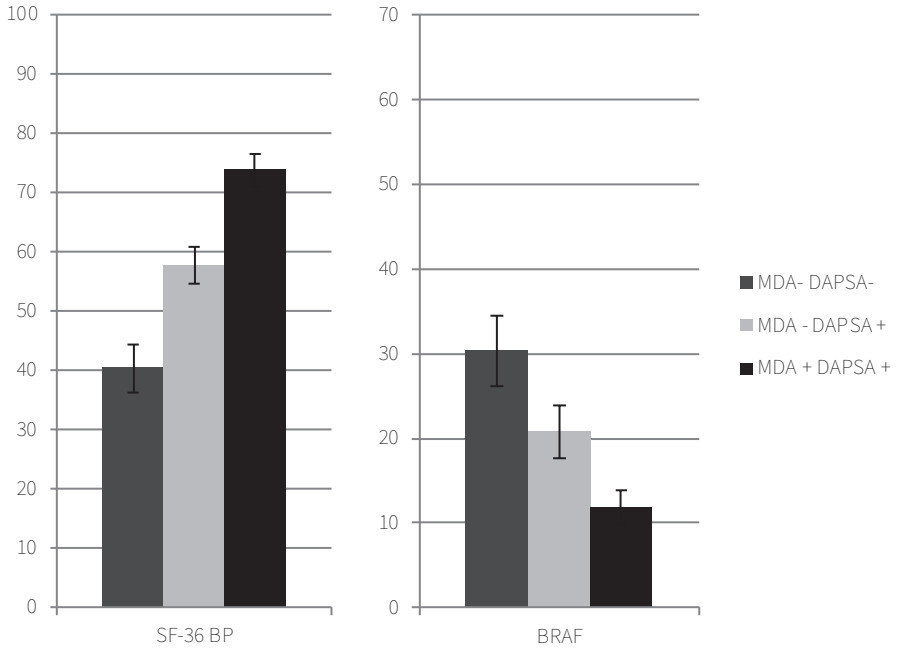
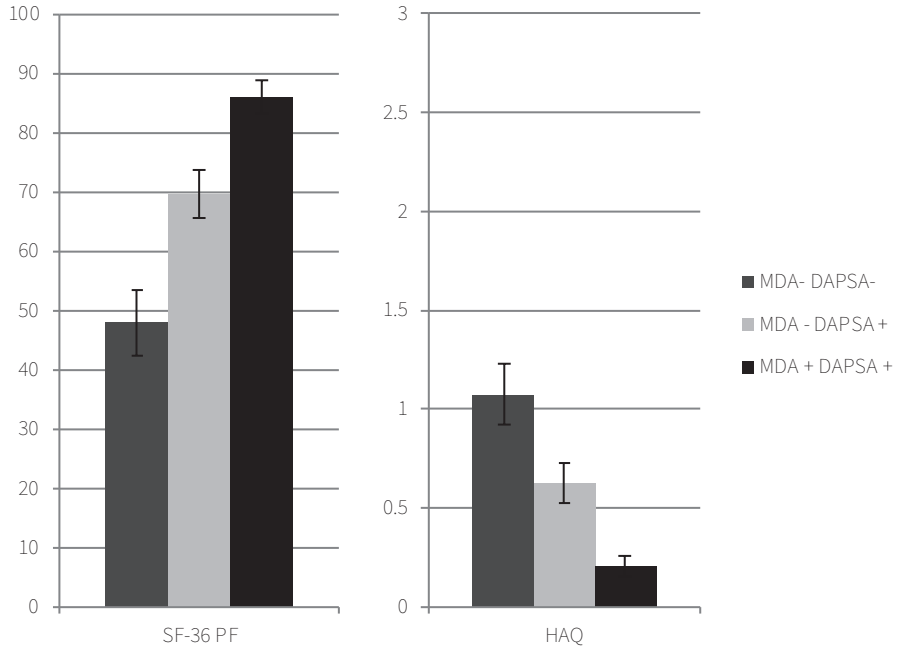
SUPPLEMENTAL DATA

Supplemental Figure 1. Body Functions in categories of MDA and DAPSA
Data shown as mean with 95% confidence intervals.
SF-36: Short Form-36; BP: Bodily Pain; BRAF: Bristol Rheumatoid Arthritis Fatigue; MDA-: not in Minimal Disease Activity (MDA); MDA+: in MDA; DAPSA-: not in Disease Activity index for Psoriatic Arthritis – Low Disease Activity (DAPSA > 14); DAPSA+: in DAPSA-LDA (DAPSA ≤ 14).



Supplemental Figure 2. Activity in categories of MDA and DAPSA
Data shown as mean with 95% confidence intervals.
SF-36: Short Form-36, PF: Physical Functioning: HAQ: Health Assessment Questionnaire, MDA-: not in Minimal Disease Activity (MDA); MDA+: in MDA; DAPSA-: not in Disease Activity index for Psoriatic Arthritis – Low Disease Activity (DAPSA > 14); DAPSA+: in DAPSA-LDA (DAPSA ≤ 14).



Supplemental Table 1. Residual Disease Activity in MDA and DAPSA categories

	MDA -		MDA +	
	DAPSA - (n=58)	DAPSA + (n=67)	DAPSA - (n=2)	DAPSA + (n=107)
TJC68 > 1	86	40	50	9
SJC66 > 1	33	22	50	7
PASI score > 1	55	58	0	36
Pain score > 1.5 (0-10 cm VAS)	100	88	50	23
Global score >2.0 (0-10 cm VAS)	97	78	50	18
HAQ score > 0.5	84	54	0	7
LEI score >1	33	13	0	1
Dactylitis	3	3	0	2
Elevated CRP level	16	18	50	6

Percentage of patients with residual disease activity.
TJC68: tender joint count in 68 joints; SJC66: swollen joint count in 66 joints; PASI: Psoriasis Area and Severity Index, VAS: Visual Analogue Scale, HAQ: Health Assessment Questionnaire, LEI: Leeds Enthesitis Index, CRP: C-reactive protein, MDA: Minimal Disease Activity, DAPSA: Disease Activity index for Psoriatic Arthritis.

CHAPTER 8

General discussion

Psoriatic arthritis (PsA) is a heterogeneous disease, in which patients can suffer from different musculoskeletal and dermatological manifestations. With treatment, the disabling consequences of the disease can be altered, and the chances of doing so are probably highest at an early stage of the disease.[1-4] We do however need more knowledge on disease activity and outcomes at time of diagnosis and in the early course of disease. The aims of this thesis therefore were to investigate in early PsA:

- ultrasound abnormalities of the entheses
- burden of disease at time of diagnosis and its relation with disease manifestations
- the relation between time to minimal disease activity and outcomes
- performance of disease activity measures

These questions were addressed in the DEPAR study (Dutch southwest Early Psoriatic Arthritis cohoRt) and its sub-studies. Patients with a new diagnosis of PsA were eligible to participate in DEPAR. They were seen for a baseline assessment before starting treatment with disease-modifying antirheumatic drug (DMARD) therapy for PsA. DMARD use with indication of psoriasis and use of non-steroidal anti-inflammatory drugs were allowed. Patients visited research nurses for clinical assessment and completed questionnaires every 3 months in their first year after inclusion. A subset of patients underwent sonographic evaluation of the entheses at baseline, and these data were compared with those of patients with established disease and with those young, healthy volunteers. In a second sub-study, a larger group of established PsA patients were assessed, together with an older control group of healthy volunteers, to determine which clinical factors in PsA patients were associated with having ultrasound abnormalities.

