LEONIEKE J.J. VAN MENS

TOWARDS CLINICAL REMISSION in PSORIATIC ARTHRITIS

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TOWARDS CLINICAL REMISSION IN PSORIATIC ARTHRITIS

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General introduction and outline

GENERAL INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease with a prevalence of 1-2 per 1000 people.[1,2] Patients with psoriasis are prone to develop PsA. It is estimated that 30% of the patients with psoriasis will develop PsA over time.[3] PsA is regarded as a form of spondyloarthropathy (SpA), an inflammatory musculoskeletal disease group consisting of different phenotypic subsets with a common genetic, radiologic, and clinical presentation.[4,5] SpA can be clinically subdivided in axial SpA and peripheral SpA, with ankylosing spondylitis and psoriatic arthritis, respectively, as the most representative forms.

Clinical features of PsA

PsA is a clinically heterogeneous disease as patients can present with various symptoms such as peripheral arthritis, skin and nail psoriasis, enthesitis, dactylitis, and inflammation of the spine and/or sacro-iliac joints. Peripheral arthritis is characterized by pain, swelling, and stiffness of the affected joint(s) and follows, in contrast to rheumatoid arthritis (RA), either an oligoarticular pattern (i.e. 1-5 joints) or an asymmetrical polyarticular pattern (i.e. 6 or more joints). Arthritis can be accompanied by extensive cartilage and bone destruction (i.e. erosions, bone loss), but also by new bone formation. Psoriasis vulgaris, the most common psoriasis subtype, presents with thickened, red, scaly plaques mostly on the extensor side of the elbows and knees and the scalp. The nails can be affected by psoriasis as well, in this case pitting, white spots (also known as leukonychia) and loosening of the nail from the nailbed occurs. Enthesitis, inflammation of the insertion of a tendon to the bone, is most commonly observed at the Achilles tendon and plantar fascia but can also affect other entheseal sites.[6,7] In case of dactylitis an entire digit of hands or feet is swollen, also called sausage toe or sausage finger, due to the appearance. Usually, PsA patients test negative for rheumatoid factor and anti-citrullinated antibodies.

Impact of PsA

The clinical features can be relatively mild for some patients, but may also lead to severe physical disability, as well as significant psychological and social burden.[8] The impact of PsA on daily functioning and quality of life (QoL) is as severe as in RA.[9] Other important aspects of the disease are the associated comorbidities, for example an increased cardiovascular disease risk. [10,11] This is thought to be related to a combination of systemic inflammation caused by PsA and shared risk factors for cardiovascular disease, such as

obesity, diabetes mellitus type 2, metabolic syndrome, hypertension, dyslipidemia. In comparison with healthy individuals this results in an increased cardiovascular risk leading to a higher morbidity[12,13].

Diagnosing and the classification of psoriatic arthritis

In clinical practice the diagnosis PsA is made by the judgement of a rheumatologist, and not by specific rules or criteria. This decision is based on the recognition of the clinical pattern and radiologic features, as there are no additional biomarkers known to obtain from blood or other tissues. For research purposes, the Classification of Psoriatic Arthritis (CASPAR) criteria have been developed [14]

To meet the CASPAR criteria for PsA, a patient must have inflammatory articular disease (joint, spine or entheseal) and score ≥3 points based on these categories.

	POINTS
1: Evidence of psoriasis	
Current psoriasis	2 or
Personal history of psoriasis	1 or
Family history of psoriasis	1
2: Psoriatic nail dystrophy (pitting, onycholysis, hyperkeratosis)	1
3: Negative test result for rheumatoid factor	1
4: Dactylitis	
Current swelling of an entire digit	1 or
History of dactylitis	1
5: Radiologic evidence of juxta-articular new bone formation ill defined ossification near joint margins on plain x-rays of hand or foot	1

CASPAR: ClASsification criteria for Psoriatic ARthritis. Taylor W et al., Arthritis Rheum 2006; 54-2665-2673

Disease activity in PsA

Management of the disease is a challenge for rheumatologists as it encompasses multiple forms of musculoskeletal involvement (arthritis, enthesitis, dactylitis, spondylitis) that all require appropriate treatment. As not only the joints are involved, the skin disease and other extra articular disease activity should be monitored and treated adequately as well. To monitor disease activity the physician should assess the severity of skin disease, arthritis, dactylitis, enthesitis, and spondylitis, and adjust treatment when there is active disease present in any of the domains.[15,16] In this multifaceted disease it is important to measure all relevant disease domain outcomes, and some advocate to integrate these into one composite score. There are many different outcome measures in use as endpoints in PsA clinical trials, but these are not commonly used in current

clinical practice.[17] The composite scores can largely be subdivided in two categories: either limited to joint and patient reported outcomes (PROs), or including additional domains important for PsA, such as skin and enthesitis measures. The measurements limited to joints and PROs are the ACR response, used in many clinical trials as a primary outcome, the DAS score, and the DAPSA.[18] The latter was specifically developed and validated for PsA, whereas the first two were 'borrowed' from work in the rheumatoid arthritis-field. Measures including not only the joints but also other domains are MDA[19], PASDAS, GRACE[20] , and CPDAI [21]score. These measures were developed specifically for PsA and include additional PsA specific domains, such as enthesitis, daily functioning, skin psoriasis, and dactylitis.[22,23] These measures slightly differ between each other. The difference can mainly be found in the domains they include and the method of how they are combined. Table 2 shows these composite scores in more detail. What the ideal measurement is, and whether a combined or individual tool should be used for clinical practice and clinical trials is still under debate.

Treatment of PsA

Treatment options for PsA have tremendously increased over the last two decades. The initial treatment in most patients consists of conventional synthetic disease modifying antirheumatic drugs (csDMARDS), such as methotrexate and leflunomide. Although recommended by all major treatment recommendations for PsA, an important point to mention is that the evidence supporting the efficacy of methotrexate is limited to even debatable.[24,25] PsA patients with persistent moderate to high disease activity are eligible for TNF inhibitors (TNFi). In sharp contrast to methotrexate, ample evidence from RCTs with multiple TNFi support their marked efficacy to suppress disease activity of arthritis, enthesitis, dactylitis, and spondylitis as well as skin psoriasis.[26] Despite this profound clinical efficacy a significant proportion of patients do not respond, only partially respond, or lose response overtime. This resulted in the search for other therapeutic targets, which eventually led to several new treatment modalities over the last couple of years. New therapeutics with other mechanism of action, which have been tested and approved in recent years, include abatacept (cytotoxic T-lymphocyte associated protein-4 (CTLA-4)-Fc construct)[27], ustekinumab (IL-12/IL23 inhibitor)[28], secukinumab and ixekizumab (anti-IL-17A)[29,30], apremilast (a phosphor-diesterase inhibitor)[31], and tofacitinib (a JAK inhibitor).[32] The positioning of these new treatments is difficult as there are no head-to-head data available. More importantly, only very few strategy studies have been performed in PsA to study the clinical use of these different treatment options.

Outcome measure:	Included disease domains:										
	Patient VAS pain	Patient VAS global	Physician VAS global	Joint scores	Skin	Serum inflammatory marker (ESR or CRP)	Enthesitis score	Dactylitis	Spine	Quality of Life	Physical functioning
ACR	X	X	X	X		X					
MDA	X	X		X	X		X	X			X
DAPSA	X	X		X		X*					
DAS		X		X		X					
PASDAS		X	X	X		X	X			X	
CPDAI				X	X		X	X	X	X	X
GRACE	X	X		X	X					X	X

ACR: ≥20% improvement in: swollen joint count (SJC) and tender joint count (TJC) and 3/5 of the following criteria: CRP or ESR, patient VAS pain, patient VAS global, physician VAS global, HAQ score. An ACR 50 of 70 is an improvement of at least 50 and respectively 70% instead of the 20% in the above formula.

MDA: A patient is classified as achieving MDA when meeting 5 of the 7 following criteria: TJC < or =1; SJC < or =1; Psoriasis Activity and Severity Index (PASI) < or =1 or body surface area < or =3; patient pain visual analogue score (VAS) < or =15; patient global disease activity VAS < or =20; health assessment questionnaire < or =0.5; tender entheseal points < or =1

(m)DAPSA: SJC + TJC + patient VAS pain + patient VAS global + CRP* there is a modified DAPSA (mDAPSA) without CRP

DAS: several formulas; DAS CRP (4): (0.54*√(Ritchi articular Index)+ 0.065*SJC(44) + 0.17*ln(CRP+1) + 0.0072*patient VAS global + 0.45)

PASDAS: (((0. 18 √ (physician VAS global) + 0.159 √ (patient VAS global) – 0.253 √ (SF36 – physical component score) + 0.101 lognat (SJC66 + 1)) + 0.048 × lognat (SJC68 + 1)) + 0.23 × lognat (Leeds enthesitis index + 1)) + 0.37 × lognat (tender dactylitis count + 1) + 0.102 × lognat (CRP + 1) + 2 × 1.5.

CPDAI: Classifies the PsA activity into mild, moderate, and severe taking into account the assessment of different domains such as peripheral arthritis, skin disease, spinal disease, enthesitis, and dactylitis. The CPDAI assigns a score of 0–3 to each of the 5 domains of PsA based on disease activity and impact of disease for this domain (as measured by a quality of life questionnaire (AQoL and DLQI) and a HAQ).

GRACE: 8 categories of variables are transformed to a 0-1 scale. (TJC, SJC, HAQ, patient VAS global, patient VAS skin, patient VAS joints, PASI score, PsAQoL). These 8 transformed variables are then combined using the arithmetic mean. (1-the sum of the 8 variables) x10.

AIMS AND OUTLINE OF THIS THESIS

The growing number of effective treatments for PsA resulted in new opportunities to improve outcome and quality of life of patients with PsA. However, aiming for better disease control and ultimately even clinical remission does not only require the availability of novel therapeutic options but also a better understanding of when and how to use them. Rather than starting from the therapeutics as such, this requires first of all a detailed understanding of the remaining unmet needs in clinical practice, followed by RCT and/or strategy trials to assess how to best address these unmet needs. Therefore, **the overarching aim of this thesis is to investigate how we can achieve clinical remission in PsA**.

In **Chapter 2,** we first review the recent rapid expansion of therapeutic options in SpA (including PsA). We additionally focus on the optimal clinical use of these drugs in general and on treatment strategy questions in particular.

Part I of this thesis focuses on residual disease in clinical practice and the way we define residual disease.

The aim of **Chapter 3** is to assess the rationale behind treatment decisions in current clinical practice. We focus on the current practice in defining residual disease and the subsequent treatment decisions made in PsA patients.

In **Chapter 4** we describe a cross sectional cohort where we evaluated how many PsA patients with an acceptable disease state according to the treating rheumatologist have quiescent disease when we use the Minimal Disease Activity criteria (MDA) to define quiescent disease. MDA is a previously developed outcome measure to define a minimal disease activity state in PsA.

There are multiple outcome measures in use and validated for PsA. Guidelines on the treatment of PsA recommend the use of an outcome measure (or treatment target) as a therapeutic goal (with concepts such as remission or low disease activity as a disease state to aim for), without specifying which one. To answer the question if these different measures do aim for a similar disease state we used the real-life cohort from Chapter 4 to compare several candidate targets for 'remission' and 'low disease activity' in **Chapter 5.**

Part II of this thesis describes a study on the early intensive treatment of PsA

One of the treatment strategy questions we address in Chapter 2 is the use of early aggressive combination treatment in PsA. Whereas this approach was proven very

efficacious in RA in terms of both increased clinical response rates and prevention of structural damage, there are only sparse data on the validity of this approach in PsA. In **Chapter 6** we describe an investigator initiated, randomized, double blind placebo controlled trial which aimed to investigate if the early use of an TNFi combined with methotrexate is superior to methotrexate alone, the standard first line treatment, in achieving remission in early PsA.

Part III focuses on the immunological effects of one of the new targeted treatments, IL-17A blockade, to see if the clinical response is paralleled by a reversal and/or normalization of the immunopathology.

In **Chapter 7** we performed an investigator initiated study with secukinumab, one of the available IL-17A blocking biologicals, to study the immunomodulatory effect on the synovium (the target tissue of the disease) as well as the systemic immunomodulatory effects of this therapy.

Additionally, in **Chapter 8** we studied the effect of IL-17A blocking therapy on the inflammatory activity in the vessel wall as measured by PET-CT, which is a proxy for cardiovascular risk.

Finally, **Chapter 9** contains the summary and conclusions of the studies presented in this thesis.

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New treatment paradigms in spondyloarthritis

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Abstract

Purpose of review: This review presents the recent rapid expansion of therapeutical options in spondyloarthritis. Additionally it focuses on the importance of additional questions raised by the growing therapeutic possibilities related to the optimal use of these drugs.

Recent findings: The emergence of new treatment options opens new avenues and opportunities for treating patients with non-response, contra indications or intolerance for classic drugs. However, it becomes more relevant than ever to define not only drugs and treatment options but also treatment strategies. We address current literature and remaining questions on strategies such as early intervention, combination treatment, personalized medicine and treat-to-target.

Summary: Not only the treatment as such, but also the treatment strategy is crucial to reveal the full therapeutic potential and benefit for patients. Whereas cautious but crucial steps have been taken in the last years to explore these aspects, related to timing and sequence of treatment (including combination treatments), stratified medicine approaches, and treat-to-target strategies it is now time for full scale investment in prospective strategy trials.

INTRODUCTION

Spondyloarthritis (SpA) is an inflammatory musculoskeletal disease comprising different phenotypic subsets with common genetic, radiologic and clinical features.[1,2] SpA is subdivided clinically in axial SpA (AxSpA)and peripheral SpA(pSpA), with ankylosing spondylitis(AS) and psoriatic arthritis(PsA) as clinical prototypes, respectively.[3] The key features of AxSpA are inflammatory back pain, sacroiliitis, and new bone formation leading to ankylosis of the spine. Historically, AxSpA patients with visible radiographic damage of the sacro-iliac joints on X-ray were classified as AS, whereas patients without this radiologic feature are classified as non-radiographic AxSpA. pSpA is mainly characterized by arthritis of peripheral joints, dactylitis, and enthesitis; in case of PsA, this is associated with skin psoriasis(PsO). Whereas these classifications are very useful in clinical research, it should be noted that in clinical practice the population is very heterogeneous and many patients have a mix of axial and peripheral clinical symptoms, either at presentation or during the evolution of the disease.

Classical treatment paradigm in SpA

The current treatment paradigms in AxSpA and PsA have been extensively reviewed elsewhere.[4,5] Briefly, nondrug interventions such as physiotherapy, and non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for both AxSpA and pSpA. Conventional disease modifying anti-rheumatic drugs (csDMARDs) are a next step for patients with peripheral disease, albeit these drugs have mainly been studied in PsA (not in other pSpAs) and, even in PsA, the evidence supporting their efficacy is limited to even debatable.[6,7] Local corticosteroids are a useful addition for pSpA. In contrast to peripheral SpA, there is no evidence supporting the use of csDMARDs or corticosteroids in axial disease.

SpA patients with persistent moderate to high disease activity despite the previous treatments are eligible for Tumor necrosis factor (TNF) blocking biologics (TNFi). There is ample clinical trial and real world evidence that TNFi have a major impact on both peripheral and axial disease as well as on function and quality of life (QoL). Moreover, TNFi can also have a therapeutic effect on associated symptoms, such as skin psoriasis. All five originators of TNFi (infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab) have been approved for treatment of PsA and AS, with the four latter ones also being approved for nonradiographic AxSpA in Europe.

Despite the profound clinical efficacy of TNFi in SpA, a significant proportion of patients have either no response, a partial response with residual disease activity, or a loss of response over time. Moreover, the use of TNFi may be limited by adverse events,

tolerability issues, and/or comorbidities(such as current or recent history of malignancy). This has triggered extensive research for other therapeutic targets, resulting in the recent emergence of new treatment modalities for SpA.