ULTRASOUND ABNORMALITIES OF THE ENTHESES

Though it is well known that enthesitis is a manifestation of PsA, no gold standard or a definition of the diagnosis is available. There is an abundance of evidence showing enthesitis is related to PsA: patients report complaints and tenderness of entheses at clinical examination; in imaging abnormalities we recognize signs of inflammation and signs of structural consequences of chronic inflammation;[5, 6] and in clinical trials in which medication aimed at reducing inflammation is tested, patients report improvement of their pain in the entheses.[7] Several researchers even propose that enthesitis could be the primary source of inflammation and synovitis is a result of extension of inflammation at the enthesis.[8] Our clinical interest however is the individual patient, for whom it needs to be decided whether or not treatment is indicated because of PsA-related enthesitis.

In an individual patient, it is often difficult to determine presence of enthesitis with clinical examination alone. Tendon complaints occur frequently in the healthy population,[9, 10] and are related to several other causes, such as metabolic, degenerative or mechanical pathologies.[11] The presence of inflammatory enthesitis might be distinguished from other pathologies with imaging, as is done with ultrasound in patients suspected of arthritis. In these patients, grey-scale signs of synovitis and presence of power Doppler (PD) as a measure of increased vascularisation are interpreted as indicators of inflammation.[12] The same interpretation has been applied to the enthesis, but entheseal tissue differs substantially from synovial tissue. The enthesis has a more tight, fibrillary organisation, is barely vascularized or innervated, and is known to regenerate at a slow rate.[8] Inflammation of the enthesis might give a different aspect on ultrasound than arthritis or might be less visible, so we need more knowledge on the difference in aspect of entheses of PsA patients and healthy volunteers.

In the first ultrasound study, we performed a comparison of extreme cases. For the study of 'normal' enthesis, we chose to investigate the entheses of young, healthy volunteers as we expected their entheses to be fully matured, but having suffered the least possible degenerative, mechanical or metabolic stress. Interestingly, many signs we would have interpreted as active inflammation on ultrasound were present in these young, healthy volunteers, as well as in the older healthy control we investigated in the second ultrasound study. This left us questioning whether these sonographic signs were truly related to inflammation or rather reflected normal physiology.

The signs suggestive of enthesitis that were frequently present in healthy volunteers were increased thickness and PD signal. With respect to increased thickness, we strongly suspect that the reference values used in the MAdrid Sonographic Enthesitis Index (MASEI) are not suitable for all entheses. This could be caused by the way these references values were determined. For example, for the cut-off for the proximal and distal patellar tendon entheses, data from cadaveric limbs of humans aged 67 to 87 were used.[13] We chose to exclude the assessment of increased thickness of all knee entheses as it did not seem that specific to entheses of PsA patients. Alternatively, age and gender specific reference values or the aspect of the entheses (e.g. a bulging aspect) could be used in the assessment of increased thickness. Also, considering that the young, healthy volunteers had a more physically active life style and suffered less from obesity than patients, we suspected increased thickness and PD signals were part of the physiological reaction of entheses to physical activity. These signs were also found more often in patients that reported not to avoid physical activity.

Not all that glittered was enthesitis related to PsA, but we certainly did observe differences between entheses of patients and those of healthy volunteers. Patients with PsA had in fact more structural damage of the entheses, both compared with young volunteers and with an older control group of healthy volunteers. This is seen in other studies comparing PsA and healthy volunteers as well.[14, 15] These signs of structural damage of the entheses could

be interpreted as cumulative exposure of the entheses to inflammation and as a sign of PsA. In our multivariable analysis of factors associated with structural damage within PsA patients, only age was associated with structural damage. It is suggestive for an effect of time. Corrected for age, disease duration had no additional association with structural damage, but both are strongly correlated. To test the prognostic value of structural changes of the entheses on ultrasound, prospective observational studies are needed.

Our studies of ultrasound in enthesitis had an exploratory nature. We did not have the power to assess less strong effects or effects with a low prevalence. Also, both studies have a cross-sectional design, which means that we could not assess the direction of the relationship. We realize that the relations between physical activity, avoiding of physical activity, obesity, disease activity, and medication use are not captured in a single model, even without considering their impact on ultrasound of the entheses. These need to be studied in observational studies, preferably one investigating the efficacy of physical activity or medical therapy on enthesitis. Instead of trying to diagnose enthesitis, we could test whether imaging is able to diagnose therapy-responsive enthesitis.

BURDEN OF DISEASE AT TIME OF DIAGNOSIS

At time of diagnosis and before starting treatment for PsA, patients had a significantly reduced health-related quality of life (HRQOL). The disease had a clinically relevant impact on mental aspects of HRQOL, and an even bigger impact on the physical aspects of HRQOL. Reduction of HRQOL was highest in those patients reporting more tender joints, enthesitis at clinical examination, chronic back pain, or a combination of those. The number of swollen joints, presence of dactylitis and severity of psoriasis had no additional impact on HRQOL at the time of diagnosis. Our data affirm the importance of taking all manifestations into account when choosing treatment, because manifestations other than arthritis also add to the burden of disease.

The vast majority of patients in DEPAR received methotrexate as first treatment, indicating that arthritis is initially the main focus of therapy, despite presence of other manifestations. The European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines for treatment of PsA, however, recommend not to use methotrexate if manifestations of enthesitis or axial involvement are also present. Reluctance to adhere to these guidelines could be explained by the level of evidence for each of the recommendations, which is higher for treatment of arthritis and psoriasis than it is for that of other manifestations. Enthesitis is only a secondary outcome in trials including patients with severe arthritis and/or severe psoriasis.[7] Also, absence of evidence might be interpreted as evidence of absence: many DMARDs and other

therapies such as physical therapy have not been studied in randomized controlled trials. Similarly, methotrexate is used extensively because of clinical experience rather than because of evidence from randomized trials. We have shown that these other manifestations are very relevant to patients, so more evidence of treatment effects of these other manifestations is needed.

A second explanation for the reluctance to choose other treatment than methotrexate, is the uncertainty of these other manifestations being related to PsA, as we have described above for enthesitis. With respect to disease activity, pain and HRQOL, physicians are exceptionally often concerned with the phenomenon of fibromyalgia. We indeed believe that comorbidities, fibromyalgia being one of them, modify the relation between disease activity and HRQOL and that in some patients, PsA treatment will not improve HRQOL. Fibromyalgia is characterized by widespread pain, while many patients in our cohort reported having only one or a few tender entheses. Also, trials have shown that enthesitis indeed can be improved with biological DMARDs, confirming an inflammatory origin.[7] Further, fibromyalgia is a diagnosis per exclusionem: it can only be diagnosed if the pain cannot be explained by another disorder.[16] At time of PsA diagnosis, pain is more likely to be related to inflammation than to structural damage or central sensitization. PsA-related enthesitis should not be miscalled fibromyalgia, as it might lead to underestimation of disease burden and possibly deprivation of effective therapy.

Similar to the problem of relating enthesitis to PsA, diagnosing axial involvement cannot be done with clinical evaluation alone. Many believe the pattern of back involvement in patients with PsA differs from the pattern in patients with axial SpA.[17, 18] Aydin et al. reported that the Assessment of Spondyloarthritis international Society criteria for inflammatory back pain have a lower sensitivity in PsA than in axial SpA, which could lead to underdiagnosis of axial involvement in PsA.[19] In our study, a few patients were diagnosed with a predominantly axial phenotype, but axial involvement could be present in other patients as well. We showed that chronic back pain is an important determinant of HRQOL in patients, suggesting that more attention to axial involvement in PsA is justified.

Our findings of disease burden and its relation with manifestations can be translated to patients with a new diagnosis, but this relation might change with progression of the disease. The pattern of manifestations is known to change over time within patients,[20] and use of coping mechanisms might change impact of disease manifestations by means of response shift. The relation should be studied longitudinally, to assess whether burden of disease is relieved if the manifestations are treated successfully.

TIME TO MINIMAL DISEASE ACTIVITY

We hypothesized that patients who were treated successfully earlier in the disease had better outcomes 1 year after diagnosis than patients in whom treatment was successful later. We defined successful treatment as achieving Minimal Disease Activity (MDA), and related this to outcomes at 1 year after diagnosis. We found a third of patients was in MDA early and a third late, and a third was not in MDA in the first year after diagnosis of PsA. In patients who achieved MDA, disability and burden of disease improved once MDA was achieved. Patients in the early group were significantly longer in MDA in the first year, and consequently, they had lower burden and better physical functioning throughout the first year. The late group benefitted less from achieving MDA throughout the first year, but were still able to achieve the same level of physical functioning and disease burden as patients who achieved MDA early. From the perspective of outcomes after 1 year, the therapeutic window of opportunity has not closed after the first 3 months after diagnosis of PsA. Future studies of longer follow up of these patients are needed, to assess whether disease activity and outcomes remain similar for patients who have achieved MDA in their first year after diagnosis.

Patients who achieved MDA early had lower disease activity and lower disease burden at baseline, and had sooner reached a stable level of functioning than patients achieving MDA late. Those patients reached a similar level, despite higher disease activity and higher disease burden at baseline. The optimistic interpretation is that no damage has been done and all is reversible in the first year. We do however not know what the maximum achievable physical functioning is, would they have been achieved MDA earlier. A pessimistic interpretation is that patients who achieved MDA early should have had a higher potential than those who achieved MDA late, and underestimation of severity at the start has led to under treatment. This might also be related to the manifestations and the predominant phenotype at time of diagnosis.

Patients that achieved MDA late or not at all within the first year seemed comparable at time of diagnosis, with similar disease activity and disease burden. If we were able to predict, at time of diagnosis, whether the time to achieving MDA will be longer, we may be able to intervene earlier. These patients may benefit from being monitored more closely or having treatment escalated more quickly. A subject of future research is longer follow up of these patients that did not achieve MDA within a year. That will show whether these patients will be able to achieve MDA after 1 year, and if so, whether they are able to reach similar improvement of burden of disease and functioning.

One of the goals of treatment is preventing structural damage. We hypothesized that radiological progression would be lower if the target of MDA had been achieved early. This hypothesis was not confirmed by the data. In total, 14% of patients had radiological progression, and this was seen in all MDA groups. There are several explanations for the low progression rates. First, we assessed a usual care population with follow-up 1 year after

diagnosis of PsA. The effects of slightly longer high disease activity within the first year might become apparent later in the disease, or the effects might not be destructive enough to be seen on an X-ray. Second, the majority of patients had a monoarticular or oligoarticular phenotype with arthritis of other, bigger joints, such as the knee, shoulder and ankle. Progression in these would be missed in a PsA-modified Sharp-van der Heijde score. In this scoring method, the small joints of hand and feet are assessed for joint space narrowing and erosions, but not for progression in bigger joints. Third, joint space narrowing and erosions are scored, while new bone formation might be a more appropriate sign of structural progression specifically in PsA.[21, 22] However, we regard it unlikely that this explains the low progression rates. Though not part of the scores we used for the analysis, we did register new bone formation and found that it often occurred simultaneously with radiological progression.

Though not analysed as such, the patterns of restoring of disease burden and productivity in the late MDA group provide insight in how patients compensate disease activity. In the patients who achieved MDA late, work productivity is restored months before the disease burden is resolved and even before MDA is actually achieved. This might be interpreted as follows: restoring work productivity is a priority to patients, and loss of work productivity can be interpreted as a sign that the extent or the duration of high disease activity can no longer be compensated by coping mechanisms. This should be prevented, because employment is difficult to restore once lost.[23] It is another argument why active disease should be treated early, in order to maintain participation and reduce societal impact of disease.

PERFORMANCE OF DISEASE ACTIVITY MEASURES

Our analysis of performance of different disease activity measures really comes down to the question: what is disease activity of PsA? PsA is an inflammatory disease and disease activity is the extent to which symptoms resulting from inflammation are present. We have many ways of assessing symptoms of PsA, though many of them are heavily debated as discussed in previous sections. The measures MDA, GRAppa Composite ScorE (GRACE), Psoriatic ArthritiS Disease Activity Score (PASDAS), and Composite Psoriatic Disease Activity Index (CPDAI) include disease activity in domains other than arthritis (i.e. psoriasis and enthesitis), and also some aspects of patient-reported impact of disease with questionnaires about disability (i.e. the Health Assessment Questionnaire) or HRQOL (i.e. Short Form-36, : PsA-specific Quality of Life). MDA and the continuous measures PASDAS and GRACE had the best relation with evolvement of burden of disease, functioning and productivity in the first year after diagnosis, as compared with more articular measures such as Disease Activity Score 28 (DAS28) and Disease Activity index for PSoriatic Arthritis (DAPSA).

The concept of treat-to-target (T2T) has been adopted from treatment of other

chronic conditions, such as diabetes: instead of the same treatment for all patients, treatment is intensified if the target of Hb1Ac has not been met.[24] Subclinical, chronic exposure to high glucose levels leads to complications in diabetes.[25, 26] The translation to PsA then is: chronic inflammation leads to structural damage and needs to be controlled tightly. In PsA, however, the risk of structural damage as a result of inflammation cannot be determined based on one symptom or a single laboratory test. Also, PsA activity is not subclinical and treatment is not only given to prevent long-term structural damage, but also to improve current functioning. For these reasons, composite disease activity measures have been developed, in which disease activity as measured with different manifestations and patient-reported outcomes (PROs) are combined in a single measure. There is no consensus on what to include in this composite disease measure, mainly because the inclusion of manifestations of enthesitis, dactylitis, spondylitis, and psoriasis has been debated. It has not been established that patients with these manifestations have a higher risk of developing structural damage, as is the case for the manifestation of arthritis. For example, psoriasis patients – with or without PsA – in the care of dermatologists do not receive T2T with prespecified targets, as is common in rheumatology. There is no consensus on a definition of severe psoriasis is, though a Psoriasis Area and Severity Index (PASI) above 10 or 12, or a severe impact on HRQOL is a commonly used definition.[27, 28]

We have shown that measures including multiple manifestations, such as the GRACE, PASDAS and MDA, are a better reflection of disease burden and have superior responsiveness and longitudinal validity in the first year after diagnosis. The impact of disease is not completely captured by DAPSA and DAS28. Related to this, we have also shown that manifestations beside arthritis lower HRQOL at time of diagnosis. Rheumatologists need to be aware of this and they should take it into account when choosing treatment. With respect to psoriasis, they should consult a dermatologist when necessary. Whether PASDAS, GRACE and MDA are also superior in determining outcomes after 1 year and at predicting structural damage remains to be investigated in a study with longer follow up. It will show whether high disease activity in domains other than arthritis needs to be controlled as well in order to prevent future disability. In that study it would also be possible to investigate whether the measures can be simplified without losing its ability to predict current and future functioning. A simpler measure is more likely to be incorporated in clinical practice.

Besides including multiple manifestations, the measures PASDAS, GRACE and MDA also include more PROs than DAS28 or DAPSA. Adding patient-reported disease burden to objective measures of disease activity is a more personalized measurement: all aspects of disease are assessed in a total score of disease activity, incorporating also how much the patient suffers from these aspects of disease. This could aid in choosing the appropriate type of treatment. In the analysis of these composite measures related to outcomes, two considerations need to be taken into account. First, the objectivity of including PROs in a disease measure has

been debated. PROs are more likely to be affected by for example comorbidities,[29-31] capturing more than disease activity alone. It is however not true that only PROs have this problem: a swollen or tender joint could be a symptom of osteoarthritis, increased acute phase reactants can have many other causes than PsA, and radiographic damage of DIP joint especially can also be caused by osteoarthritis.[32] Also, in RA it is known that the best predictor of flare or achieving low disease activity are PROs,[33, 34] suggesting these are more sensitive than for example a swollen joint count. Luckily, the treating physician is tasked with the interpretation of a disease activity measure before prescribing treatment. Second, it should be noted that the outcomes of our analysis contains some circular reasoning: something that combines X and Y is expected to be related to X in the long term. The true value of different disease measures therefore needs to be studied in interventional studies: do treatment and outcomes improve if treatment is chosen based on PASDAS or GRACE, rather than usual care?