New targeted therapies in PsA

In Table 1, we summarize the published phase II/III studies in PsA and AS from recent years. Ustekinumab, a monoclonal antibody (mAb) toward the p40 subunit of interleukin (IL)-23 and IL-12, was the first approved non-TNFi biologic in PsA. Two pivotal phase three studies demonstrated the efficacy of ustekinumab on peripheral arthritis, enthesitis, dactylitis, and skin disease in PsA.[8,9] Efficacy was maintained overtime, inhibited radiographic progression, and was present albeit lower in patients previously exposed to TNFi. No specific safety signals emerged. In the absence of head-to-head trials with TNFi in PsA, the trend towards lower and slower response with ustekinumab on the joint but its good efficacy on skin may favor the use of this drug in TNFi-incomplete responders (TNF-IR) and in PsA patients with extensive skin disease.

Apremilast, a small molecule drug, is also approved for the treatment of PsA. Apremilast is an inhibitor of PDE4, which allows to modulate a number of key cytokine axes in different immune and effector cells. Again in the absence of head-to-head trials, clinical efficacy on joints and skin in PsA seems modest in comparison with TNFi.[10,11] No significant effect on dactylitis and enthesitis was seen, and the impact on structural progression has not been evaluated. The oral administration and the lack of monitoring requirements, however, could justify its use as a prebiologic and/or as a treatment for milder disease.

Two mAbs targeting IL-17A have been approved for PsO and tested in PsA. Secukinumab demonstrated good efficacy on arthritis, enthesitis, dactylitis, skin and QoL in two pivotal trials in TNFi naïve and TNF-IR, and inhibited structural progression.[12,13] This drug has been approved but, as the overall clinical response seems to be similar as TNFi, the exact positioning in the treatment paradigm remains to be further refined. Ixekizumab, another anti-IL-17A, showed very similar clinical and radiographic efficacy; interestingly, this trial included an adalimumab control arm, confirming that at par with TNFi.[14] Ixekizumab is not yet approved for PsA. Both IL-17A blockers are associated with dose-dependent mild fungal infections, which reflects the mechanism of this class of drugs.

Drug	Target	Disease subtype	Approved	Highest phase published	Study name	Primary endpoint met
Ustekinumab	Anti-p40 (IL-23)	PsA	Yes	III	PSUMMIT I/II(Kavanaugh et al., 2016; McInnes et al., 2013)	Yes
		AS	No	II	TOPAS(Poddubnyy et al., 2014)(Open label proof of concept)	Yes
Apremilast	PDE-4 Inhibitor	PsA	Yes	III	PALACE I/II/III(Kavanaugh et al., 2014; Schett et al., 2012)	Yes
		AS	No	II	START(Pathan et al., 2013)	No
Secukinumab	Anti-IL-17A	PsA	Yes	III	FUTURE I/II(Mease et al., 2015, Mcinnes, c2015)	Yes
		AS/nrAxSpA	Yes	III	Measure I /II (Baeten et al., 2015)	Yes
Ixekizumab	Anti-IL-17A	PsA	No	III	SPIRIT-P1&2 (Mease et al., 2016; Nash et al., 2017)	Yes
		AS	No	n/a		n/a
Abatacept	CTLA-4	PsA	Yes	III	ASTRAEA(Mease et al., 2017)	Yes
		AS	No	n/a		n/a

Most recently, the cytotoxic T-lymfocyte-associated-protein-4-immunoglobulin-molecule (CTLA4-Ig), abatacept, has been approved for PsA. Abatacept demonstrated clinical efficacy on arthritis, but a smaller benefit on other musculoskeletal symptoms as well as radiographic progression in PsA patients.[15] Again, important to note is the only modest effect in comparison with TNFi.

Finally, a number of new drugs are currently in clinical development for PsA. This includes the anti-IL-17RA antibody brodalumab (which reported phase II data but the clinical program was interrupted because of a signal for suicidal ideation),[16] the monoclonal anti-IL17A/F antibody bimekizumab,[17] several antibodies towards the p19 subunit of IL-23 (guselkumab, tildrakizumab and risankizumab),[18] and several Janus Kinase inhibitors (JAKi) (tofacitinib, baracitinib). If and when these treatments will be approved and will become available in clinical practice remains to be determined.

New targeted therapies in Axial SpA

The number of emerging treatment options in AxSpA is smaller than in PsA. The only targeted therapy, other than TNFi which has been approved for AS is secukinumab. Two trials showed efficacy on clinical signs and symptoms as well as function and quality of life, both in TNFi-naïve and TNFi-IR patients.[19,20] The safety profile is similar as in PsA, with a signal for mild fungal infections. Further data on radiographic progression,[21] head-to-head trials with TNFi, and data in non-radiographic AxSpA would help to define the exact position of this drug in the treatment of AxSpA.

No other drugs have been approved or reported phase III data. Ustekinumab showed preliminary efficacy in an open label proof of concept study, but phase III data have not yet been released.[22] Apremilast failed to reach its primary endpoint in phase II[23] and phase III data have not yet been released. Ixekizumab is in phase III in AS and nrAxSpA. As to phase II, tofacitinib showed moderate efficacy but does not seem to progress to phase III.[24] Several other compounds, including risankizumab and bimekizumab, are in phase II in AS, without any efficacy data being public at this time.

Treatment strategies in SpA

The emergence of new treatment options in PsA, and to a lesser degree, in AxSpA, opens new avenues and opportunities for treating patients with nonresponse, contraindications, side effects, or intolerance to classical drugs. However, it raised a couple of additional questions related to the optimal use of these drugs. In line with the evolutions in the field of rheumatoid arthritis (RA) treatment over the last decade, it becomes more relevant than ever to define not only drugs and treatment options

but also treatment strategies. In particular, are treatment strategies such as early intervention, combination treatment, personalized medicine, treat-to-target and tight control relevant and useful in SpA? What type of evidence needs to be generated to validate these strategies? And what are the hurdles that hamper the implementation of these strategies in clinical practice?

Early aggressive treatment in SpA

In RA, early aggressive treatment did not only result in prevention of structural damage but also in increased clinical response rates, especially with regard to low disease activity and remission.[25] Both aspects are important to achieve a more favorable long term outcome. A similar concept has not yet fully been established in SpA, partially because early diagnosis remains often a challenge and because NSAID and/or csDMARD are considered the cornerstones of a gradual step-up treatment paradigm.

The modest and even sometimes debatable efficacy of csDMARD in pSpA triggered a couple of clinical trials that challenge the concept of gradual step-up therapy. A first study compared the use of infliximab plus methotrexate (MTX) with MTX alone in PsA patients naïve for methotrexate in an open label fashion.[26] Both arms show a high response rate although the combination therapy was far superior in achieving remission outcomes. Confirmation of the superior efficacy of TNFi+MTX versus MTX alone awaits confirmation in a double-blind randomized setting.

Based on the demonstration that TNFI are not only effective in PsA but also in other subtypes of pSpA,[27–29] the CRESPA study investigated the efficacy of NSAIDs and golimumab versus NSAIDs alone in pSpA patients very early in the disease.[30] The study showed a substantially higher remission rate at 24 weeks, with 75% of golimumab treated patients reaching a status of complete absence of disease symptoms compared with 20% in the NSAID only group ($P<0.001$).

The concept that early initiation of TNFi may lead to higher remission rates was also explored in AxSpA. Sieper et al [31]showed a superior efficacy of TNFi in early AxSpA versus NSAIDs alone. The INFAST study evaluated the use of infliximab and naproxen with naproxen alone in patients with active early AxSpA(<3years of disease duration). A greater ASAS partial remission response occured in the TNFi group (62%vs.35%). This study supports the early diagnosis and treatment of SpA with full dose of NSAIDs and a fast escalating combination of NSAID+TNFi treatment in patients with an insufficient response.

Whereas these studies tend to indicate that early aggressive treatment is useful in both pSpA and AxSpA, a couple of key questions remain unanswered. First, are the high remission rates because of the use of more effective drugs (TNFi) and/or to the earlier initiation? Indirect comparison between trials suggest, that the remission rate of 35% upon NSAID therapy in the INFAST trial is higher than reported previous with NSAID in established disease(12-15%).[32,33] Multiple factors may bias this comparison and direct analysis is mandatory to come to firm conclusions. Second, is early aggressive treatment also associated with reduced radiographic progression? Whereas most targeted therapies, with the exception of apremilast, have demonstrated an impact on progression of structural damage in established PsA, this is not the case for new bone formation in AxSpA. Certainly for this subgroup, it would thus be crucial to see if earlier initiation of TNFi may have a significant impact on structural damage over time. Third, the few early intervention studies described above were all conducted with TNFi, leaving the question open whether the same concept holds true for other mechanism of action treatments. Fourth, it needs to be better determined if 'immediate' initiation of targeted therapies is required to obtain high remission rates in SpA, or if it would be sufficient to decrease the time intervals in the current step-up approach? For example, the INFAST study showed that response to NSAIDs is noticed within the first 2-4weeks and the need for a TNFi could be considered in an early state.[31] Similarly, should csDMARDS really be used for 6 months before escalating to a targeted therapy in PsA.[34] Finally, an important and unanswered question is if rapid induction of remission upon early aggressive treatment may allow tapering and/or stopping of the targeted therapy over time? The targeted therapy would then be used in an 'induction' strategy, with maintenance using NSAIDs and/or csDMARDs.

Beyond these scientific questions about early aggressive treatment strategies in SpA, one should also consider potential barriers to implement this in clinical practice. Early diagnosis, which is still a major challenge in AxSpA,[35] early referral of psoriasis patients with musculoskeletal symptoms and early access to targeted therapies are just a few examples of obvious challenges that need to be addressed to use this strategy effectively.[36–38]

Sequential versus combination therapy in spondyloarthritis

Another ongoing discussion is whether the use of a concomitant csDMARD might increase response rates or prolong drug survival of biologics in SpA. In RA, the continuation of TNFi with methotrexate is supported by current guidelines because the combination is proven to be more effective than TNFi monotherapy. Two prospective cohorts in PsA reported that patients already taking not using concomitant methotrexate before

starting TNFi was associated with a poorer clinical response.[39, 40] Other studies could not confirm this[41], emphasizing the inherent biases and limitations of such studies and the importance of prospective randomized trials. In PsA, multiple randomized controlled trials (RCTs) showed no difference in response rates to TNFi in patients with or without concomitant MTX.[42–44] Similar results were reported in an AS trial with infliximab.[45] The key limitation, however, is that they included patients who failed already on MTX. We do not have a randomized prospective study comparing a biologic with or without concomitant MTX. We also lack prospective randomized data on tapering/stopping MTX in patients with good clinical response to a biologic.

Considering the fact that MTX is not effective for AxSpA, the benefit/risk balance of MTX combination versus mono/sequential therapy is most relevant to PsA. However, similar questions can be raised about the combination of NSAIDs and TNFi in AxSpA: Should TNFi be added to NSAIDs or replace it in IRs? And could NSAIDs be stopped when a patient is in remission with the combination therapy?

Adding further complexity to the treatment strategy, we have no evidence that the potential benefit of combination of MTX and/or NSAIDs with a TNFi in SpA would also translate to a similar benefit with other biologics such as IL-17Ai or ustekinumab. Moreover, we also lack data on the combination of other synthetic drugs, such as leflunomide but certainly also the newer compounds such as apremilast or JAKi, with TNFi and IL-17Ai. Finally, combination of biologics failed to increase efficacy but jeopardized safety in a couple of RA trials[46–48], but may be a realistic option in SpA considering the differences in disease, comorbidities and MoAs. Case reports suggest, for example, that combination of ustekinumab with TNFi might be considered in refractory PsA.[49] And bispecific antibodies blocking TNF and IL-17A, and IL-17A and IL-17F are in clinical trials in PsA and AxSpA.

In terms of potential hurdles for implementation of combination treatment strategy, one should consider access, costs, tolerability, and safety. It should also be better defined in which patients such combination treatments hit the right benefit/risk/cost balance and, in particular, whether all patients or only refractory patients would be eligible for such an approach.

Personalized/stratified medicine in SpA

This raises another important treatment strategy question: should distinct subpopulations of SpA patients require different treatments? The global answer to this

question is definitively yes as it is evident that not all treatments are as effective for peripheral versus axial disease, with as prototypical example csDMARDs. The question, however, is if and how these strata could be further refined.

Within axial disease there is no evidence that AS and nraxSpA respond differently to specific treatments. This has been best evidenced for TNFi.[50] There are currently no data on IL-17Ai in nrAxSpA but it is reasonable to expect a similar efficacy as in AS. The same holds through for pSpA: different TNFi have demonstrated efficacy not only in PsA but also other pSpA.[27,28,30,51,52] Whether this also applies to other drugs approved for PsA, remains to be determined. An additional question in pSpA is if patients should be stratified according to arthritis versus enthesitis/dactylitis. Based on animal data, it has been hypothesized that enthesitis may be more IL-23/IL-17 dependent.[53] However, other models indicated both the relevance of IL-23 for synovitis and the relevance of TNF for enthesitis.[54] Accordingly, significant improvements in enthesitis/dactylitis have been seen in PsA trials with both TNFi,[55,56] ustekinumab,[57] and IL-17Ai.[9,14] In the absence of clear head-to-head data, there is thus no strong evidence for such treatment stratification.

Beyond axial and peripheral disease, the presence of extraarticular manifestations represents a clear base for a stratified treatment strategy in SpA. Skin psoriasis can be treated with both TNFi and drugs targeted the IL-23/IL17 axis, but the latter have shown superiority in head-to-head trials in PsO[58,59] and may thus favor their use in patients with extensive/refractory skin disease. In contrast, apremilast and abatacept have only limited efficacy on skin.[10, 15] For SpA-associated gut inflammation, monoclonal anti-TNF antibodies and ustekinumab have shown clear efficacy in Crohn's disease,[60, 61] which is not the case for etanercept and secukinumab.[62,63] Although less strongly supported by direct evidence from RCTs, TNFi may also be more effective for the treatment of uveitis.[64–67]

An additional dimension for stratification is the presence and/or prognosis of structural damage. In PsA, most targeted therapies have demonstrated impact on structural progression with the exception of apremilast, questioning the use of the latter drug in patients with erosions and/or poor prognostic factors. In AxSpA, the question may become even more important as, despite some debate, TNFi have no proven impact on osteoproliferation[68,69] whereas preclinical data[70] and very preliminary clinical evidence[20] suggest that IL-17Ai such as secukinumab may have a more profound impact. This hypothesis requires now mandatory confirmation in well-designed clinical trials. If confirmed it could help to position the use of TNFi versus IL-17Ai in AxSpA without or with signs of rapid structural progression, respectively.

A final and clinically very relevant form of stratification is to adapt the treatment strategy to previous treatments, in particular for TNFi. Previously, the only option in PsA or AxSpA patients with incomplete response to a first TNFi was to switch to another TNFi. Although guidelines do recommend switching, there is a lack of prospective controlled data to support these.[71,72] Randomized studies with both secukinumab and ustekinumab in AS and PsA have demonstrated significant responses in TNF-naive and TNFi-IR patients. Whereas these data prove that these treatments are good options for TNFi-IR, further studies need to compare switch to a second TNFi versus to another MoA to determine the best treatment strategy.

As to implementation of a stratified/personalized treatment strategy in clinical practice, obvious hurdles are the fact that the phenotype of the disease may be mixed and may even vary overtime in a single individual. More importantly, the biggest obstacle may be the fact that volume rather than value-based contract by payers and insurance companies may not allow health care professionals to use all available treatment options in a personalized medicine approach.

Treat-to-target and tight control in SpA

Treat-to-target is a very successful treatment strategy in the treatment of RA. Treat-to-target is a treatment strategy where the clinician treats the disease aggressively enough to reach and maintain a pre-specified and sequentially monitored target. In RA, treat-to-target improves clinical outcomes and limits radiographic progression.[73] Treatment recommendations recommend to treat-to-target in SpA although evidence supporting the beneficial effect over standard care is limited in this patient group.[74,75] The Tight Control of Psoriatic Arthritis(TICOPA) trial is the first treat-to-target study in SpA and demonstrated that the tight control of disease activity of PsA through a treat-to-target approach significantly improves clinical outcomes for patients with early disease in comparison with standard care.[76] However, an effect on enthesitis/dactylitis or radiographical outcome was not different between the groups. And the treat-to-target approach increased the occurrence of adverse events. Further studies are needed to confirm the clinical and long term benefits of treat-to-target in the several SpA subtypes as well as the cost, risk, and additional adverse event burden of this approach.