GENERAL CONSIDERATIONS

Some sources of bias have been discussed in the previous sections if they were specific to the research question discussed. Regarding generalisability, measurement error, and missing data, some general considerations in the interpretation of the results in this thesis are discussed below.

Generalizability

The patients in our studies that investigated ultrasound of the entheses were consecutive PsA patients attending the outpatient clinic of secondary hospitals and a tertiary hospital. Patients were not selected based on their risk of enthesitis, reflected also in the absence of enthesitis at clinical examination and on ultrasound in some patients. We aimed to study the spectrum of entheseal abnormalities in an average PsA patient, to conclude which changes were specific to PsA and which were not. We believe our results are generalizable to PsA patients receiving outpatient care by a rheumatologist, though the high percentage of biological use suggests we selected patients with slightly more severe disease. Our results cannot be extrapolated to patients who are suspected of having enthesitis.

All patients with a new diagnosis of PsA, as defined by the expert opinion of the treating rheumatologist, are eligible to participate in the DEPAR study. It should be noted that not all patients with a new diagnosis participated in the study. Taking this into account, in contrast with observational studies of established PsA patients or clinical trials, our study population represents PsA patients in daily clinical care. Fulfilling classification criteria for PsA was not a requirement, though many patients happened to fulfil the CASPAR classification criteria. At the expense of slightly less comparability with other studies, our findings of disease

burden and disease activity can be translated to patients with a new diagnosis.

Measurement error

Disease activity was determined based on data collected by research nurses, which might differ from the assessment of the physician who actually prescribed treatment. Some patients could have been classified as having active disease according to the research nurse, but might be considered in low disease activity according to the physician. In that case, the disease was recorded as active, whereas treatment was not intensified for these patients. The systematic overestimation of disease activity by nurse or underestimation by physician (and vice versa) will lead to bias if patients of one physician have worse HRQOL and productivity outcomes. For example if the physician does not ask patients with mild disease to participate. This can be corrected for in a mixed model, by adding another level of correlation (i.e. treating physician). We did however not have the power to do so with the many physicians and sometimes only a few patients per physician. We encouraged physicians to include all patients with a new diagnosis, and we suspect patients physicians are consistent in their treatment of PsA.

Missing Data

In the ideal study, all patients included in the study complete their follow up, they do not miss any study visits, they have all their clinical data collected at each study visit, and they complete all their questionnaires. In the real world however, we are faced with the problem of missing data, which could be a source of bias in our analyses . Conceptually, there are 3 forms of missing data: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).[35] Data are MCAR if missingness is unrelated to what we observed and what we could not observe because of the missingness: an example of MCAR we observed in the DEPAR study was that some patients were not able to visit the research nurse because the rheumatology department was relocating. This is completely unrelated to disease activity or the outcomes of the patient. The data we have is a random sample of the complete data we would have, which leads to less efficiency but not to bias.

Data are MAR if missingness is related to what we observed, but not to what we could not observe; for example, patients with a lower baseline disease activity are more often discharged from care by their physician and less likely to complete the study. We recorded the baseline disease activity and if we correct for that in a mixed model analysis, the results of the analysis are unbiased. In our analysis of time to MDA and outcomes of HRQOL and productivity we corrected for baseline disease activity factors, as well as age and gender, thereby producing valid results if missingness of data is related to any of these factors. There is however still a chance of bias of the estimated effect of time to MDA on outcomes, if our missing data are MNAR.

Data are MNAR if the missingness is related to something we did not observe: for

example, patients with worse HRQOL were so ill that they were less likely to complete their questionnaire about HRQOL, even after we corrected for baseline factors. Since we cannot test an association with something we do not know, there is no way to test whether data is MNAR. The strength of the conclusions can be assessed by making different assumptions about the missing data and testing whether the conclusions are altered. We did not perform a formal sensitivity analysis, but we are able to speculate about the consequences of this MNAR. Based on the reasons patients provided for stopping with the study, we suspect patients drop out because of two main reasons. Some are doing very well, are discharged from care, and have difficulty combining visits to the research nurse with work. Their outcomes are likely to be better those of patients without missing data. Others suffer from severe comorbidities or have had other life events, whose outcomes are likely to be worse. We deem it most likely that the first group are mostly patients achieving MDA early (i.e. patients early in MDA are discharged from care within the first year) and the second group are mostly patients not in MDA (i.e. patients suffering from severe comorbidities or life events are not in MDA). In that case the effect between time to MDA and outcomes was an underestimation of the true effect. In our comparison of performance, this mechanism of missing data might bias the relation between other disease activity measures and outcomes as well, but the bias will be the same for all measures. Hence, the performance of disease measures relative to each other will not be biased.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Based on the new insights provided in this thesis and discussed above, and in light of their considerations, we have the following recommendations for clinical practice for each aim.

Ultrasound abnormalities of the entheses

For the purpose of confirming a suspicion of enthesitis on the enthesis-level, ultrasound of the entheses should be used with caution, given the many changes also found in healthy adults.

Burden of disease at time of diagnosis

More attention to manifestations of PsA other than arthritis is needed, as burden of disease is determined by enthesitis and chronic back pain as well.

Time to minimal disease activity

Outcomes improve if patients achieve low disease activity, and therefore treatment should be aimed at achieving a state of low disease activity.

A third of patients is not able to achieve low disease activity in the first year after diagnosis and as a result these patients continue having a high impact of disease. These patients might benefit from earlier escalation of therapy.

Patients achieving MDA late in the first year are able to reach a similar level of functioning as patients achieving MDA early, suggesting that the window of opportunity has not yet closed in the first 3 months after diagnosis.

Performance of disease activity measures

Articular measures DAS28 and DAPSA should not be used as a target in T2T for PsA, as they underestimate impact of disease. It could potentially lead to under treatment of patients with residual active disease.

As an alternative to DAPSA, the disease measures GRACE or PASDAS could be used to measure disease activity on a continuous scale.

RECOMMENDATIONS FOR FUTURE RESEARCH

To further aid clinical decision making, more research is needed and the following recommendations are considered the most relevant with respect to measuring disease activity and outcomes in early PsA.

Ultrasound abnormalities of the entheses

A better reference frame of the ‘normal’ enthesis is needed: more research of the entheses of healthy volunteers and factors associated with changes of the entheses on ultrasound and other imaging techniques should be carried out.

The effects of physical activity and medication on the entheses of patients with PsA should be studied in longitudinal, prospective studies. This could be done in interventional studies, in which patients suspected of enthesitis are randomized to receive an intervention (either medical or physical therapy) or usual care, and monitored with ultrasound. It would show whether ultrasound is able to identify those patients most likely to respond to therapy.

Patients with PsA have on average more signs of structural damage at the entheses, which is possibly a result of longstanding inflammation in the enthesis. Instead of relating abnormalities of one enthesis to enthesitis, a total score such as the MASEI might be used. The prognostic purposes of the MASEI should be studied in a cohort study of psoriasis patients, to test whether MASEI is able to predict incidence of PsA in a psoriasis population.

Burden of disease at time of diagnosis

The effect of treatment on enthesitis, dactylitis and spondylitis should be studied in patients who have this as primary manifestation. In the currently available data, effects on manifestations besides arthritis were secondary outcomes, which were studied in a population that had a predominant phenotype of polyarthritis.