Moreover, several potential hurdles to implement the treat-to-target strategy in clinical practice remain. For example, consensus on the definition of remission and response criteria to use is still in debate. One should consider costs (increase in agents used and more outpatient visits), outweigh risk of increase in adverse events versus clinical benefit, feasibility in clinical practice and the willingness of rheumatologists to implement this strategy, and the availability of the treatments.

CONCLUSION

The rapid expansion of the therapeutic options in SpA carries a lot of promise for our patients with peripheral and/or axial disease. At the same time, this expansion emphasizes the fact that not only the treatment as such but also the treatment strategy is crucial to reveal the full therapeutic potential and benefit for patients. Key aspects to develop optimal treatment strategies in SpA relate to timing and sequence of treatment (including combination treatments), stratified medicine approaches, and treat-to-target strategies. Whereas cautious but crucial steps have been taken in the last years to explore these aspects, it is now time for full scale investment in prospective strategy trials. Finally, it will be critical to connect the strategy trial outcomes with real world evidence (cohort studies, payer and access ecosystem), to identify and overcome issues that may complicate or even prevent the implementation of these treatment strategies in clinical practice.

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HOW CLINICAL PRACTICE DEFINES RESIDUAL DISEASE

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Residual disease activity and treatment adjustments in psoriatic arthritis in current clinical practice

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Background: With expanding therapeutic possibilities for the treatment of psoriatic arthritis (PsA) it will be increasingly important to determine residual disease and define when to adjust treatment. The rationale behind treatment decisions in current daily clinical practice and the relation with residual disease activity has not been investigated. The aim of this study was to assess the current clinical practice on defining residual disease and subsequent treatment decisions made in PsA patients.

Methods: This cross-sectional study scored disease activity and treatment decisions prospectively in 142 consecutive PsA patients visiting the outpatient clinic for routine follow up. Disease activity parameters were scored by patient and the treating rheumatologist; the rheumatologist additionally registered his opinion on the presence of remaining disease activity despite current treatment (further mentioned as remaining disease) and subsequent treatment decisions.

Results: Two thirds (90/142) of patients had remaining disease activity according to the treating rheumatologist. Almost half (46%) of these patients had moderate to high disease activity according to the clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA). Residual disease activity was determined by joint disease and pain rather than by active psoriasis. Demographic and clinical features were similar between groups with or without residual disease. Among patients with residual disease activity, 74% were treated with either a conventional synthetic disease modifying anti-rheumatic drug (csDMARD) only or a first TNF inhibiting biological agent, suggesting opportunities for treatment modification. However, treatment adjustment was initiated in only 21 (23%) of the 90 patients with residual disease. When comparing patients with remaining disease activity with and without treatment adjustment, we found no differences in objective disease activity measures, such as joint counts and patient scores. These data suggest that treatment is not adjusted in a large majority of patients with residual disease activity, although options for treatment changes are available.

Conclusions: Remaining disease activity is present in almost two thirds of the patients with PsA when scored by the treating rheumatologist, but triggers treatment adjustment in only a minority. Further research to understand why disease activity does not lead to treatment adjustment is required to enable the implementation of treatment strategies in clinical practice.

Abstract

BACKGROUND

Treatment options for psoriatic arthritis (PsA) increased significantly in the last decade with leflunomide and Tumor Necrosis Factor (TNF) inhibitors (TNFi) becoming part of our standard therapeutic arsenal.[1] Several other new treatments became available in recent years, including ustekinumab, apremilast, and secukinumab.[2–5] Additionally, the first trial comparing target steered treatment vs standard care in PsA, the Tight Control of Psoriatic Arthritis (TICOPA) trial, demonstrated that not only the availability of treatments but also the strategy on how to use these treatments determines the clinical outcome. The treat-to-target arm of the study shows significantly better outcomes in peripheral arthritis, skin, and patient reported outcomes in comparison with the standard-care arm, with more patients reaching a minimal disease activity state in the treat-to-target arm.[6] Therefore, the combination of additional treatment options and better treatment strategies holds great promise to improve the outcome in PsA in daily clinical practice.

Intriguingly, the few available publications on real-life clinical PsA practice indicate that not many patients are in a minimal disease state despite treatment.[7] Potential reasons for residual disease activity in this group of patients could be categorized as follows: (1) patients not responding to all available treatments - for this category, new treatment options obviously open up new perspectives; (2) patients in whom comorbidities, side effects, and/or incompliance results in the inability or unwillingness to use available medication - in this case, new treatments may not have an additional value; and (3) patients in whom the currently available treatments are not optimally used - this category could benefit from stricter definition and implementation of treatment strategies.

To quantify the presence of remaining disease activity in PsA in daily clinical practice and understand the underlying reasons, we set up a cross-sectional cohort documenting disease activity and treatment use in consecutive patients with PsA and analyzed the treatment decisions that were made by the treating rheumatologist. Importantly, the available treatment options in clinical practice during the inclusion period of this study were limited to conventional disease modifying anti-rheumatic drugs (csDMARDs), such as methotrexate and leflunomide, and TNFi. Ustekinumab became available for use in clinical practice just before this study and was therefore not a common drug to prescribe at the time.

METHODS

This observational cross-sectional study was conducted at the rheumatology outpatient clinics of two centers in Amsterdam (AMC and Reade) between October 2014 and September 2015. Sixteen participating rheumatologists recruited consecutive patients with PsA visiting their outpatient clinic, including a total of 152 patients. The inclusion criteria were (1) clinical diagnosis of psoriatic arthritis, (2) age of 18 years or older, (3) disease duration of at least 6 months, (4) fulfillment of the Classification criteria for Psoriatic Arthritis (CASPAR)[8], and (5) current or previous treatment with synthetic and/or biological DMARD therapy. Patients currently participating in a clinical trial were excluded from the study. This observational study did not require ethical approval and/or patient informed consent as the Medical Research Involving Human subjects Act (WMO) does not apply to these types of studies in the Netherlands, as confirmed by the Ethics Committee of the Academic Medical Center/University of Amsterdam. The study was conducted in accordance to the Declaration of Helsinki (2008) and ICH/Good Clinical Practice (GCP) standards.

Data collection

Data on demographics, disease characteristics, current treatment, treatment history, and medical history were extracted from the patient files by the study physician (L.vM). To reflect decision-making in real-life clinical practice, the disease activity scores and the statements on the presence of remaining disease and the decisions on treatment adjustment were made by the treating rheumatologist during a routine clinical visit. At the time of the visit the treating rheumatologist performed a physical examination, collected outcome measures, and answered questions on remaining disease activity and treatment modifications. Physical assessments included scoring of swelling and tenderness of the joints (swollen joint count (SJC) 66/ tender joint count (TJC) 68), an enthesitis count, recording the number of enthesial sites with enthesitis according to the rheumatologist, and a dactylitis count. Disease activity measures were the Physician global Assessment on disease activity (VASPhysGlobal) and a Physician Assessment of psoriatic skin activity (VASPhysSkin) on a visual analog scale (VAS) of 0-10cm and the Bath Ankylosing Spondylitis Activity Disease Index (BASDAI). The following questions were answered by the Rheumatologist. Do you think there is remaining disease activity in this patient, despite current treatment regimen? (further mentioned in this manuscript as 'remaining disease'). Will you start additional therapy or change current therapy for the remaining disease activity? If yes, what will you start or change? If no, what is the reason not to treat this remaining disease activity?

Patients completed the Patient Global Assessment of Disease Activity (VASPtGlobal) on a VAS of 0-10cm and the Patient Assessment Of Pain (VASPtPain) on a VAS of 0-10cm. To grade the severity of the disease activity in a composite index, we used the clinical Disease Activity in PsA score (cDAPSA) calculated as SJC66 + TJC68 + VASptglobal + VASptPain and divided by categories: remission, cDAPSA ≤ 4; low disease activity, cDAPSA > 4 and ≤ 13; moderate disease activity, cDAPSA >13 and ≤ 27; high disease activity, cDAPSA > 27.[9,10]

Data analysis

Data are presented as mean and standard deviation (SD) or as median and interquartile range (IQR) where applicable. Statistical comparisons between remaining disease groups and treatment yes/no groups were performed using *t* test or, alternatively, Mann-Whitney U test when data were not normally distributed. Statistical tests were two-sided and P values <0.05 were considered statistically significant. Analysis was performed in SPSS Statistics (V22.0).

RESULTS

A total of 152 patients were included, anddata scored by rheumatologist as well as patient scores were available for 142 patients. The remaining 10 were excluded from analysis as either the physician or the patient data were missing. Disease characteristics and demographics are shown in Table 1.

TABLE 1. Clinical characteristics and disease activity of patients with and without residual disease activity

	Total group (N=142)	Residual disease activity according to rheumatologist (N=90)	No residual disease activity according to rheumatologist (N=52)	Residual disease v.s. no residual disease P value
Age mean (SD)	53.0(12.6)	53.6(6.3)	51.9(13.6)	0.000
Male/Female N/N	92/60	53/37	33/19	0.865
Disease duration diagnosis mean (SD)	10.3(7.9)	11,0(9.2)	10.1(6.8)	0.494
on treatment >6months %	93	86	94	0.618
Current only DMARD user n(%)	110(49)	52(58)	23(44)	0.032
Current 1st TNF user n(%)	32(22)	14(16)	18(35)	
Current >1 TNF user n(%)	35(24)	24(27)	11(21)	
Swollen joints	0(0-0)	0(0-1)	0(0-0)	0.000
SJC of 0 n(%)	111(77)	63(70)	49(94)	
SJC of 1 n(%)	10(7)	8(9)	2 (4)	
SJC of 2 n(%)	5(3)	5(6)	0 (0)	
SJC of ≥3 n(%)	15(10)	14(16)	1 (2)	
Tender Joints	1(0-2)	1(0-3)	0(0-0)	0.000
TJC of 0 n(%)	82(57)	36(40)	46(88)	
TJC of 1 n(%)	21(13)	16(18)	5(10)	
TJC of 2 n(%)	12(13)	12(13)	0(-)	
TJC of 3 n(%)	25(17)	24(27)	1(2)	
Number of dactylitic digits	0(0-0)	0(0-0)	0(0-0)	0.017
Dactylitis count of 1 n(%)	8(6)	8(9)	0(-)	
Number of enthesitis points	0(0-0)	0(0-0)	0(0-0)	0.001
Enthesitis count of 1 n(%)	14(10)	14(16)	0(-)	
Enthesitis count of 2-4 n(%)	2(1)	2(2)	0(-)	
VAS physician skin severity	1(0-2)	1(1-2.5)	1(0-1)	0.000
VAS physician overall disease activity	1(1-3)	2(1-4)	1(0-1)	0.000
VAS patient global disease activity	2(1-6)	5(2-7)	1(0-2)	0.000
VAS pt pain	2(1-6)	5(2-7)	1(0-2)	0.000
BASDAI	2,65(1-4.8)	4.1(2.5-5.9)	0.9(0.4-1.8)	0.000
cDAPSA Remission n(%)	45(32)	9(10)	36(69)	0.000
cDAPSA Low disease activity n(%)	49 (35)	34(38)	15(29)	
cDAPSA Moderate disease activity n(%)	35(25)	35(39)	0(-)	
cDAPSA High disease activity n(%)	6(4)	6(7)	0(-)	
cDAPSA missing	7(5)	6(7)	1(2)	

Values are Median (IQR) unless stated otherwise. Significance of the comparisons was determined by the independent sample t test for continues variables and the Mann Whitney U test for non normally distributed variables. The comparisons within cDAPSA groups were determined by the Kruskall Wallis test. csDMARD= conventional synthetic disease modifying antirheumatic drugs; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; TNFi= Tumor Necrosis Factor Inhibitor; cDAPSA = clinical Disease Activity in PsA score

We first analyzed the disease activity present in patients with or without residual disease according to their treating rheumatologist. Fifty-two patients were considered by the treating rheumatologist not to have remaining disease activity (Table 1). These patients indeed had low disease activity in all measured objective disease domains: there were only three patients with a swollen joint count >0, three patients with a tender joint count >0, and no patients at all with dactylitis or enthesitis. The median skin severity score was 1 on the 10-point scale. This was confirmed by patient-reported severity and pain scores (median VASpatient global and VASpt pain score of 1 out of 10). Accordingly, all patients were in remission (36/52) or low disease activity (15/52) (there was insufficient data on one patient to calculate the cDAPSA) as defined by the cDAPSA composite score.

Of the 142 patients, 90 (63%) were considered in the opinion of the treating rheumatologist to have remaining disease (Table 1). This was supported by disease activity across all measured domains, with 31% of patients having at least one swollen joint (including 16% with three or more swollen joints), 60% having one or more tender joints, 18% having enthesitis, 9% having dactylitis, and 30% who had a VASphys skin score >2. This was reflected by higher scores on patient-reported severity of pain and in the global health score (median score of 5/10). The cDAPSA composite score indicated that 46% of these patients had moderate to high disease activity. Overall, these data indicate that almost two thirds of the patients had some kind of objective residual disease activity, with almost half of those having even moderate to high disease activity. The remaining disease activity was mainly determined by joint disease and pain rather than by skin psoriasis, partly driven by an overall low burden of skin psoriasis in this cohort.

In order to better define which patients had remaining disease activity, we compared demographic and clinical features between those with and without residual disease activity. There were no differences in gender, disease duration, comorbidity, current treatment duration, or number of previously used csDMARDS. Residual disease activity was more frequently reported in patients treated with a csDMARD only (66%) or a second TNFi (69%) in comparison with patients on their first TNFi (44%) (P=0,019). As 74% of the patients with residual disease activity were currently treated with either a csDMARD only or a first TNFi, suggests that treatment modification could be an option.

We asked the rheumatologist whether the presence of remaining disease activity would lead to a treatment adjustment. Of the 90 patients with remaining disease activity, treatment was modified in only 21 (23%). These treatment adjustments included start of analgesic treatment (n=6), local or intramuscular corticosteroid therapy (n=5), switch of csDMARD to another csDMARD (n=4), referral to other specialists (hand surgeon,

orthopedic surgery) (n=2), start of a second and a third TNFi in a patient already using TNFi treatment (n=2), addition of a csDMARD to current TNFi therapy (n=1), and start of a TNFi in a patient only using csDMARDs (n=1).

In order to understand why treatment adjustment was only initiated in 23% of the patients with remaining disease activity, we compared those with and without treatment adjustment for clinical and demographic features (Table 2). With the exception of VAS physician (median 3(IQR2-5) v.s. 2(2-3), p=0.007), none of the disease activity measures were different between the two groups, not even objective measures such as the SJC. Also demographic features such as gender, disease duration, and treatment durations were similar (Table 2). However, treatment was less frequently changed in patients treated already with a second TNFi (in 3/24 (13%) of patients) in comparison with the csDMARD only or first TNFi groups (15/51 (28%) and 4/14 (29%) respectively).

We additionally investigated the reasons not to adjust treatment. In 39/69 (57%) patients, the rheumatologist judged the complaints as 'minor'. This group included 8 patients with a SJC ≥1, 19 with a TJC ≥1, and 6 with an enthesitis. cDAPSA scores categorized these patients as having moderate disease activity (n=12), low disease activity (n=19), and remission (n=5) (with 4 patients having incomplete data to calculate a cDAPSA score). In the remaining 30 patients the following reasons were reported: patients' preference not to adjust medication (10/69 (14%)); absence of additional treatment options (5/69 (7%)) (these patients were all currently treated with a second or third TNFi); lack of compliance and/or adverse events (5/69 (7%)); and other reasons (20/69 (29%)) (more than one reason could be reported per patient). Other reasons included: disease activity reflects symptoms of comorbidity instead of the PsA (non inflammatory joint problems/ disease including osteoarthritis of the knee/hand, trigger finger, meniscial tear, recent fracture) (n=4); awaiting therapeutic effect of recent change (n=3); side effects resulted in a disruption of treatment, recently restarted therapy (n=3), no therapeutic options left in this patient (n=2), first await results of MRI scan (n=1), task of the dermatologist (n=2), comorbidity prohibits treatment intensification, one patient was recently diagnosed with breast cancer and one patient had undergone surgery complicated by insufficient wound healing) (n=2); side effects limit me to use optimal dosage of treatment (n=1), patient is incompliant to therapy (n=1),Overall, judgment by the rheumatologist and/ or patient rather than objective hurdles to intensify treatment (absence of additional treatment options, lack of compliance, intolerance) drove the decision not to modify treatment despite the presence of residual disease activity.

TABLE 2. Disease activity in patients with residual disease activity resulting or not resulting in additional treatment.

	Total group (n=90)	Additional treatment (n=21)	No additional treatment=69)	Additional treatment v.s. No additional treatment P value
Age mean (SD)	53.6(12.2)	52.6(10.8)	53.9(12.7)	0.270
Male/Female N/N	53/37	15/6	38/31	0.167
Disease duration diagnosis mean (SD)	11.0(9.2)	10.8(8.6)	11.2(9.4)	0.837
on treatment >6months %	92	90	93	0.057
Swollen joints	0(-0-1)	0(0-1.5)	0(0-1)	0.359
SJC of 0 n(%)	63(70)	13 (62)	50(72)	
SJC of 1 n(%)	8(9)	3(14)	5(7)	
SJC of 2 n(%)	5(6)	2(10)	3(4)	
SJC of N≥3 n(%)	14(16)	3(14)	11(16)	
Tender Joints	1(0-3)	1(0-2)	1(0-3)	0.923
TJC of 0 n(%)	36(40)	7(33)	29(42)	
TJC of 1 n(%)	16(18)	8(38)	8(12)	
TJC of 2 n(%)	12(13)	2(10)	10(15)	
TJC of ≥3 n(%)	25(27)	4(20)	21(30)	
Number of dactylitic digits	0(0-0)	0(0-0)	0(0-0)	0.310
Dactylitic digits ≥ 1 n(%)	8(9)	3 (14)	5 (8)	
Number of enthesitis points	0(0-0)	0(0-0)	0(0-0)	0.384
Enthesitis points ≥ 1 n(%)	16(18)	5 (24)	11 (16)	
VAS physician skin severity	1(1-3)	2(1-3.5)	1(1-2)	0.478
VAS physician overall disease activity	2(1-4)	3(2-5)	2(1-3)	0.007
VAS patient global disease activity	5(2-7)	6(3-7)	5(2-7)	0.157
VAS pt pain	5(2-7)	6(3-7)	4(2-7)	0.225
BASDAI	4.1(2.5-5.9)	4.2(2.7-5.8)	3.7(2.5-5.9)	0.907
cDAPSA Remission n(%)	9 (10)	1(5)	8(12)	0.594
cDAPSA Low disease activity n(%)	34(38)	7(33)	27(39)	
cDAPSA Moderate disease activity n(%)	35(39)	11(52)	23(33)	
cDAPSA High disease activity n(%)	6(7)	2(10)	4(6)	
cDAPSA missing	6(7)	0	6(9)	

Numbers are Median (IQR) unless stated otherwise. Significance of the comparisons is determined by independent sample t test for continues variables and the Mann Whitney U test when for non-normally distributed variables. The comparisons within the cDAPSA groups were determined by the Kruskall Wallis test. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; SJC= swollen joint count; TJC= tender joint count; VAS visual analogue scale; cDAPSA = clinical Disease Activity in PsA score

DISCUSSION

This prospective, cross-sectional study in 142 patients with PsA in daily clinical practice showed that despite being on stable treatment and follow up, almost two third of the patients were considered by their treating rheumatologist to have residual disease activity. Almost half (46%) of these patients had moderate to high disease activity according to cDAPSA. Residual disease activity was determined by joint disease and pain rather than by active psoriasis. Our findings are perfectly aligned with recently published data from Michelsen et al., showing that only few PsA patients fulfilled remission criteria and only 25% fulfilled Minimal Disease Activity (MDA) in daily clinical practice.[7] Whereas these data suggest that a majority of patients may benefit from treatment modification and/or intensification, certainly in an era with emerging novel treatment options, treatment was adjusted in only 21 of the patients with residual disease (23%) in our cohort. While the cDAPSA showed moderate to high disease activity in almost half of these patients, the rheumatologists reported in a majority of patients that (a) the residual disease was not substantial enough to justify treatment adjustment or (b) that the patient did not wish to adjust treatment. When comparing patients with remaining disease activity with and without treatment adjustment, we found no differences in objective disease activity measures, such as joint counts and patient scores. And albeit remaining disease was more prevalently found in patients treated with either csDMARDs alone or a second TNFi treatment, these groups were not more likely to receive a treatment adjustment. These data suggest that treatment is not adjusted in a large majority of patients with residual disease activity, although options for treatment changes are still available.

The only published treat to target study in PsA (TICOPA) reported that despite the clear protocol stating to adjust treatment when MDA was not fulfilled, in 37% no treatment adjustment followed.[6] Reported reasons for non-escalation (and not following the TICOPA study protocol) were (1) recent start of current therapy, (2) comorbidity, (3) no therapeutic options left, and (4) unable to tolerate escalated dose. In our cohort, only a few patients started or adjusted treatment recently or had severe comorbidity resulting in contraindications for TNFi or csDMARDs. As in TICOPA, the absence of therapeutic options was a decisive factor in a fraction of patients as we observed more patients with residual disease activity in the group treated with a second TNFi group, keeping in mind the new treatments such as ustekinumab only recently came to market and apremilast and secukinumab were not available at the time of our study. Intriguingly, however, residual disease activity was more frequently reported not only in patients treated with a second TNFi (69%), or first TNFi (44%), but also in patients on a csDMARD only (66%). In the latter group, the addition of a TNFi was at that time a very obvious, well validated

and recommended therapeutic alternative, which was not used despite ongoing disease activity.[5,11] Important to note, in the Netherlands csDMARDS, TNFi as well as the newer treatments are approved treatments. They are available and reimbursed to all patients with active PsA when prescribed by a rheumatologist, therefore payer issues can be excluded as an argument for not adjusting treatment.

Collectively, these data suggest that absence of treatment modification/intensification was not due to the absence of therapeutic options in a vast majority of patients. Alternative reasons for not adjusting treatment in PsA patients with residual disease activity despite additional therapeutic options could include (1) lack of structural disease activity assessment in clinical practice, (2) limited availability of evidence that aggressive treatments result in improved short and long-term clinical outcomes, and (3) poor implementation of guidelines and treatment strategies in clinical practice.

As to lack of structural disease activity assessment in clinical practice, Coates et al. reported that PsA-specific measurements are not often used in routine clinical practice and that a target for treatment is defined in less than half of the visits.[12] Measuring activity in all domains and consensus on the definition of residual disease activity are warranted here as guidelines recommend "to achieve the lowest possible level of disease activity in all domains of disease". Although the present study required a systematic evaluation of the different domains of PsA (arthritis, pain, enthesitis, dactylitis, skin) the rheumatologist was not asked to integrate these data in a comprehensive disease activity measure. Relying exclusively on the activity of the joints and/or more global questions, could potentially explain why the rheumatologists considered the complaints as minor in 57% of the PsA patients with residual disease activity. It would be interesting to study if the use of a comprehensive measure such as MDA or a treat-to-target-strategy based on MDA or DAPSA/cDAPSA would change the rheumatologist's opinion on disease activity in the same patients.

A second factor to consider is the familiarity of the rheumatologist with the evidence that profound disease suppression is associated with better short and long-term outcomes in PsA. MDA is a well-validated measure.[13] Post-hoc analyses show that a sustained MDA state upon treatment results in better clinical and radiological outcomes.[14,15] The TICOPA trial confirmed the benefit of the treat-to-target approach in a randomized clinical trial with better clinical and patient reported outcomes in the treat-to-target arm compared with standard clinical care.[6] Importantly, the data from TICOPA became available after the inclusion of patients in the present study was completed. It would be interesting to assess if the availability of these new data would change the opinion of the rheumatologist.

The third and final factor is to what extent guidelines and treatment strategies are really implemented in daily clinical practice. The implementation of guidelines in rheumatology clinical practice has been shown to be a challenge. Studies in rheumatoid arthritis indicate that there is a discrepancy between the reported acceptance of guidelines and the application of these in clinical practice.[16,17] The IRIS study even showed that despite participation in a 2 years educational training, rheumatologists seem to be reluctant to apply recommendations in real life clinical practice.[18] These factors could play a role in PsA as well, and attention for the implementation of concepts and guidelines may even be the most important factor to consider when developing treatment strategies for PsA.

As this was a real-life, non interventional study, limitations to our study include (a) we did not have any influence on the treatment strategy applied by the rheumatologists However csDMARDS (oral and subcutaneous) as well as TNFi are available and reimbursed to all patients with active PsA when prescribed by a rheumatologist; (b) we incorporated measurements feasible for use in our current clinical practice and therefore did not include a measurement for nail disease or physical functioning, and did not collect laboratory or radiological data (c) not including multiple additional measurements resulted in an inability to calculate more comprehensive measures of PsA disease activity such as the Psoriatic Arthritis Disease Activity Score (PASDAS) or MDA, capturing more domains of the disease. Nevertheless, the DAPSA and cDAPSA are measurements suggested to use in the treat-to-target setting of PsA[10]; and (d) we did not have sufficient power to look into different subsets of patients.

CONCLUSIONS

Within the limits of this cross-sectional evaluation, we conclude that residual disease activity was present in almost two thirds of PsA patients in a daily clinical practice cohort but triggered treatment adjustment in only a quarter of those patients. Subjective opinions of rheumatologist and/or patient rather than comorbidities or a lack of treatment options drove the decision not to adjust treatment despite residual disease activity. With the increasing availability of novel drugs to treat PsA and the ongoing efforts on a consensus for treatment target, better understanding as to why residual disease activity does not lead to treatment adjustment in clinical practice is a third important pillar in developing and implementing treatment strategies to improve outcome in PsA.

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Residual disease activity in psoriatic arthritis: discordance between the rheumatologist's opinion and minimal disease activity measurement

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Abstract

Objective: To assess how many PsA patients with an acceptable disease state according to the treating rheumatologist have quiescent disease defined as minimal disease activity (MDA).

Methods: This cross-sectional study included 250 PsA patients. To assess current clinical practice as close as possible, acceptable disease state was not determined by predefined activity measures, instead was defined by asking rheumatologists to refer those patients whom they considered sufficiently treated. Patients were evaluated for current disease activity including clinical assessments and patient reported outcomes (PROs).

Results: One-third (88/250) of the patients with acceptable disease state according to the rheumatologist did not fulfill MDA(MDA-). The presence of tender joint counts and patient pain and global disease activity scores most frequently contributed to not fulfilling MDA (not achieved in 83, 82 and 80%, respectively). However, also objective signs of disease activity were higher in the MDA- than MDA+ patient group: a swollen joint count >1 occurred in 35% versus 7% ($P<0.001$), enthesitis>1 in 14% versus 3% ($P=0.002$), and Psoriasis Area and Severity Index >1 in 43% versus 26% ($P=0.002$). Residual disease was more frequent in females, elder patients and those with a raised BMI, independent of the treatment schedule, and negatively influenced PROs of function and quality of life.

Conclusions: One third of the PsA patients with acceptable disease state according to the treating rheumatologist did not fulfill the MDA criteria and had residual disease activity on both subjective and objective disease activity measurements. As residual disease activity was associated with worse PROs, future strategy trials should evaluate if treatment adjustments are beneficial for this patient group.

INTRODUCTION

Several new drugs, including ustekinumab,[1,2] apremilast,[3] and secukinumab,[4] have recently been approved for the treatment of PsA, broadening our therapeutic armentarium for this severe and potentially debilitating condition.[5,6] These novel drugs obviously open up perspectives for the PsA patients not responding to treatment with conventional disease-modifying antirheumatic drugs (cDMARDs) and/or TNF inhibitors (TNFi).[1] Obviously the question arises of weather those PsA patients not responding sufficiently to cDMARDs and/or TNFi could benefit from the new treatment options.

An equally important question is whether these novel drugs could also be used to improve disease control in patients with a partial response to cDMARDs and/or TNFi. To address this question, one should first know what proportion of patients treated succesfully with cDMARDs and/or TNFi actually achieve low disease activity. Recent clinical trials showed that only half to one-third of the patients responding to treatment as defined by an ACR20 response, did also achieved a quiescent disease state as defined by the minimal disease activity criteria (MDA). The MDA criteria aim to define low-to-minimal disease activity and represent a disease state rather than a change in disease activity.[7] They have been well validated and are increasingly proposed as target for treatment, as achieving MDA upon treatment is associated with better long-term functional outcome, better patient reported disease activity scores and less radiographic progression.[8,9,10,11] Furthermore, only half to one-third of the patients achieving an ACR20 response also achieved an MDA state in two clinical trials.[11,12] These data suggest substantial residual disease activity even in the patients defined as responders in these trials.

In clinical practice we aim to improve disease activity of patients with active PsA, but a measure such as ACR response is not used, and a treatment target is not very well defined. The relation between MDA and the currently used target in clinical practice, namely acceptable disease activity in the opinion of the rheumatologist, is unknown.

The fact that a significant proportion of PsA patients who improve upon treatment with cDMARDs and/or TNFi in clinical trials do not reach a low disease activity state raises three important questions. First, what proportion of PsA patients considered to be in a acceptable disease state in current clinical practice do really achieve a low disease activity state? Second, what factors contribute to residual disease activity and is residual disease present in specific subgroups as determined by demographic factors and/or treatment? And, third, does residual disease activity negatively impact function and quality of life of these patients? To address these questions, we conducted an observational, cross-sectional study of 250 PsA patients considered to have an acceptable disease state by

their treating rheumatologist and who were on a stable treatment regimen. We assessed what proportion of patients did not fulfill MDA, which factors contributed to residual disease activity, and to what extend the residual disease activity related to the patients' scores on quality of life and disability questionnaires.

PATIENTS AND METHODS

This cross-sectional multicentre observational cohort study was conducted in two rheumatology outpatient clinics in Amsterdam, the Netherlands (Academic Medical Center (AMC) and Reade). Two hundred and fifty PsA patients, referred by twenty rheumatologists and ten rheumatologists in training, were enrolled in the study between February 2013 and June 2015. The study protocol was in compliance with the Declaration of Helsinki and approved by the Institutional Review Board of the AMC in Amsterdam. Written informed consent for participation was obtained from each participant.

Eligible patients were those who (i) were aged ≥18 years; (ii) had the clinical diagnosis of PsA and fulfilled the Classification Criteria for Psoriatic Arthritis[13]; (iii) were considered as having an acceptable disease state by their treating rheumatologist. In order to assess current clinical practice as closely as possible, acceptable disease state was not determined by predefined activity measures but rather by asking rheumatologists to refer those patients whom they considered sufficiently treated regardless of the type of treatment used at that time. Accordingly, patients in whom the treating rheumatologist had considered and/or performed treatment modifications in the past six months were excluded.

Data collection

All patients were seen by one independent study physician (L.vM.) during a dedicated study visit for data collection, planned between 0 and 4 weeks after referral. During the trial visit demographics, disease characteristics and comorbidity were documented. Physical assessment included scoring of swelling and tenderness in 76/78 joints [swollen joint count (SJC) and tender joint count (TJC)], Leeds Enthesitis Index including the plantar fascii (LEI), Dactylitis Count, Psoriasis Area and Severity Index (PASI), and a physician global assessment on disease activity on a 0-100 visual analogue scale (VAS) (VASphys). Patient reported outcomes (PROs) included: the Disability Index of the Health Assessment Questionnaire (HAQ DI)[14], the Short Form 36 (SF-36) health survey[15], the Dermatology Quality of Life Index (DQLI), the Hospital Anxiety and Depression Scale (HADS), the Bath Ankylosing Spondylitis Activity Disease Index (BASDAI)[16], the

Work Productivity Assessment Index (WPAI)[17], the patient global assessment of disease activity on a 0-100 VAS (VASptGlobal), and the patient assessment of pain on a 0-100 VAS (VASptPain).