The association between each manifestation and burden of disease should be studied longitudinally, to see whether manifestations other than arthritis are treatable and whether their impact on disease burden is reversible or resistant to treatment.

Time to minimal disease activity

In patients who were able to achieve MDA in the first year, similar levels of functioning were achieved. To be sure the therapeutic window has not closed in the first 3 months, more research regarding long-term outcomes is needed. These include effects on disease activity and outcomes after one year, as well as the radiological progression after 1 year.

Regarding patients who are not able to achieve MDA in the first year, we need to know whether these patients will get in MDA after 1 year or not at all. If they are able to achieve MDA, the reversibility on the same outcomes as mentioned before should be assessed.

As MDA is worthwhile to achieve, it is relevant to know whether we can predict the time to MDA. The ability of baseline disease activity, age, gender, and perhaps even factors such as biomarkers to predict time to MDA at time of diagnosis needs to be tested. If we know which patients will be less likely to achieve MDA soon, we could potentially improve outcomes for these patients by monitoring more frequently and escalating treatment more quickly.

Performance of disease activity measures

We have shown that disease activity measures differ in their assessment of HRQOL and functioning in the first year after diagnosis. To choose the best measure for use in clinical practice, disease activity measures need to be compared in their ability to predict radiologic progression, and disability beyond 1 year after diagnosis.

Some disease activity measures are not likely to be incorporated in current clinical practice, as they require too much information in their calculation. It needs to be tested whether some components are not needed to predict current and long-term functioning, and disease progression.

The efficacy of T2T with the best target - based on analyses of observational research - needs to be shown in a randomized clinical trial. In this trial, patients in current usual care should be randomized to receive either usual care, T2T with DAS28, or T2T with the best target for PsA. The primary outcome should be disability or HRQOL. Secondary outcomes should include radiographic progression, adverse events, and cost-effectiveness.

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ADDENDUM

SUMMARY

Psoriatic Arthritis (PsA) is a heterogeneous disease, characterized by manifestations of peripheral arthritis, dactylitis, enthesitis, spondylitis, and psoriasis. Patients with PsA experience the impact of disease as loss of functional ability, decreased health-related quality of life (HRQOL) and loss of productivity. Treatment is aimed at preventing these consequences. It is recommended that treatment is given as early as possible, with all manifestations taken into account, and in a treat-to-target strategy. In a treat-to-target strategy, treatment is intensified if a certain target – a composite disease activity measure – has not been achieved. Good measures of disease activity are needed to improve outcomes for patients with PsA. For this purpose, more information is needed on disease activity and outcomes early in the disease course. These are studied in the Dutch southwest Early Psoriatic Arthritis cohoRt (DEPAR) and related sub-studies.

This thesis aims to investigate the following four aspects of disease activity and outcomes in early PsA: ultrasound abnormalities of the entheses, burden of disease at time of diagnosis and its relation with disease manifestations, the relation between time to minimal disease activity and outcomes, and the performance of disease activity measures.

Ultrasound abnormalities of the entheses

In **Chapter 2**, we compare the prevalence of ultrasound abnormalities at the entheses in patients with a new diagnosis, in patients with established disease, and in young, healthy volunteers aged 20 to 30 years. Participants were included consecutively, irrespective of complaints suggestive of enthesitis. In healthy volunteers, the entheses around the knees often had increased thickness, and also a mild power Doppler (PD) signal often occurred. We therefore excluded thickness of knee entheses from the Madrid Sonographic Enthesitis Index (MASEI) and recoded PD signal, resulting in a modified MASEI score. The modified MASEI showed better discrimination between PsA patients and healthy volunteers. No differences in the modified MASEI scores were observed between patients with a new diagnosis and patients with established disease.

The modified MASEI was studied in a larger population of established PsA patients and older healthy volunteers (aged 35 to 60 years). Also within the established PsA population, we studied which factors were associated with ultrasound abnormalities of the entheses. These results are displayed in **Chapter 3**. The structural components of the modified MASEI (i.e. calcifications, erosions, and structural changes) were again significantly higher in PsA patients than in healthy volunteers. The inflammatory components of the modified MASEI (i.e. increased thickness except knee entheses, bursitis, and PD signal) however did not differ significantly. Within PsA patients with established disease, higher age and current use of biologicals were associated with a higher inflammatory modified MASEI score. Patients who

reported avoiding physical activities had significantly lower modified MASEI scores. More structural abnormalities of the entheses were seen in older PsA patients.

Burden of disease at time of diagnosis

The burden of disease at time of diagnosis of PsA, as measured with HRQOL, is studied in **Chapter 4**. HRQOL is significantly lower in PsA patients compared with the general population. This is seen in both the mental and physical aspects of HRQOL, with a higher impact on the physical aspects. In this chapter, we also study which manifestations are responsible for the burden of disease at time of diagnosis. Besides having more tender joints, both enthesitis at clinical examination – present in 46% of patients – and presence of chronic back (39% of patients) were associated with a higher burden of disease. Given these, more swollen joints, presence of dactylitis and more severe psoriasis did not add to the burden of disease.

Time to minimal disease activity

The window of opportunity in PsA is studied in **Chapter 5**. We investigated the time patients needed to achieve a certain target of low disease activity for the first time in the first year, using Minimal Disease Activity (MDA). Of all patients with a new diagnosis of PsA, 32% were able to achieve MDA within 3 months (early MDA) and another 26% within the first year after diagnosis (late MDA). The exact time to MDA could not be determined in 8% and 33% was never in MDA in the first year after diagnosis. The outcomes of HRQOL and productivity significantly improved once MDA was achieved. Patients in MDA early were significantly longer in MDA during the first year after diagnosis, and as a result their outcomes throughout the first year were significantly better than those of patients late in MDA or never in MDA in the first year. The patients late in MDA had worse outcomes throughout the first year, but were able to reach a similar level of HRQOL and productivity at 1 year after diagnosis. Impact on outcomes in patients never in MDA in the first year remained as high as at time of diagnosis. No differences were observed in radiographic progression between the 3 groups.

Performance of disease activity measures

In **Chapter 6**, the validity of 2 disease activity measures, recommended for use in clinical practice by an international task force, is tested: the measures MDA and Disease Activity index for PsA (DAPSA). We tested whether patients fulfilled definitions of MDA and DAPSA low disease activity (DAPSA-LDA, i.e. DAPSA ≤ 14), and within these different definitions of low disease activity we compared the burden of disease in the domains body functions and activity. One year after diagnosis and receiving usual care, 48% of patients was in MDA and 74% was in DAPSA-LDA. MDA was a stricter definition of low disease activity and burden of disease was significantly lower in patients in MDA than in patients in DAPSA-LDA. In patients with complete data on both MDA and DAPSA-LDA, 46% had achieved both MDA and DAPSA-LDA and 25% had

achieved neither definition of low disease activity. Only 2 (1%) patients were in MDA and not in DAPSA-LDA, while 29% of all patients were in DAPSA-LDA but not in MDA. The latter group of patients who had achieved DAPSA-LDA, but not MDA, had worse outcomes of body functions and activity than patients who had achieved both DAPSA-LDA and MDA.