Data analysis

Patients were divided in two groups: those who met MDA criteria (MDA+) and those who did not (MDA-). A patient was considered MDA+ when meeting at least five of the seven following criteria: TJC ≤ 1; SJC ≤ 1; PASI ≤ 1; VASptPain ≤ 15mm; VASptGlobal ≤ 20mm; HAQ ≤ 0.5; LEI ≤ 1.[7] Data were presented as the mean with S.D., as a median and interquartile range (IQR) where applicable, and as absolute percentages of patients. Statistical comparisons between the two groups were performed by *t*-test or Mann-Whitney U test and Kruskall Wallis test when non normally distributed. To investigate which factors contribute to the fulfillment of MDA backward, multivariate logistic regression was applied. Statistical tests were two sided and $P < 0.05$ was considered statistically significant. Analysis was performed in SPSS Statistics v. 22.0 (IBM corp., Armonk, NY, USA).

RESULTS

Patient characteristics and overall disease activity

The demographics, disease characteristics, current treatment and comorbidity of the 250 patients included in the study are shown in Table 1. The scores for disease activity are shown in Table 2. In line with the inclusion criteria of the study, the average activity in the different disease domains was low at the group level.

MDA

Despite the overall low disease activity at the group level, scoring for MDA revealed a significant proportion of patients with residual disease activity: of the 250 patients, 88 (35%) did not meet the MDA criteria (MDA-) (Fig. 1). The residual disease activity in MDA- patients was not only due to high subjective disease activity measures such as tender joint count and VASptPain score, which could potentially be related to other causes than active PsA, but was also reflected by more objective outcomes such as the presence of swollen joints, skin psoriasis and enthesitis. (Table 2 and Fig. 2A). Accordingly, not only the patient global disease activity VAS score but also the physician global disease activity VAS score was higher in MDA- patients than in MDA+ patients.

TABLE 1. Clinical characteristics of study patients

Characteristics	Total	MDA+	MDA-
Patients, n (%)	250 (100)	162 (65)	88 (35)
Age mean (S.D.), years	55 (11)	53 (12)	59 (10)
Male/female, (n)	168/82	120/42	48/40
Disease duration, mean (S.D.) years	12.7 (9.2)	11.9 (8.5)	14.1 (10.2)
Age at onset of arthritis, mean (S.D.) years	42.7 (12.3)	41.4 (12.5)	45.1 (11.5)
History of psoriasis, n(%)	229 (91.6)	143 (88.3)	86 (97.7)
BMI, mean (S.D.), kg/m^2	27.3 (4.6)	26.7 (4.6)	28.2 (4.6)
Normal, BMI <25kg/m^2), n(%)	86 (34%)	64 (39.5%)	22 (25%)
Overweight, BMI 25-30 kg/m^2), n(%)	98 (39%)	64 (39.5%)	34 (38.6%)
Obese, BMI >30 kg/m^2), n(%)	53 (21)	28 (17.3)	25 (28.4)
Only NSAID or analgesic, n(%)	24 (9.5)	13 (8)	11 (12)
Current cDMARD only, n(%)	99 (39.5)	65 (40)	34 (39)
MTZ, n/cDMARD group	85/99	60/65	25/34
LEF, n/cDMARD group	8/99	3/65	5/34
SSZ, n/cDMARD group	5/99	2/65	3/34
MTX+SSZ, n/cDMARD group	1/99	0/65	1/34
Current TNFi No concomitant cDMARD, n(%)	59 (24)	43 (27)	16 (18)
Current TNFi with cDMARD, n(%)	68 (27)	41 (25)	27 (31)

MDA: minimal disease activity; cDMARD: conventional DMARD

Characteristics of MDA- patients

On average, MDA- patients were older than MDA+ patients (Table 1), and had a longer disease duration, and a higher Body mass index (BMI). Most strikingly, failure to achieve MDA was more frequently observed in women (49%) than in men (29%) (P=0.002). Men and women did not differ on activity in the different disease activity domains (Figure 2 panel B). A multivariate analysis model correcting for age, disease duration, gender, BMI, medication use and smoking status shows an effect of age (per 10years) (odds ratio (OR) = 0.589 (95% CI: 0.479, 0.789), BMI (OR = 0.524 (95% CI: 0.350, 0.784), and gender (OR = 2.96 (95% CI: 1.60, 5.48). No significant effect remained for treatment use, smoking and disease duration.

TABLE 2. Disease activity according to minimal disease activity and other disease activity measures.

Disease activity measures	Total n = 250	MDA + n = 162	MDA – n = 88	P-value MDA– *vs* MDA+
Swollen joint count	0 (0-1)	0 (0-0)	1 (0-2)	P=0.000
Tender joint count	1 (0-5)	0 (0-2)	6 (2-10)	P=0.000
PASI	0.3 (0-1.5)	0 (0-1.2)	0.8 (0-2.4)	P=0.002
VASptGlobal	10 (3-29)	6 (1-11)	37 (23-56)	P=0.000
VASptPain	8 (2-23)	3 (0-8)	32 (20-53)	P=0.000
HAQ	0.25 (0-0.625)	0 (0-0.38)	0.75 (0.5-1.38)	P=0.000
Enthesitis: LEI	0 (0-0)	0 (0-0)	0 (0-0)	P=0.002
(no. of patients with an enthesitis on the LEI), n	17	5	12	
Dactylitis, n	2	0	2	P=0.055
ESR, (mm/h)	6 (4-11)	5 (3-9)	8 (5-16)	P=0.000
BASDAI	14.6 (5.7-35.5)	9 (3-18.2)	41.4 (21-53.5)	P=0.000
VASphys	11 (4-26)	7 (3-17)	23 (9-42)	P=0.000

Except where indicated otherwise, values are the median (IQR). Significance of the comparisons is determined by an independent sample t-test for continues variables and chi-square test for categorical variables. P<0.05 was considered significant.

LEI: Leeds Enthesitis Index; MDA: minimal disease activity; PASI: Psoriasis Area Severity Index; VASphys: experience of global disease activity on a visual analogue scale, scored by the research physician; VASptGlobal: the patient global assessment of disease activity on a 0-100 VAS; VASptPain: the patient assessment of pain on a 0-100 VAS.

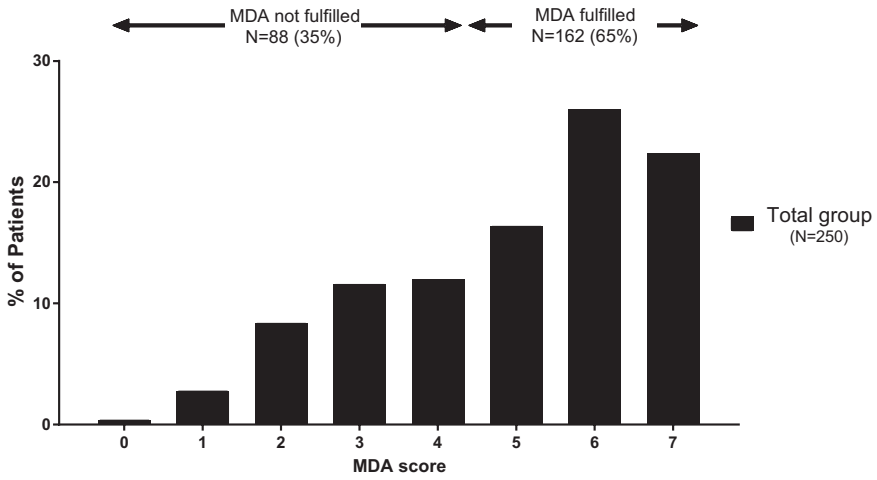

FIGURE 1. Minimal disease activity score.

Patients were considered not in MDA (MDA_) with a score of 0, 1, 2, 3 or 4 points and in MDA (MDA+) with a score of 5, 6 or 7 points. MDA: minimal disease activity.

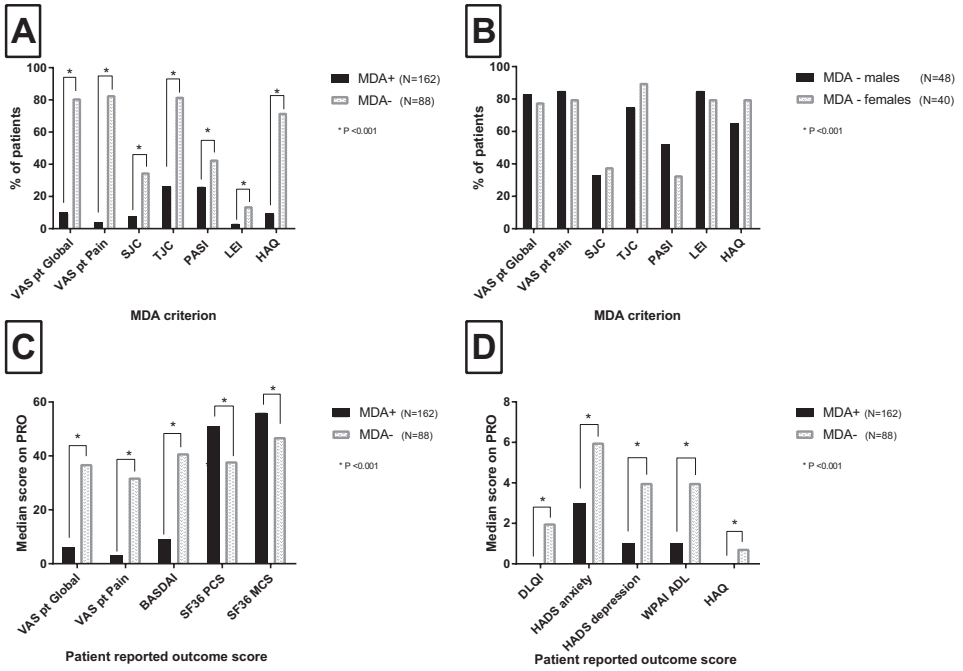

FIGURE 2. Criterion scores and patient reported outcomes in minimal disease activity and gender subgroups
(A) The percentage of patients failing specific MDA criterion in the MDA subgroups.
(B) Percentage of MDA patients failing specific MDA criterion according to gender.
(C and D) PRO scores in MDA subgroups.

Significance of the comparisons is determined by an independent sample t-test for continues variables and mann_Whitney U test when nonnormally distributed. P<0.05 was considered significant and indicated with an asterisks. Cutoff points for values were used according to the MDA scoring: VASptGlobal>20 mm; VASptPain>15 mm; SJC>1; TJC>1; PASI>1; LEI>1; HAQ>0.5. DLQI: Dermatology Quality of Life Index; HADS: Hospital Anxiety and Depression Scale; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; PASI: Psoriasis Area Severity Index; PRO: patient reported outcome; SF-36 MCS:Short Form 36, mental impact of disease; SF-36 PCS: Short Form 36, physical disability; SJC: swollen joint count; TJC:tender joint count; VASptGlobal: the patient global assessment of disease activity on a 0-100 VAS; VASptPain: the patient assessment of pain on a 0-100 VAS; WPAI ADL: Work Productivity Assessment Index, patient perception on impairment in daily life activities.

When exploring the potential impact of treatment regimen on residual disease activity, most disease activity measures tended to be numerically worse in the neither cDMARD nor TNFi group and to be numerically best in the TNFi +/- cDMARD group, but none of these differences reached statistical significance (Table 3).

TABLE 3. Disease activity in minimal disease activity and other disease activity measures according to treatment groups

	No cDMARD or TNFi n=24	cDMARD only n=99	TNFi +/- cDMARD n=127	P-value (Kruskall-Wallis Test)
MDA+, n (%)	13 (54%)	65 (66%)	84 (66%)	Ns
Swollen joint count	1(0-1)	0(0-1)	0(0-0)	Ns
Tender joint count	2(0-8)	1(0-5)	0(0-3)	Ns
PASI	1.2(0.1-2.7)	0.6(0-1.5)	0.3(0-2)	Ns
VASptglobal	13(3-36)	10(4-27)	10(3-23)	Ns
VASptPain	16(7-33)	7(2-22)	8(0-27)	Ns
HAQ	0(0-0.5)	0.25(0-0.63)	0.12(0-0.9)	Ns
Enthesitis: LEI	0(0-0)	0(0-0)	0(0-0)	Ns
Patients with an enthesitis, n	1	6	10	
Dactylitis	0(0-0)	0(0-0)	0(0-0)	Ns
Patients with a dactylitis, n	0	1	1	
ESR (mm/h)	5(2-8)	7(5-16)	5(4-10)	Ns
BASDAI	19.5(6.4-42.2)	17.5(6.2-37.4)	13.1(4.1-22.3)	Ns
VASphys	21(4-46)	13(3-27)	11(4-19)	Ns

Except where indicated otherwise, values are the median (IQR). Difference between the two groups were compared with a Kruskal_Wallis test and a P<0.05 was considered significant. DLQI: Dermatology Quality of Life Index; LEI: Leeds Enthesitis Index; MDA: minimal disease activity; PASI: Psoriasis Area Severity Index; VASphys: experience of global disease activity on a visual analogue scale, scored by the research physician; VASptGlobal: experience of disease activity on a visual analogue scale, scored by the patient; VASptPain: experience of pain on a visual analogue scale, scored by the patient.

Impact of residual disease activity on PROs

Measures of daily functioning (HAQ), quality of life (DLQI), daily activity impairment (WPAI), BASDAI, and the mental and physical components of the SF36 all revealed a significantly higher disease burden in MDA- patients in comparison with the MDA+ group (Fig. 2C/D and Table 2). In the MDA+ group, only a few patients (9.5%) experienced impairments affecting their daily life in contrast with 63 (72%) of MDA- patients (reported

HAQ score >0.5). Overall, the MDA score (expressed as number of criteria achieved out of the seven MDA criteria) correlated well with the HAQ score, as well as with the other PROs not included in the MDA score (see supplementary Table S1).

DISCUSSION

This study assessed the presence of residual disease activity in PsA patients considered to have an acceptable disease state according to their treating rheumatologist. One third of the 250 patients did not meet the MDA criteria, with residual disease activity across all MDA disease domains. Patients not in MDA were more frequently female and had a longer disease duration then those who did fulfil MDA criteria and the proportions of MDA- patients were similar across the different treatment groups (neither cDMARD nor TNFi group, cDMARD only, TNFi +/- cDMARD). Not reaching MDA was associated with poorer PROs of function and quality of life.

There is limited information on residual disease activity in routine clinical settings. Cantini *et al.*[18] report only 24% treated with either cDMARDs and/or TNFi reached MDA. The present study confirms and extends the concept of significant residual disease activity in PsA despite treatment with cDMARDs and biologics by demonstrating that even within this group of patients considered to have an acceptable disease state by their treating rheumatologist, a substantial proportion failed to reach MDA. MDA has previously been validated as a measure of quiescent disease in observational and interventional cohort studies.[8,10,12] Also in the present study, patients achieving MDA had no or minimal signs and symptoms of musculoskeletal inflammation. In contrast, the residual disease present in MDA- patients was reflected by both high subjective disease activity measures such as tender joint count and VASptpain scores, and by more objective measurements of musculoskeletal and skin inflammation, such as the presence of swollen joints, a PASI score >1 and the presence of enthesitis. These data confirm that the perceived residual disease activity observed in the MDA- group was genuinely related to PsA disease activity and could not be completely explained by other factors leading to pain and/or subjective discomfort.

To understand why the disease state was considered acceptable by the treating rheumatologist despite persistent PsA disease activity in a significant proportion of the patients, it is important to explore what determines the persistence of residual disease activity. Several factors have been reported to influence the achievement of MDA, including female gender, disease duration, and obesity.[9,12,19-21] These factors were also negatively correlated with MDA in our cohort and upon multivariate analysis.

Importantly, also in the female patients residual disease was observed across the different MDA domains, supporting the idea that not achieving MDA in female patients is not only due to high scores on subjective disease measurements.

Another important factor that may explain that residual disease activity is accepted by patients and physicians is obviously the absence of alternative treatments. This could have been the case for patients on cDMARDs + TNFi in our study as other treatments such as ustekinumab, apremilast, and secukinumab, were not yet available at the time of the study. Accordingly, 40% of patients in the TNFi group did not achieve MDA in our study. This subgroup of patients could therefore potentially benefit from the treatment options that became available recently. In patients not treated with a TNFi +/- cDMARDs, however, the presence of residual disease activity would be expected to trigger treatment escalation. However, almost one-third of the patients not treated with any cDMARD or TNFi or treated with a cDMARD only also showed residual disease activity. Potential reasons for still considering this an acceptable disease state include the potential presence of comorbidities precluding intensive treatment, unwillingness or non-compliance of patients, the absence of systematic monitoring of all disease domains in clinical practice, and/or a conservative approach by rheumatologists. The key question in this subgroup of patients is thus not so much the availability of newer treatments, but rather if one or more of these potential causes can be overcome and, if so, if this would result in a gain in function and quality of life for the patient.

Albeit prospective strategy studies are required to formally address the latter question, our data show a clear relationship between the absence of MDA and lower scores on quality of life and daily functioning, suggesting that a tighter disease control may result in better long term outcome. Interestingly, a tight control strategy treating patients with recent onset PsA to MDA was recently tested in the tight control of inflammation in early psoriatic arthritis (TICOPA) study and compared with standard of care.[11] This study showed that tight control resulted in higher ACR20 responses (62 *v.s.* 45%) and better outcomes on ACR50 and PASI75. The higher response in the tight control group was also associated with a higher proportion of patients reaching a minimal clinical important difference on HAQ, BASDAI and Bath Ankylosing Spondylitis Functionality Index scores. Our study indicates that an equally important clinical research question is to what extent a similar tight control strategy may benefit PsA patients with a partial response to cDMARDs and/or TNFi and whether such a tight control strategy may not only improve function and quality of life, but may also prevent structural damage and comorbidities.

This study gives a good reflection of the real-life clinical situation but also has its limitations as the patient selection may be biased. First, the population in the two rheumatology outpatient clinics (one academic hospital and one specialized center for rheumatology and rehabilitation, both teaching hospitals) may be different from the general rheumatology clinics. This is reflected by the large proportion of TNFi treated patients, which is higher than average in the Netherlands. Second, for referral of patients we were depending on the rheumatologists (in training) in these two centers and we did not assess what percentage of the total PsA population did fulfill the inclusion criteria of the study. On the other hand, patients were referred by a large number of physicians (in total 30 clinicians), making it unlikely that the results are biased by the opinion of a few individual physicians. Third, the single assessment in this cross-sectional study does not allow to determine if the residual disease activity is stable over time, is waxing and waning or, alternatively, is slowly but steadily increasing. These factors should be taken into account when considering the risk/benefit ratio of a tight control strategy in PsA patients not reaching MDA.

In conclusion, one-third of the PsA patients with acceptable disease state according to the treating rheumatologist do not achieve the MDA criteria. These patients have higher disease activity both on subjective and objective disease activity measurements. As residual disease activity is associated with worse PROs and function, future strategy trials should focus on this patient group with partial response on cDMARDs and/or TNFi in order to evaluate if and how treatment escalation could beneficially impact function and QoL as well as prevent structural damage and co-morbidities.

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The ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real life cohort

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Abstract

Background: Psoriatic arthritis (PsA) recommendations state that the target of treatment should be remission or low disease activity (LDA). We used a real-life dataset to compare different potential targets.

Methods: 250 patients with PsA considered in an acceptable disease state according to their rheumatologist were included. Targets for remission were the Disease Activity Index for Psoriatic Arthritis (DAPSA) and clinical DAPSA (cDAPSA) remission (≤4), very low disease activity (VLDA) and Psoriatic Arthritis Disease Activity Score ≤ 1.9. LDA targets analyzed were the DAPSA ≤14, clinical cDAPSA ≤13, minimal disease activity (MDA) and adjusted MDA targets: MDAjoints with both tender joint count (TJC) and swollen joint count (SJC) mandated, MDAskin (skin domain mandated), MDAjoints&skin with TJC, SJC and skin mandated.

Results: Comparison of the several candidate targets demonstrates that VLDA is achieved by the lowest proportion of patients and includes patients with the lowest residual disease activity compared with the other remission targets. The modified MDA measures are the most stringent targets for low disease activity in terms of residual disease on joints, psoriasis and enthesitis within patients achieving the target. In both remission and LDA, the inclusion of C reactive protein did not show an added value. The exclusion of a skin domain, as in the DAPSA measures, resulted in negligence of skin disease and a negative impact on the quality of life in some patients.

Conclusions: The different remission and LDA targets show us significant overlap between measures, but these measures targeting the same definition do differ in terms of allowance of residual disease. Inclusion of laboratory markers seems unnecessary, although exclusion of a skin domain may result in psoriasis not being assessed resulting in residual impactful skin disease.

INTRODUCTION

Treatment guidelines for psoriatic arthritis(PsA) by European League Against Rheumatism and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend to aim for remission or the lowest possible disease activity in all involved domains of the disease.[1-2] Clinical remission in psoriatic arthritis is mostly defined as a complete absence of disease activity, with no signs or symptoms of in all domains of the disease.[3] However, the specific target to define remission or low disease activity is not specified further by the treatment recommendations.

It is still under debate what the target to measure the disease state should be. Several composite scores are developed specifically for PsA, most focusing on multiple domains considered important to assess: 1) the minimal disease activity (MDA) which is a 7 component score including skin, enthesitis, tender and swollen joint counts and patient reported domains including pain and global disease activity score as well as the health assessment questionnaire (HAQ),[4-5] 2) the Psoriatic Arthritis Disease Activity Score (PASDAS) which includes swollen joint count, enthesitis, dactylitis, skin, c-reactive protein (CRP), patient reported and physician reported global disease activity and the SF-36 questionnaire on physical functioning,[6] 3) the Disease Activity Index for Psoriatic Arthritis (DAPSA) which focuses on peripheral arthritis and includes tender and swollen joint counts, CRP and patient reported pain and global disease activity scoring adjusted later to exclude the CRP, the clinical DAPSA (cDAPSA).[7]

All three measures can be used to define remission or low disease state. For MDA, a modified version was developed to use as a remission target, the very low disease activity (VLDA).[8] Furthermore, adjusted versions of the MDA, with a focus on joint and skin symptoms were developed. Specific cutoff values to define remission or low disease activity were developed for (c)DAPSA, as well as a cutoff for near remission in PASDAS.[9-10] However, little data is published on comparing these measures and it is unknown if these measures reflect the same clinical disease activity on the various disease domains. We have previously set up a cohort of patients with psoriatic arthritis focusing on a quiescent disease state.[11] As the disease targets will be a complimentary tool in clinical practice this cohort is an ideal group of patients to assess their performance in.

In the present study we aimed to compare these composite scores proposed as a target for remission or low disease activity in PsA using an existing real-life data set of PsA patients with quiescent disease according to their rheumatologist. We investigated

which patients fulfill definitions of these criteria, how much overlap there is in fulfilling the different targets and how much residual disease in the various domains is present in the different composite scores.

METHODS

An existing dataset was used: data from a cross-sectional study of 250 PsA patients with quiescent disease according to the treating rheumatologist was used recruited from routine clinical visits. Patients had to have been on stable treatment for at least six months, regardless of therapy. Mean age 55years, two-thirds of the patients were male, mean disease duration was 12.7(9.2)years , age at arthritis onset was 42.7(12.3) years. On group level, disease activity was low, with a mean SJC of (median(IQR)) 0(0-1), tender joint count of 1(0-5), PASI score of 0.3(0-1.5), enthesitis present in 17 of 250 patients and dactylitis in 2/250. The patients' characteristics are shown in more detail in supplementary table 1.[11]

Four potential definitions of remission/inactive disease were used where all items required for the definitions were available in this dataset:

1. VLDA where all 7 of the MDA cut points are met: tender joint count (TJC)≤1; swollen joint count(SJC)≤1; enthesitis count≤1; psoriasis area and severity index(PASI)≤1; patient global visual analogue scale (VASptGlobal)≤20mm; patient pain (VASptPain)≤15mm; and health assessment questionnaire(HAQ)≤0.5.
2. DAPSA remission[4] where DAPSA≤4:TJC + SJC + VASptGlobal(cm) + VASptPain(cm) + CRP (mg/l)
3. Clinical DAPSA remission where cDAPSA≤4: TJC + SJC + VASptGlobal(cm) + VASptPain(cm)
4. Near remission in the psoriatic arthritis disease activity score (PASDAS) where PASDAS≤1.9

Six potential definitions for low or minimal disease activity were used:

1. DAPSA low disease (DAPSA=TJC+SJC+VASptGlobal+VASptPain+CRP) ≤14
2. cDAPSA low disease (DAPSA=TJC+SJC+VASptGlobal+VASptPain) ≤13
3. MDA 5/7 where any 5 of the 7 cut points are required to be met
4. MDA joints where both the tender and swollen joint count cut points are required to be met with any 3/5 of the remaining cut points (enthesitis, skin, VASptGlobal, VASptPain, HAQ)

5. MDA skin where skin is required plus 4/6 remaining cut points (TJC, SJC, enthesitis, VASptGlobal, VASptPain, HAQ)
6. MDA joints and skin where the TJC, SJC and skin cut points are required to be met with any 2/4 of the remaining cut points(enthesitis, VASptGlobal, VASptPain, HAQ)

Proportions achieving each criteria were calculated. The agreement between the tested definitions was established using 2x2 tables and percentage exact agreement (PEA) and calculation of a kappa. The proportion of residual disease was established for key clinical domains of PsA (peripheral arthritis, enthesitis, psoriasis, dactylitis) and levels of systemic inflammation, as measured by CRP, were assessed.

RESULTS

Comparisons of the measures for remission/inactive disease

Of the total population (250 patients), 107(43,7%) fulfilled DAPSA remission, 113(45,7%) were in cDAPSA remission, 56(22,5%) met VLDA and 37(19,5%) were in PASDAS near remission. The DAPSA could not be calculated in 4/250 patients due to missing CRP values; 1/250 patients had incomplete data to calculate the VLDA(missing PASI score) the PASDAS score could not be calculated in 23/250 patients due to missing SF36 scores, the majority of these patients did not fulfill any of the remission targets(18/23). There was a very high agreement between DAPSA and cDAPSA remission(Kappa 0.959) reflecting the similarity of the two definitions(the inclusion of CRP is different). The agreement between both DAPSA/cDAPSA and VLDA was moderate (kappa of 0.516 and 0.544 resp). The agreement between VLDA/cDAPSA/DAPSA and PASDAS is considered fair, with a kappa of 0.403, 0.321, 0.319 respectively.(Table 1A)

TABLE 1A. Kappa scores of remission/inactive disease and low disease activity measures

	PASDAS	VLDA	cDAPSA	DAPSA
PASDAS	X	0,403	0,321	0,319
VLDA	0.403	X	0,516	0,544
cDAPSA	0,321	0,516	X	0,959
DAPSA	0,319	0,544	0,959	X

The concordance in fulfillment of the criteria is presented in figure 1.

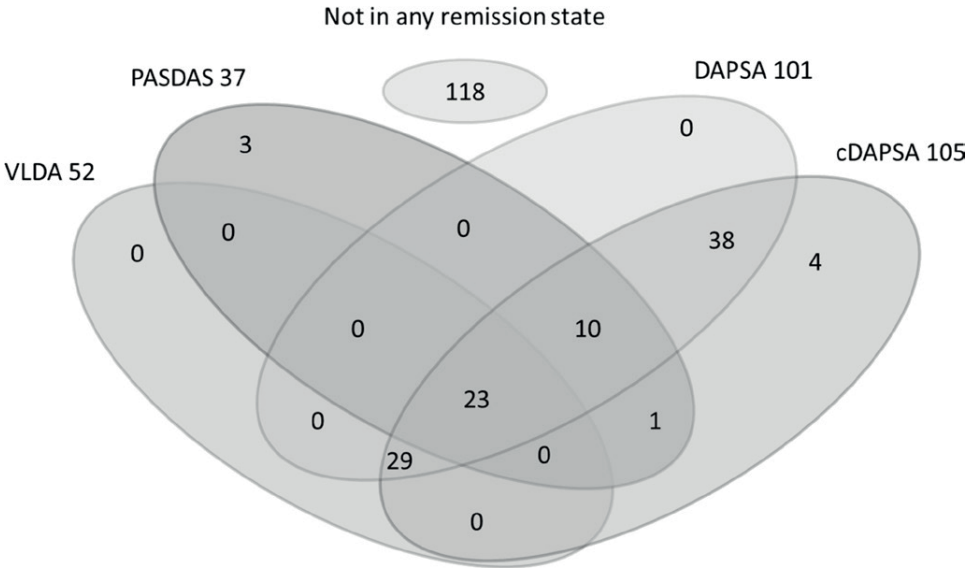


FIGURE 1. Venn diagram representing the number of patients meeting different remission criteria. The graph only includes those patients where all criteria were available (n=226). cDAPSA, clinical DAPSA; DAPSA, Disease Activity Index for Psoriatic Arthritis; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity.

VLDA is the most stringent and the DAPSA scores the least. All patients who met VLDA were in DAPSA/cDAPSA remission. Of those patients in DAPSA remission but not in VLDA 43/56 patients did not fulfill 1/7 domains, whilst 9 did not fulfill 2/7 domains. Domains not fulfilled were skin (n = 33), tender joints (n= 7), swollen joints (n= 1), enthesitis (n= 3), VAS scores (n= 6), or HAQ (n= 9). In the 9 patients who did not achieve VLDA due to a high HAQ score, 8 of them met the MDA criteria suggesting that they would have fulfilled an alternative LDA target. In 4/9 the HAQ domain was the only criteria that was not met; in 5/9 there were other residual domains (PASI n=2, enthesitis score n=2 and VASglobal n=2).

Residual disease activity in patients fulfilling the remission/inactive disease measures

Levels of residual disease activity in patients meeting the different measures for remission/inactive disease are shown in table 2 and figure 2.

TABLE 1B. Kappa scores of low disease activity measures

	MDA	MDA skin	MDA joints	MDA skin&joints	cDAPSA LDA	DAPSA LDA
MDA	X	0,668	0,647	0,425	0,611	0,596
MDA skin	0,668	X	0,431	0,700	0,356	0,343
MDA joints	0,647	0,431	X	0,722	0,372	0,360
MDA joints&skin	0,425	0,700	0,722	X	0,227	0,218
cDAPSA_LDA	0,611	0,356	0,372	0,227	X	0,988
DAPSA LDA	0,596	0,343	0,360	0,218	0,988	X

cDAPSA, clinical DAPSA; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity

TABLE 2. Residual disease activity in different measures for remission

		cDAPSA remission (total 113)	DAPSA remission (total 107)	VLDA (total 56)	PASDAS <1,9 (n=37)
PASDAS	Mean(SD)	2,16(0,52)	2,13 (0,49)	1,97(0,42)	1,6(0,20)
Swollen joint count N(%)	0	101(89)	96(90)	53(95)	33 (89)
	1-3	12(11)	11(10)	3(5)	4(11)
	4-6	0(-)	0(-)	0(-)	0(-)
Tender joint count N(%)	0	93(82)	89 (83)	51 (91)	28 (76)
	1-3	20(18)	18(17)	5(9)	6(16)
	4-7	0(-)	0(-)	0(-)	2(8)
	8+	0(-)	0(-)	0(-)	0(-)
Leeds Enthesitis index N(%)	0	108 (96)	102 (96)	56 (100)	37 (100)
	1-2	4(-)	4(-)	0(-)	0(-)
	4	1(-)	1(-)	0(-)	0(-)
Dactylitis count N(%)	0	113(100)	107(100)	56(100)	37(100)
PASI N(%)	0-1	79 (70)	74 (69)	56(100)	32(86)
	>1	34(30)	33(31)	0(-)	5(14)
CRP > normal value (5mg/L) N(%)		11 (10)	8 (7,5)	5(9)	1(3)

cDAPSA, clinical DAPSA; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, psoriasis area and severity index; VLDA, very low disease activity.