The responsiveness and longitudinal validity of all available disease activity measures for PsA are compared in **Chapter 7**. These measures were disease activity score 28 (DAS28), DAPSA, Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic ArthritiS Disease Activity Score (PASDAS), GRAppa Composite scorE (GRACE) and MDA. Responsiveness of continuous measures (i.e. all but MDA) was tested using the effect size, standardized response mean, and discrimination between different general health states. The effect size and standardized response mean of the first year after diagnosis were highest for PASDAS and lowest for DAPSA. Differences in general health could best be discriminated by GRACE and PASDAS. DAS28 and CPDAI were not able to discriminate between patients reporting stable general health and those reporting worsening of general health. In order to compare longitudinal validity of each measure, the longitudinal evolvement relative to the longitudinal evolvement of outcomes of HRQOL, productivity and disability was analyzed for all measures. This was done by comparing the fit of mixed models with different disease activity measures as variables. The longitudinal evolvement of HRQOL (using the Short Form-36 Physical Component Summary) and work productivity was best captured with GRACE, PASDAS and MDA. For the outcome disability as measured with the HAQ, the association was highest with GRACE, MDA and CPDAI. Summarizing, in terms of both responsiveness and longitudinal validity, PASDAS, GRACE and MDA were superior to DAS28, DAPSA and CPDAI.

In **Chapter 8**, the results for each of the four aims are summarized and discussed, and general considerations with respect to generalizability and missing data are given. This thesis ends with recommendations both for clinical practice and for future research.

SAMENVATTING

Artritis psoriatica is een auto-immuunziekte, waarbij ontstekingscellen van het afweersysteem zich richten tegen de cellen van het eigen lichaam. Hierdoor ontstaat er een chronische ontsteking. Zo'n ontsteking kan bij artritis psoriatica ontstaan in: de gewrichten (artritis), de peesaanhechtingen (enthesitis), de rug (spondylitis), de gehele vinger of teen (worstteen of worstvinger: dit wordt dactylitis genoemd), de huid (psoriasis) en de nagels (nagelpsoriasis, zie ook Figuur 1 van de introductie). Patiënten hebben onder andere last van pijn, stijfheid en vermoeidheid, waardoor ze minder goed kunnen functioneren en een lagere kwaliteit van leven hebben dan gezonde mensen. In de meeste gevallen krijgen patiënten eerst psoriasis.

Bij psoriasis is er sprake van een chronische ontsteking die gericht is tegen de cellen in de huid. Door deze ontsteking gaan de huidcellen veel sneller delen dan normaal en zo ontstaan er rode, schilferende plekken op de huid. Deze plekken worden psoriasisplekken genoemd. Deze kunnen jeuken en pijn doen, maar zijn niet besmettelijk. Een deel van de patiënten met psoriasis krijgt om nog onbekende reden ook een chronische ontsteking van het bewegingsstelsel. Deze patiënten krijgen dan de diagnose artritis psoriatica. Geschat wordt dat 6-42% van de patiënten met psoriasis uiteindelijk artritis psoriatica zal ontwikkelen, meestal op een leeftijd tussen de 30 en 50 jaar. Het komt even vaak voor bij mannen als bij vrouwen. In totaal heeft 0,19% van de bevolking in Europa artritis psoriatica. De diagnose artritis psoriatica wordt gesteld door een reumatoloog, op basis van de klachten van de patiënt, het lichamelijk onderzoek, de ontstekingswaarden in het bloed en op basis van de afwijkingen aan de gewrichten op röntgenfoto's.

Patiënten met artritis psoriatica worden behandeld met reumaremmers, die de ontstekingscellen afremmen zodat ook de chronische ontsteking verdwijnt. Het is belangrijk dat de ontsteking snel onderdrukt wordt en onderdrukt blijft, zodat er geen blijvende schade ontstaat aan bijvoorbeeld de gewrichten. Er zijn verschillende reumaremmers beschikbaar, die allemaal net iets anders werken en bovendien niet bij iedere patiënt even goed werken. Na het starten van de therapie worden patiënten regelmatig door hun reumatoloog gecontroleerd om te kijken of er bijwerkingen optreden en of de ontsteking goed genoeg onderdrukt is. Dat controleren van de onderdrukking van de ontsteking wordt gedaan met een maat voor de ziekteactiviteit. In deze maat worden verschillende metingen gecombineerd tot één getal. Als dit getal te hoog is (wat wil zeggen dat de ziekteactiviteit hoog is), wordt de therapie aangepast.

In dit proefschrift is het meten van de ziekteactiviteit en uitkomsten (zoals ziektelast, kwaliteit van leven en productiviteit op werk) van patiënten met vroege artritis psoriatica onderzocht. Het doel was om de volgende 4 aspecten te onderzoeken:

- het echografisch onderzoek van de peesaanhechtingen
- de ziektelast op het moment van diagnose en het effect van verschillende symptomen op die ziektelast

- de relatie tussen de tijdsduur totdat een lage ziekteactiviteit was bereikt en uitkomsten
- het vergelijken van verschillende maten voor het meten van ziekteactiviteit

Dit onderzoek is uitgevoerd bij deelnemers aan de DEPAR studie, wat staat voor Dutch southwest Early Psoriatic Arthritis cohoRt. Patiënten werden gevraagd mee te doen, net nadat ze de diagnose artritis psoriatica hadden gekregen van hun reumatoloog. In het eerste jaar na de diagnose bezochten patiënten een onderzoeksverpleegkundige die de ziekteactiviteit registreerde. Ook werden patiënten gevraagd vragenlijsten in te vullen over onder andere de ziekteactiviteit, de kwaliteit van leven, hun functioneren en hun werk. Bij ieder bezoek liet de patiënt bloed prikken zodat de ontstekingswaarden in het bloed gemeten konden worden en werden er jaarlijks röntgenfoto's van handen en voeten gemaakt om eventuele schade aan de gewrichten op te sporen.

Het echografisch onderzoek van de peesaanhechtingen

Een chronische ontsteking van de peesaanhechtingen (enthesitis) kan klachten geven die lijken op normale klachten van de pezen zelf. Deze normale klachten komen veel voor in de algemene bevolking en ontstaan vaak op de leeftijd waarin meestal ook artritis psoriatica ontstaat: 30 tot 50 jaar. Met echografie kunnen de peesaanhechtingen in beeld gebracht worden, om te kijken of er tekenen van ontsteking zijn. Welke afwijkingen op de echo echter specifiek zijn voor artritis psoriatica is nog niet goed onderzocht.

In **hoofdstuk 2** is onderzocht welke afwijkingen van de peesaanhechtingen gezien worden bij artritis psoriatica op het moment van de diagnose. Dit werd vergeleken tussen patiënten die al wat langer de ziekte hadden en met jonge, gezonde volwassenen. De peesaanhechtingen van deze groep jonge, gezonde vrijwilligers zijn naar verwachting volgroeid, maar hebben nog geen schade opgelopen. Er waren 2 opvallende bevindingen bij gezonde vrijwilligers. Bij deze groep was de dikte van de peesaanhechtingen rond de knie vaak hoger dan de normaalwaarden. Ook waren er tekenen van verhoogde doorbloeding te zien in deze peesaanhechtingen, wat als een teken van ontsteking gezien zou kunnen worden (zie ook Tabel 2 van hoofdstuk 2). In vergelijking met de peesaanhechtingen van patiënten met artritis psoriatica was er wel een verschil in intensiteit van het doorbloedingssignaal op echografie. Daarom is er een score gegeven aan de ernst van het signaal in plaats van de aan- of afwezigheid van het doorbloedingssignaal te registeren. Deze twee bevindingen hebben geleid tot een aanpassing van de totaalscore van de echoafwijkingen: bij het optellen van alle afwijkingen op de echobeelden is de dikte van de kniepezen niet meegenomen en is gebruik gemaakt de gradering in intensiteit van doorbloedingssignaal. Deze nieuwe scoringsmethode maakte een beter onderscheid tussen de peesaanhechtingen van jonge, gezonde volwassenen en patiënten met artritis psoriatica. Er was geen verschil in deze score tussen patiënten die net de diagnose hebben gehad en patiënten die al wat langer de ziekte hadden.