These measures do not represent similar numbers of residual disease in all domains. The presence of swollen joints and active enthesitis was similar across the different measures (SJC≥1 in 5-10% of patients and enthesitis≥ 1 in 4-0%). Tender joint counts were lower in VLDA (TJC≥1 in 9%) and higher in the DAPSA, cDAPSA, and PASDAS remission group(TJC≥1 in 17%, 18% and 25% resp). Skin disease was more prevalent in both DAPSA measures (a PASI≥1 in resp. 30% of cDAPSA and 31% of DAPSA patients) in contrast with 14% in the PASDAS patients and 0% in VLDA. cDAPSA and VLDA had similar proportions of patients with raised CRP(10% and 9%) in comparison with DAPSA and PASDAS(8%), although CRP is not assessed in either cDAPSA or VLDA definitions.

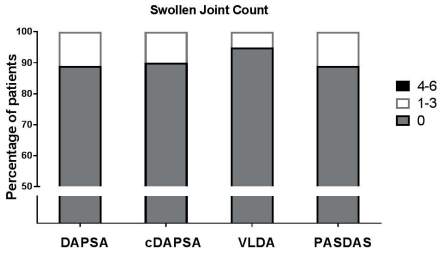
VLDA presents as a more stringent cutoff with the least residual disease in PASI and tender joint count. PASDAS seems to include more patients with tender joints but less with an elevated CRP and less patients with active skin disease in comparison with the other measures. Both DAPSA scores considered more patients in remission, but did allow for more residual disease activity in the domains tender joints, skin disease and enthesitis in comparison with the other measures.

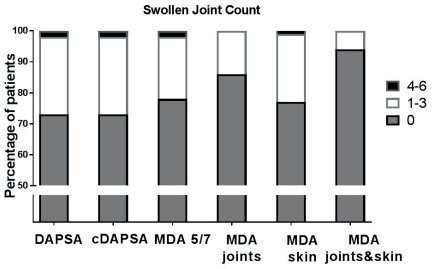
Residual disease activity in remission measures related to quality of life

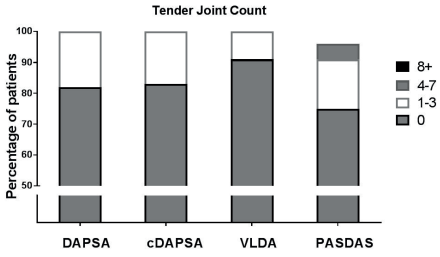
In those patients with a raised CRP, no differences were found on PROs on quality of life and functionality. Very few patients had residual enthesitis in any definition and those in remission with an enthesitis did not report significantly worse functioning or QoL, although some of the BASDAI scores were higher. Residual skin disease did affect DLQI, although not to a very high extent. For patients with 'active' skin disease (with PASI scores ≥1) no effect is seen on all QALY measures and the 74/110 patients fulfilling DAPSA with a PASI of ≥1 do not present with a higher score on the DLQI scale. The group with a PASI of >2 (present in 20/110 pts achieving DAPSA remission) was reflected by an impact on DLQI (2,85(SD 2,9)v.s. 1(2,3)p=0.003). No conclusions can be drawn on the effects of residual dactylitis as this cohort presented with a very low amount of patients with an active dactylitis during the trial visit.

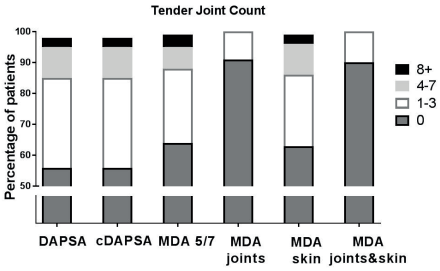
FIGURE 2. The remaining residual disease activity in different disease domains within the subgroups of patients meeting the different remission criteria. The graphs show residual disease on different disease activity measures (top to bottom: swollen joints, tender joints, enthesitis, skin and CRP) in the patient groups fulfilling the different remission measure (left graphs) or LDA measure (right graphs). Stacked bars divide the patients fulfilling each remission/LDA measure in groups according to the amount of residual disease present.

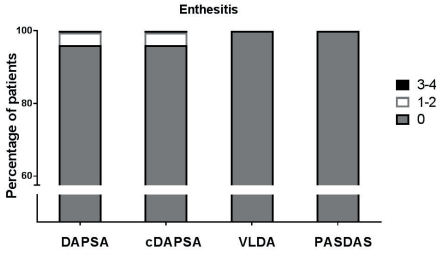
cDAPSA, clinical DAPSA; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; VLDA, very low disease activity.

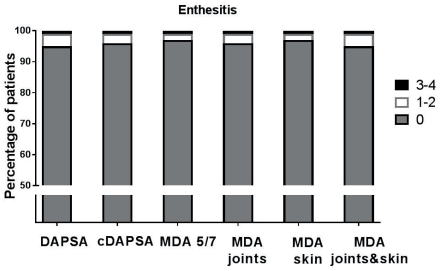

Swollen Joint Count
Percentage of patients
100
90
80
70
60
50
4-6
1-3
0
DAPSA
cDAPSA
VLDA
PASDAS

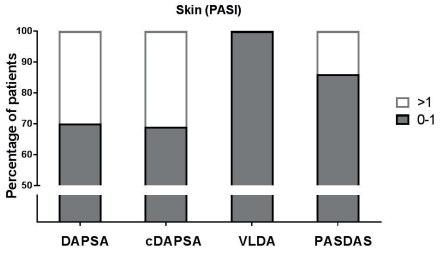

Swollen Joint Count
Percentage of patients
100
90
80
70
60
50
4-6
1-3
0
DAPSA
cDAPSA
MDA 5/7
MDA joints
MDA skin
MDA joints&skin

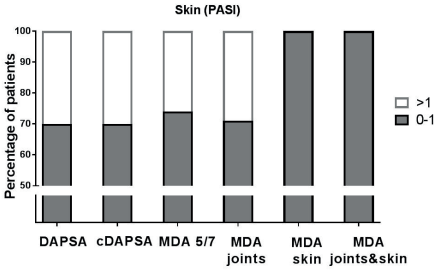

Tender Joint Count
Percentage of patients
100
90
80
70
60
50
8+
4-7
1-3
0
DAPSA
cDAPSA
VLDA
PASDAS

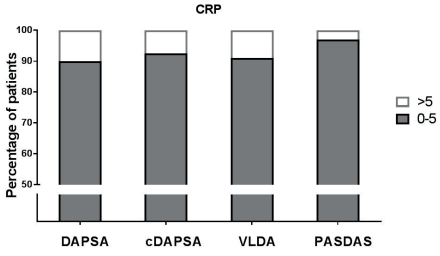

Tender Joint Count
Percentage of patients
100
90
80
70
60
50
8+
4-7
1-3
0
DAPSA
cDAPSA
MDA 5/7
MDA joints
MDA skin
MDA joints&skin

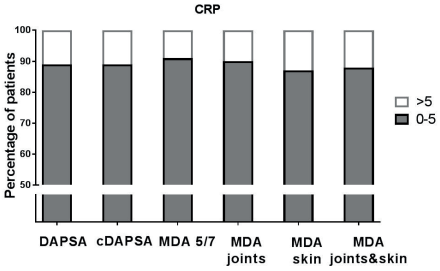

Enthesitis
Percentage of patients
100
90
80
70
60
3-4
1-2
0
DAPSA
cDAPSA
VLDA
PASDAS


Enthesitis
Percentage of patients
100
90
80
70
60
50
3-4
1-2
0
DAPSA
cDAPSA
MDA 5/7
MDA joints
MDA skin
MDA joints&skin


Skin (PASI)
Percentage of patients
100
90
80
70
60
50
>1
0-1
DAPSA
cDAPSA
VLDA
PASDAS


Skin (PASI)
Percentage of patients
100
90
80
70
60
50
>1
0-1
DAPSA
cDAPSA
MDA 5/7
MDA joints
MDA skin
MDA joints&skin


CRP
Percentage of patients
100
90
80
70
60
50
>5
0-5
DAPSA
cDAPSA
VLDA
PASDAS


CRP
Percentage of patients
100
90
80
70
60
50
>5
0-5
DAPSA
cDAPSA
MDA 5/7
MDA joints
MDA skin
MDA joints&skin

Low disease activity and inactive disease measures

Comparisons of the low disease activity/inactive disease measures

Of the total population, 162(65%) achieved MDA, 113(45,6%) achieved MDAjoints, 114(46%) achieved MDAskin, 79(31,6%) achieved MDAjoints&skin, 195(78%) achieved DAPSA LDA, 195(78%) achieved cDAPSA LDA. The concordance in fulfillment of the criteria is presented in Table 1B. A high agreement is seen between the DAPSA/cDAPSA and the MDA5/7 (kappa of 0,596 and 0,611 respectively). Agreement between the DAPSA and the alternative MDA measures (MDAjoints, MDAskin and MDAjoints&skin) is lower as these targets are more stringent.

Residual disease activity in patients fulfilling low disease activity/inactive disease measures

Levels of residual disease activity in patients meeting low disease activity/MDA/new MDA measures are shown in table 3 and figure 3.

TABLE 3. Residual disease activity in different measures for low disease activity

		DAPSA LDA (195)	cDAPSA LDA (195)	MDA 5/7 (162)	MDA joints (117)	MDA skin (120)	MDA skin & joints (83)
PASDAS	Mean (SD)	2,49(0,66)	2,48(0,66)	2,3(0,6)	2,26(0,60)	2,29(0,59)	2,2(0,63)
Swollen joint count N (%)	0	143(74)	143(73)	126(78)	101(86)	92(77)	78(94)
	1-3	48(25)	48(25)	33(20)	16(14)	26(22)	5(6)
	4-6	4(2)	4(2)	3(2)	0(0)	2(2)	0(0)
Tender joint count N (%)	0	110(56)	111(56)	103(64)	106(91)	76(63)	75(90)
	1-3	56(29)	56(29)	39(24)	11(9)	28(23)	8(10)
	4-7	19(10)	19(10)	12(7)	0(0)	12(10)	0(0)
	8+	6(3)	5(3)	6(4)	0(0)	4(3)	0(0)
Enthesitis count N (%)	0	186(95)	187(96)	157(97)	112(96)	116(97)	79(95)
	1-2	7 (4)	6(3)	4 (2)	4(3)	3(2)	3(4)
	3-4	2(1)	2(1)	1(1)	1(1)	1(1)	1(1)
Dactylitis count	0	195(100)	195(100)	162(100)	117(100)	120(100)	83(100)
PASI N(%)	0-1	136(70)	136(70)	120(74)	83(71)	120(100)	83(100)
	>1	59(30)	59(30)	42(26)	34(29)	0(0)	0(0)
CRP (Normal <5mg/dl) N (%)	Raised	22(11)	22(11)	18(11)	12(10)	15(13)	10(12)

cDAPSA, clinical DAPSA; CRP, C reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity.

Higher levels of tender and swollen joint counts and skin disease are seen in the DAPSA LDA measures in comparison with all 4 MDA scores. By their definition, MDAjoints and MDAjoints&skin show an even stricter cutoff on joint involvement, with a single swollen joint in only 10 and 5% resp, and a tender joint in only 14 and 2 percent of the patients.

Between the different outcome measures the presence of patients with a raised CRP is similar (approximately 12% in all measures).

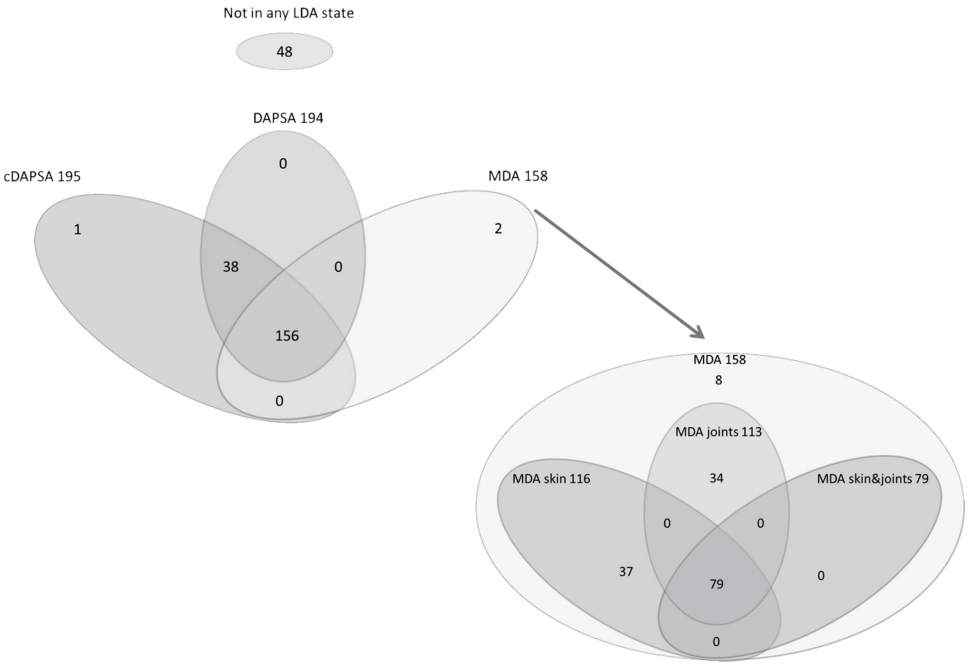


FIGURE 3. Venn diagram representing the number of patients meeting different low disease activity criteria. The graphs only include those patients where all criteria were available (n=245).

cDAPSA, clinical DAPSA; DAPSA, Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity; MDA, minimal disease activity.

Residual disease activity in remission measures related to quality of life

Not including an enthesitis measure in the score does not seem to make much difference; it does not result in a group of patients with active disease and a high disease burden, as only 5 patients with an active enthesitis fulfill (DAPSA)LDA criteria, these patients did not differ in QoL scores in comparison with other DAPSA LDA patients. No differences were found on PROs on quality of life and functionality between patients with and

without a raised CRP. A PASI score >1 was more prevalent in the DAPSA cutoff groups in comparison with the MDA/new MDA measures (46% in DAPSA LDA n and between 0-29% in the different MDA measures). The patients with active psoriasis in the DAPSA LDA group did report significantly larger impact of skin disease on dermatology related quality of life (DLQI scale) (PASI 0-1: 1,25(SD2,4)v.s.PASI>1: 1,55(SD2,7),p=0,024.

DISCUSSION

The analysis of different remission and low disease activity targets in this real life clinical cohort do show significant overlap between the measures. However it is clear that these different measures targeting the same conceptual definition (ie remission or low disease activity) do result in different levels of residual disease present in individuals. Comparison of the several candidate measures demonstrates that VLDA is achieved by the lowest proportion of patients in this cohort. This suggests that it may be the most stringent target for remission of inactive disease, although it could be difficult to attain and may be more stringent than patient and physician opinion of acceptable disease states. The modified MDA measures are the most stringent targets for low disease activity in terms of residual disease on joints, psoriasis and enthesitis within patients achieving the target. In both remission and LDA measures the addition of CRP did not show an added value. The exclusion of a domain for psoriasis, as in the DAPSA measures, resulted in negligence of skin disease and a negative impact on the QoL in some patients.

For this study we used three different measure concepts validated for psoriatic arthritis, the MDA and the adjusted versions (MDAskin/MDAjoints and MDAjoints&skin as well as VLDA), DAPSA and PASDAS. The MDA and adjusted MDA measures all use a modular approach where an individual cutoff for each domain is specified and depending on the measure used, a number of cutoffs need to be met. In contrast, the DAPSA and PASDAS measures sum the scores of the individual components into one final number. In both the DAPSA and PASDAS measures for remission and low disease activity, higher levels of residual musculoskeletal disease were seen in comparison with the VLDA and the MDAskin/joint measures. An active domain can be hidden when other domains are relatively unaffected, resulting in the inclusion of patients with active disease within the group of patients seen as in remission or low disease activity state.