Deze nieuwe score werd vervolgens toegepast in een nieuwe groep met artritis

psoriatica patiënten en vergeleken met wat oudere gezonde vrijwilligers. Daarnaast is er ook gekeken welke factoren van invloed zijn op het hebben van afwijkingen aan de peesaanhechtingen bij patiënten. De resultaten hiervan staan beschreven in **hoofdstuk 3**. De afwijkingen op de echografie kunnen ingedeeld worden in 2 groepen: een actieve ontsteking of structurele schade. De totaalscore voor de actieve ontsteking verschilde niet tussen de gezonde vrijwilligers en patiënten met artritis psoriatica, wat aangeeft dat deze afwijkingen niet specifiek bij artritis psoriatica horen. Patiënten met artritis psoriatica hadden wel meer structurele schade aan de peesaanhechtingen. De patiënten met een hogere leeftijd – en dus een langere ziekteduur – hadden meer actieve ontstekingen en structurele schade dan de groep gezonde vrijwilligers. Als patiënten aangaven dat ze fysieke activiteit vermeden vanwege de angst om klachten te krijgen, bleken deze patiënten minder tekenen van een actieve ontsteking aan de peesaanhechtingen te hebben. Patiënten die een specifiek type reumaremmers gebruikte, de biologicals, hadden meer actieve ontstekingen aan de peesaanhechtingen.

De ziektelast op het moment van diagnose

Er is nog weinig bekend over de ziektelast die patiënten in een vroeg stadium van de ziekte hebben en welke symptomen nu precies zorgen voor die ziektelast. Artritis psoriatica is een heterogene ziekte, wat inhoudt dat er veel verschillen zitten in de symptomen die patiënten kunnen hebben. In **hoofdstuk 4** staat beschreven wat de kwaliteit van leven van patiënten is vlak nadat ze gediagnosticeerd zijn met artritis psoriatica en nog voor ze begonnen zijn met de behandeling van de ziekte. Vergeleken met de algemene Nederlandse bevolking was de kwaliteit van leven een stuk lager bij patiënten met artritis psoriatica en dit effect was sterker voor de fysieke aspecten (zoals pijn en algehele gezondheid) dan voor de mentale aspecten van kwaliteit van leven (zoals sociaal functioneren en vitaliteit, zie ook Figuur 1 van hoofdstuk 4). Patiënten hadden vaak meerdere symptomen en het effect van ieder symptoom onafhankelijk van de andere symptomen op de kwaliteit van leven is geanalyseerd. Het hebben van meer pijnlijke gewrichten, meer ontstoken peesaanhechtingen en het hebben van chronische lage rugklachten was geassocieerd met een slechtere kwaliteit van leven. Daarnaast was het hebben van ernstigere psoriasis, meer gezwollen gewrichten, of het hebben van een worstteen of -vinger (dactylitis) niet van invloed op de kwaliteit van leven.

De tijdsduur tot lage ziekteactiviteit

Patiënten met artritis psoriatica krijgen reumaremmers om de chronische ontsteking te onderdrukken. Het doel van de behandeling met deze medicijnen is de ziekte een zo klein mogelijk effect te laten hebben op het functioneren en de kwaliteit van leven en het voorkomen van blijvende schade. De relatie tussen het behalen van een lage ziekteactiviteit en de kwaliteit van leven en werkproductiviteit zijn onderzocht in **hoofdstuk 5**. Ook is onderzocht hoe lang het duurde voordat patiënten een lage ziekteactiviteit hadden, en of het uitmaakte voor de

kwaliteit van leven en werkproductiviteit als het langer duurde voordat een lage ziekteactiviteit werd bereikt. Ongeveer een derde van de patiënten had binnen 3 maanden voor het eerst een lage ziekteactiviteit, en weer een derde van de patiënten later in het eerste jaar. De rest van de patiënten kon in het eerste jaar nadat ze de diagnose kregen geen lage ziekteactiviteit behalen. Op het moment dat patiënten een lage ziekteactiviteit hadden, trad er een herstel van kwaliteit van leven en werkproductiviteit op. Omdat de patiënten die vroeg een lage ziekteactiviteit bereikten hier eerder van konden profiteren, waren hun uitkomsten gemiddeld genomen over het eerste jaar beter. De uitkomsten van patiënten die niet na 3 maanden, maar wel binnen het eerste jaar voor het eerst een lage ziekteactiviteit hadden bereikt, werden later beter: een jaar na diagnose was er geen verschil meer tussen patiënten die vroeg of laat een lage ziekteactiviteit hadden behaald. Bij de patiënten die geen lage ziekteactiviteit konden behalen, bleef de ziekte een grote impact op hun kwaliteit van leven en werk houden (zie ook Figuur 1 van hoofdstuk 5). In de 3 onderzochte groepen was er geen verschil in de verergering van de schade aan de gewrichten die opgelopen was in dat eerste jaar.

Vergelijken van maten van ziekteactiviteit

Om de behandeling optimaal af te stemmen op de patiënt moet de activiteit van de ziekte goed gemeten worden. Er zijn verschillende maten voor de ziekteactiviteit beschikbaar bij artritis psoriatica. Deze maten verschillen onderling in: het meetellen van het aantal gewrichten, andere symptomen dan gewrichtsontsteking (de ernst van de psoriasis, ontstekingen aan de peesaanhechtingen of rug en het hebben van een worstteen of -vinger), ontstekingswaarden in het bloed en de soort vragenlijsten (zie ook Tabel 1 van de introductie). Het is niet makkelijk om de verschillende maten van ziekteactiviteit met elkaar te vergelijken. Dit komt doordat er geen referentiewaarde bestaat die de 'waarheid' weergeeft en waarmee de andere maten vergeleken kunnen worden.

Twee maten zijn in recente literatuur aanbevolen om te gebruiken in de klinische praktijk bij het behandelen van patiënten met artritis psoriatica: de MDA (Minimal Disease Activity) en de DAPSA (Disease Activity index for Psoriatic Arthritis). In **hoofdstuk 6** is onderzocht welke maat het beste de ziekteactiviteit meet, door de ziektelast van patiënten die aan de definitie MDA voldeden te vergelijken met de ziektelast van patiënten die aan de definitie DAPSA voor lage ziekte activiteit voldeden. Hiervoor zijn gegevens gebruikt van patiënten een jaar na hun diagnose en behandeling bij de reumatoloog. Voor de uitkomst ziektelast werd gekeken naar lichamelijke pijn, vermoeidheid, fysiek functioneren en fysieke beperkingen. Patiënten rapporteerden dit door middel van vragenlijsten. De ziekteactiviteit moest lager zijn om aan MDA te voldoen dan aan DAPSA lage ziekteactiviteit: 48% van de patiënten voldeed aan de MDA definitie, vergeleken met 74% van de patiënten volgens de DAPSA lage ziekteactiviteit definitie. Als patiënten aan de MDA voldeden, hadden ze meestal ook lage ziekteactiviteit volgens de DAPSA: 46% van de patiënten voldeed namelijk aan beide

definities. Verder voldeed 29% alleen aan lage ziekteactiviteit volgens de DAPSA, 1% alleen de MDA en 25% van de patiënten voldeed aan geen van beide definities van lage ziekteactiviteit. Patiënten die aan de definitie van MDA voldeden hadden een lagere ziektelast dan patiënten die lage ziekteactiviteit hadden volgens de DAPSA. De patiënten die alleen een lage ziekteactiviteit hadden volgens de DAPSA, hadden een lagere ziektelast dan patiënten die daar niet aan voldeden, maar nog niet zo laag als patiënten ervaarden die aan beide definities voldeden (zie ook Figuur 1, 2 en 3 in hoofdstuk 6 en Figuur 1 en 2 in het supplement bij hoofdstuk 6).

Een vergelijking van alle maten van ziekteactiviteit die er momenteel beschikbaar zijn voor artritis psoriatica staat beschreven in **hoofdstuk 7**. Wederom werden MDA en DAPSA vergeleken, maar daarnaast werden ook de DAS28 (disease activity score 28), de CDPAI (Composite Psoriatic Disease Activity Index) de PASDAS (Psoriatic ArthritiS Disease Activity Score), en de GRACE (GRAppa Composite scorE) onderzocht. Allereerst is onderzocht welke maat het beste veranderingen in de ziekteactiviteit kon meten. De verandering in het eerste jaar van de score zelf was het hoogst voor de PASDAS, en het laagst voor de DAPSA (zie ook Figuur 1 van hoofdstuk 7). Patiënten werd ook gevraagd of ze veranderingen in algehele gezondheid ten opzichte van 3 maanden geleden konden beoordelen. Hen werd gevraagd of hun algehele gezondheid nu 'veel beter', 'wat beter', 'ongeveer hetzelfde', 'wat slechter' of 'veel slechter' was. Deze 5 groepen patiënten konden het beste onderscheiden worden op basis van het verschil in PASDAS-score en GRACE-score. De patiënten konden het slechts onderscheiden worden op basis van hun CPDAI-score (zie ook Figuur 2 van hoofdstuk 7). Daarnaast is onderzocht welk verloop van de ziekteactiviteit over het eerste jaar het beste overeenkwam met het verloop in de ziektelast die patiënten rapporteerden. Voor de ziektelast werden de kwaliteit van leven, de werkproductiviteit en fysieke beperkingen onderzocht. De GRACE, PASDAS en MDA hadden de grootste associatie met de kwaliteit van leven en werk, en de GRACE, MDA en CPDAI hadden de grootste associatie met fysieke beperkingen. Alle analyses samen genomen, waren de PASDAS, GRACE en MDA beter in het meten van de ziekteactiviteit dan de DAS28, DAPSA en CPDAI.

Hoofdstuk 8 bevat een algemene discussie waarin de 4 onderzoeksdoelen besproken worden, welke bedenkingen meegenomen moeten worden bij het interpreteren van de resultaten en naar welke patiënten de resultaten te generaliseren zijn. Ten slotte worden er aanbevelingen gedaan voor de klinische praktijk en voor toekomstige onderzoeken. De belangrijkste aanbevelingen zijn dat er meer aandacht moet komen voor andere symptomen van de ziekte naast gewrichtsontsteking, dat er behandeld moet worden tot er een lage ziekteactiviteit behaald is en dat ziekteactiviteit het beste met een GRACE-, PASDAS- of MDA-score berekend kan worden.

PHD PORTFOLIO

Name	Kim Wervers
Department	Rheumatology
Research School	Netherlands Institute for Health Science (NIHES)
PhD period	November 2015 – December 2018
Promotor	Prof. dr. J.M.W. Hazes
Copromotors	Dr. M. Vis
	Dr. J.J. Luime

PhD training	Year	Workload (ECTS)
General academic and research skills		
BROK (Basiscursus Regelgeving Klinisch Onderzoek)	2016	1.5
CPO course	2016	0.3
Workshop Endnote	2016	0.3
Workshop Systematic Literature Retrieval in PubMed	2016	0.3
Biomedical English Writing and Communication	2017	3.0
Integrity in Scientific Research	2017	0.3
In-depth statistical courses, NIHES		
Biostatistical Methods I: Basic Principles	2016	5.7
Clinical Epidemiology	2016	5.7
Repeated Measurements in Clinical Studies	2016	1.4
Missing Values in Clinical Research	2016	0.7
Biostatistical Methods II: Classical Regression Models	2017	4.3
Study Design	2017	4.3
Principles of Research in Medicine and Epidemiology	2017	0.7
Methods of Public Health Research	2017	0.7
Clinical Trials	2017	0.7
Health Economics	2017	0.7
The Practice of Epidemiologic Analysis	2017	0.7
Fundamentals of Medical Decision Making	2017	0.7
Principles in Causal Inference	2018	1.4
Advanced Topics in Clinical Trials	2018	1.9
Principles of Epidemiologic Data-analysis	2018	0.7
Quality of Life Measurement	2018	0.9
Causal Inference	2018	1.4
Markers and Prediction Research	2018	0.7
Joint Models for Longitudinal and Survival Data	2018	0.7

PhD training	Year	Workload (ECTS)
Masterclass: Advances in Genomics Research	2018	0.4
Causal Mediation Analysis	2018	1.4
Erasmus Summer Lectures	2018	1.4
National conferences		
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [3 poster presentations, including 1 poster presentation in tour]	2016	1.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [3 oral presentations, 1 poster presentation]	2017	4.0
Nederlandse Vereniging voor Reumatologie (NVR) Najaarsdagen, Papendal [1 poster presentation]	2018	1.0
International conferences		
European League Against Rheumatism (EULAR) annual meeting, London, UK [1 poster presentation]	2016	1.0
American College of Rheumatology (ACR) annual meeting, Washington, US [2 poster presentations]	2016	1.0
European League Against Rheumatism (EULAR) annual meeting, Madrid, Spain [1 poster presentation]	2017	1.0
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting, Amsterdam, the Netherlands [1 poster presentation]	2017	1.0
American College of Rheumatology (ACR) annual meeting, San Diego, US [4 poster presentations]	2017	1.0
European League Against Rheumatism (EULAR) annual meeting, Amsterdam, the Netherlands [1 poster presentation in poster tour]	2018	1.0
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting, Toronto, Canada [1 poster presentation]	2018	1.0
American College of Rheumatology (ACR) annual meeting, Chicago, US [1 poster presentation]	2018	1.0
Seminars and workshops		
Department Journal club Rheumatology (organization, attendance and presentations)	2015-2018	1.0
Cicero meetings (attendance and presentations)	2015-2018	1.0
DEPAR workshops (attendance and presentations)	2016-2018	1.0
Vena workshops	2016-2018	1.0
Teaching tasks		
Teaching course 'Tutoraat' to 1st year medical students	2016-2018	2.0
Supervising research 4th year medical students	2016-2017	2.0
Teaching ultrasound of enthesitis at IRON ultrasound course	2017	1.0
Other		
Study management DEPAR study	2015-2018	
Invited speaker 'ultrasound of enthesitis' at enthesitis workshop	2017	
Workshop ultrasound Girlsday, Erasmus MC, Rotterdam	2017-2018	

PhD training	Year	Workload (ECTS)
Grants		
Travelgrants Erasmus Trustfonds, EULAR and GRAPPA	2016-2018	
Pfizer ASPIRE Grant	2017	
GRAPPA Pilot Research Grant	2018	

CURRICULUM VITAE

Kim Wervers is op 19 oktober 1993 geboren in Rotterdam. Zij groeide op in Nieuwerkerk aan den IJssel en is in 2011 cum laude geslaagd voor haar gymnasium-diploma aan het Emmauscollege in Rotterdam. Op de middelbare school had zij al interesse in wetenschappelijk onderzoek en nam zij deel aan Junior Med School, een onderzoeksprogramma van het Erasmus MC.

Na de middelbare school is zij aan de opleiding Geneeskunde begonnen aan de Erasmus Universiteit Rotterdam. In het vierde jaar van haar opleiding deed ze haar masteronderzoek bij het DEPAR project. Na dit onderzoek heeft zij in 2015 besloten om voorafgaand aan de co-schappen van de opleiding Geneeskunde te promoveren bij het DEPAR project, onder begeleiding van Prof.dr. J.M.W Hazes, Dr. J.J. Luime en Dr. M. Vis op de afdeling Reumatologie van het Erasmus MC te Rotterdam.

Tijdens haar promotieonderzoek is zij begonnen aan de Research Master in Health Sciences met specialisatie Clinical Epidemiology aan de NIHES (Netherlands Institute for Health Sciences). Deze hoopt zij gelijktijdig met haar opleiding Geneeskunde af te ronden.

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