The DAPSA focuses specifically on peripheral joint disease and some argue that this is ideal as it can reflect change accurately in this single domain. However because it does not measure other domains of the disease, active disease in these domains is missed.

Residual skin disease was highest in patients achieving DAPSA or cDAPSA remission when compared with the other remission targets as well as for the DAPSA and cDAPSA low disease cutoffs in comparison with the adjusted MDA measures. Within our group of patients this resulted in a group of patients, seen as in a low disease activity state, with remaining skin disease impacting their quality of life. This analysis highlights the need for multiple separate measures for different domains to be assessed if a multidimensional definition is not used to ensure that remission retains face validity for the patients.

The MDA domains include a measure of function as they were taken from the core domain of PsA and are in line with similar definitions in RA.[12-13] Concern has been raised that, as the HAQ will be affected by non-reversible damage as well as disease activity, this may limit their applicability.[14] In this cohort with established disease (mean disease duration of 12.7years), very few patients failed to achieve VLDA due to HAQ alone, but they did achieve MDA and its more stringent variations. Another concern that has been raised is the influence of comorbid fibromyalgia on the outcome measures and potential targets. Brikman et al have shown that fibromyalgia impacts on both DAPSA, MDA and other scores. Unfortunately we do not have fibromyalgia data on these patients but given that the items within the targets overlap significantly, we do not anticipate a differential effect of fibromyalgia between the different measures.[15]

Not all measures used in this comparison included an inflammatory marker. The DAPSA and PASDAS include a CRP and cDAPSA and MDA measures do not. These data suggest that the inclusion of CRP is unnecessary to include as a similar proportion of patients have a raised CRP in all definitions. Those patients with a raised CRP that fulfilled the disease targets did not show a difference in other disease activity measures or on PRO scores. A target without an inflammatory marker will be more practical in clinical practice and if routine laboratory assessment is not needed for other reasons a lower burden for the patient as well.

Another important factor worth considering when choosing a tool for clinical practice is the feasibility and practicality of the tool. The tool should ideally be easy to calculate, as limited time during daily practice makes a simple to obtain target easier to incorporate in clinical practice. Second, when many different outcomes need to be assessed, it will be laborious to calculate these individual scores and the chance increases that information is missing. Thirdly, the transparency and presentation of the tool after calculation is of importance as the individual components will still remain important to consider when targeting a therapy.

Several considerations can be made to the assessed measures in this study, all having their own strengths and weaknesses: the DAPSA focusses only on peripheral joint disease and does not include a skin or enthesitis component; the PASDAS is less transparent on individual components, and the complexity makes it more time consuming to calculate this measure; the MDA is a binary measure (and not a continuous one), therefore scores do not show an increase in disease activity after the bar for remission or LDA is achieved.

It is important to note that we made no attempt to perform new psychometric analyses on measures and only restricted our work to answer the question how the available, validated measures perform and compare to one each other. With the ongoing efforts on gaining consensus on a target for the treatment of PsA, more information on the impact of residual disease is needed. The cutoff for acceptable disease activity is of importance as with a stricter target more intensive treatments might be started, might lead to a more intensive treatment, and this eventually could result in overtreatment of patients with consequences in terms of side effects and an increase in costs. The ideal stringency of a target with assessment of residual disease in the various clinical domains of PsA should be a focus of future research. An observational study shows lower levels of disease activity in remission vs. low disease activity states and better quality of life.[16] It remains unknown whether meeting a strict target such as VLDA is superior in reducing impact on patient outcomes such as QoL, radiographic progression and functioning, in comparison with less stringent targets. Ideally a trial comparing remission and low disease activity, incorporating efficacy, safety, cost-benefit and patient opinion is needed.

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A STRATEGY TRIAL: EARLY INTENSIVE TREATMENT IN PsA

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Achieving remission in psoriatic arthritis by early initiation of TNF inhibition: a double-blind, randomized, placebo-controlled trial of golimumab plus methotrexate versus placebo plus methotrexate

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Abstract

Objectives: If early initiation of effective treatment favors remission in PsA is, contrary to RA, not known. Some studies started to explore this question, providing circumstantial evidence that early treatment with TNFi could favour high remission rates. This study investigates whether the combination of golimumab plus MTX as a first line treatment is superior to MTX alone in PsA.

Methods: This investigator-initiated, multicenter, double blind, randomized, placebo-controlled trial included 51 MTX and bDMARD-naive patients with PsA fulfilling the CASPAR criteria and with active disease at baseline (≥3 SJC/TJC). Patients were randomized to golimumab (50mg SC monthly) + MTX (n=26) (TNFi arm) or matched placebo + MTX (n=25) (MTX arm). MTX was started 15 mg/week and increased to 25 mg/week over 8 weeks. The primary endpoint was % of patients achieving DAS remission (<1.6) at week 22. Safety was assessed throughout the study.

Results: The primary efficacy endpoint, was achieved by 81% the in the TNFi arm versus 42% in the MTX arm (p=0.004). This difference in DAS remission was already observed at week 8. A significant difference in favor of the TNFi arm at week 22 was also observed for other response criteria such as MDA,ACR20/50/70, disease measures and PROs. The occurrence rates of AE and TEAE were similar in both arms.

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

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis affecting the joints and connective tissue and is associated with psoriasis of skin and nails. Treatment options for PsA have tremendously increased over the last two decades. The initial treatment in most patients consists of conventional synthetic disease modifying antirheumatic drugs (csDMARDS). PsA patients with persistent moderate to high disease activity are eligible for Tumour necrosis factor inhibitors (TNFi). In rheumatoid arthritis (RA) there is ample evidence that for strategies aiming to reach and maintain remission of inflammation, i.e. treat to target (T2T)[1–4] Also the early start of treatment improved outcomes, as the earlier the start of treatment the higher the remission rates seen.[5,6]

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

A couple of studies have started to explore if early initiation TNFi favours remission in PsA. Baranauskaite et. al. investigated the use of early methotrexate with or without infliximab in an open-label study in early PsA patients. They showed high response in both arms, with a significantly greater improvement in the methotrexate plus infliximab arm compared with the methotrexate alone arm (ACR20: 86.3% v.s. 66.7%). Larger differences were seen between the treatment arms with more stringent outcome measures such as ACR50, ACR70 and MDA.[18] However, the important limitation of this study was the open-label design and these data have not yet been confirmed in a placebo-controlled setting in PsA. Exploring the same concept in a slightly different population, Carron et al investigated the early initiation of TNFi treatment in a placebo-controlled study in a mixed population of early peripheral spondyloarthritis patients, of which 40% had concomitant nail or skin psoriasis.[19] Patients achieved clinical remission (defined as absence of arthritis, enthesitis, and dactylitis) in 75% in the TNFi treated arm v.s. 20% in the placebo arm.

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

METHODS

Study design

This investigator initiated, randomised, placebo-controlled, double-blind study was conducted at 3 centres in the Netherlands between September 2013 and September 2017. Patients were randomly assigned in a 1:1 ratio to receive either 5 injections with golimumab (50mg SC monthly) or matched placebo. In both arms, MTX was started at 15 mg/week orally and increased to 25mg/week over 8 weeks. Statistical minimization was applied for centre, number of swollen joints, and disease duration using a software program ALEA, a validated randomisation tool (NKI, Amsterdam, the Netherlands). The primary endpoint of the study was measured at the end of the 22-week blinded treatment period.

Patients

Patients aged 18–70 years were eligible if they had psoriatic arthritis according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and current active disease, defined as the presence of at least 3 swollen and 3 tender joints at baseline.[20] Patients previously treated with MTX or any biological DMARD were excluded. Allowed co-medication included NSAIDS and/or systemic steroids <10mg/daily at stable dosages from 2 weeks prior to baseline. Local corticosteroids were not allowed within 4 weeks prior to baseline. Three patients used concomitant fumaric acid and one patient used concomitant sulphasalazine (Table 1). Key exclusion criteria were the presence of latent or active tuberculosis, malignancy in the past 5 years (other than basal cell carcinoma of the skin), recent severe infections, or other severe diseases that may affect patient's participation to the study in the opinion of the investigator.

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

Assessments

The primary efficacy endpoint of this study was the proportion of patients achieving a status of DAS remission at week 22, defined by a DAS CRP score <1.6. (0.54*SQRT(RAI)+ 0.065*SJC44 + 0.17*ln(CRP+1) + 0.0072*GH + 0.45)[21]. Secondary endpoints included additional response criteria such as MDA[22], low disease activity status (DAS score <2.4)), DAPSA LDA, and ACR20/50/70 responses. Disease activity measures included 66/68 tender and swollen joint count, dactylitis count, leeds enthesitis index including the plantar fascii (LEI)[23], PASI, PASI75 (≥75% improvement in the PASI score) for subjects with baseline PASI ≥2.5, CRP, ESR, and VAS physician. Patient reported outcomes (PROs) were patient pain and patient global score on a Visual Analogue Scale (VAS) from 0-100 mm, morning stiffness duration, and Bath Ankylosing Spondylitis Index (BASDAI). Function and quality of life were assessed using the Short Form 36 (SF36), Health Assessment Questionnaire (HAQ), and Dermatology Quality of Life Index (DLQI) scores. All efficacy endpoints were evaluated at week 22 as well as at week 8.

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

Statistical analysis

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

Baseline characteristics and safety analyses included all randomised patients who received at least one dose of trial medication (51 patients). For efficacy analyses, one individual with wrong administration of golimumab versus placebo due to protocol violation was excluded from the MTX arm. Therefore, the intention to treat population for efficacy included 50 patients. Missing data were handled using non-responder imputation for the primary endpoint as well as all other binary endpoints and using last observation carried forward for continuous variables. Values are reported as mean (SD) or median (IQR) as applicable. At each time point, differences between placebo and golimumab were tested using a Chi square test for the categorical variables, and an ANCOVA with the baseline variable as covariate for continuous variables. All statistical tests were two sided and p values of <0.05 were considered statistically significant.

RESULTS

Study population and patient disposition

A total of 59 patients were screened at 3 rheumatology clinics in The Netherlands between September 2013 and September 2017 (Figure 1). Fifty-one patients were randomized to receive either golimumab + MTX (n=26) (TNFi arm) or placebo + MTX (n=25) (MTX arm). The baseline characteristics were similar in the two treatment arms (Table 1).

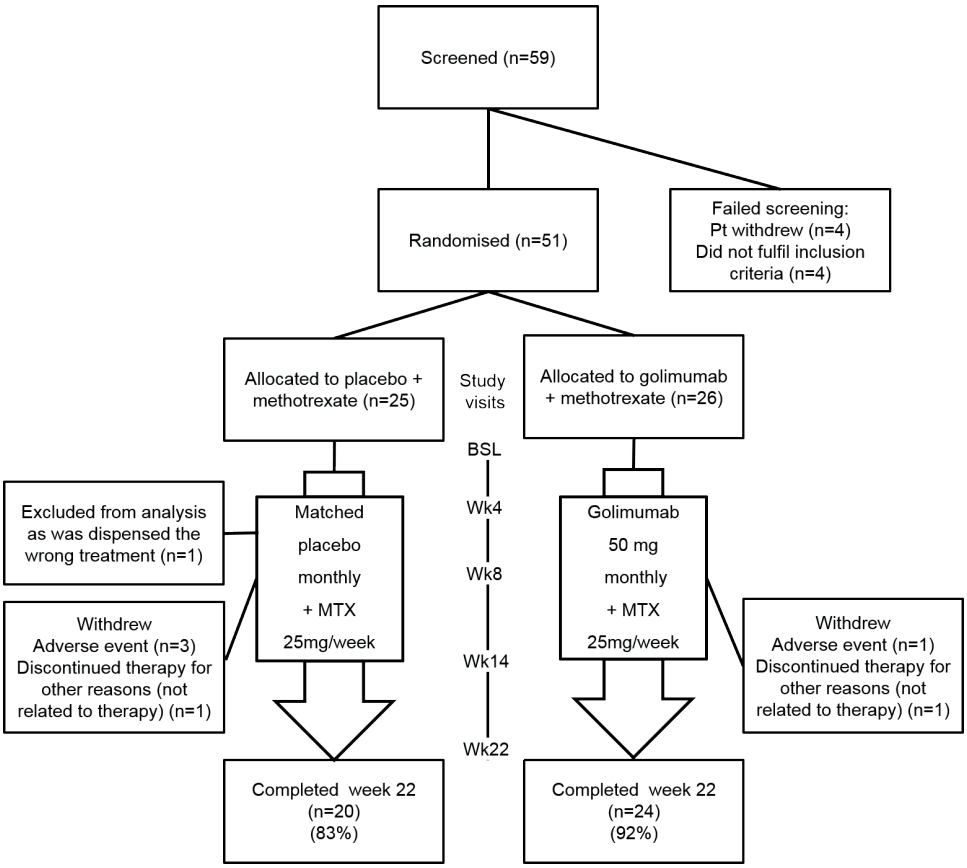

FIGURE 1. Overview of patient disposition and study design. Patients were randomly assigned in a 1:1 ratio to receive either 5 injections with golimumab (50mg SC monthly) or matched placebo. In both arms, methotrexate (MTX) was started at 15 mg/week orally and increased to 25mg/week over 8 weeks.

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

	Golimumab + MTX (N=26)	Placebo + MTX (N=25)
Age, yrs	47.5(11.8)	45.8 (11.0)
Gender (male/female)	18/8	20/5
Disease duration arthritis, yrs	0.5(0.5-1.8)	0.5(0.4-3.0)
Disease duration skin, yrs	6.0(1-20)	11(4-19)
Prior use of csDMARD (leflunomide)	1	0
Concomitant use of topical psoriasis treatment	6	13
Concomitant use of fumaric acid (N)	1	2
Concomitant use of sulfasalazine (N)	0	1
Concomitant NSAID use at baseline (N)	16	17
Concomitant corticosteroid use at baseline (N)	0	0
DAS CRP	2.3(1.03)	2.46(0,87)
Swollen joint count (median(IQR))	7(4-8.25)	5(4-9.5)
Tender joint count (median(IQR))	9.5 (4-15.25)	10 (5.5-17)
PASI score (median(IQR)	1.6(0.32-3.3)	2.3(0.3-6.8)
No. of patients with baseline PASI >2.5	10	10
No. of patients with Enthesitis	4	7
No. of patients with Dactylitis	9	8
ESR(mm/hr)	20.5(6.5-33.3)	15.0(5.0-29)
No of patients with raised ESR (>20mm/hr)	13	14
CRP (mg/dl)	4.5(1.23-13.3)	7.0(2-15.9)
No. of patients with raised CRP (>5mg/dl)	14	9
VAS patient global (mm)	44.7(24.7)	39.3(23.4)
VAS patient pain (mm)	43.5(24.2)	41.3(28.4)
VAS physician (mm)	44.5(14.5)	47(19.7)
Morning stiffness (min)	44(32.5)	42.3(33.3)
BASDAI	41.0(18.6)	41.3(23.3)

Values are mean (SD), N or median (p25, p75). MTX = methotrexate, NSAID = non steroidal anti inflammatory drug, PASI = psoriasis activity and severity index, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, VAS = Visual analogue scale on a 0-100mm scale, BASDAI = Bath ankylosing spondylitis disease activity index.

Median time since diagnosis was 0.5 (0.5-2) years, most patients (35/50) presented with a polyarticular disease pattern, the median swollen joint count was 5(4-8), tender joint count 10(5-15). 20 patients had a PASI score ≥2.5 at baseline, enthesitis was present in 11 patients and dactylitis in 17 patients.

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

During the 22 weeks period in total six patients did not complete the study period as scheduled, reasons reported for drop out were: 2 patients were lost to follow up due to adverse events (1 in the TNFi arm and 1 in the MTX arm both at week 14 of the study) and 4 patients withdrew their informed consent (1 in the TNFi arm and 3 in the MTX arm).

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

Efficacy

The study met the primary efficacy endpoint with DAS remission at week 22 achieved by a greater number of patients in the TNFi arm (21/26; 81%) vs. the MTX arm (10/24; 42%) (p=0.004), [figure 2].

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

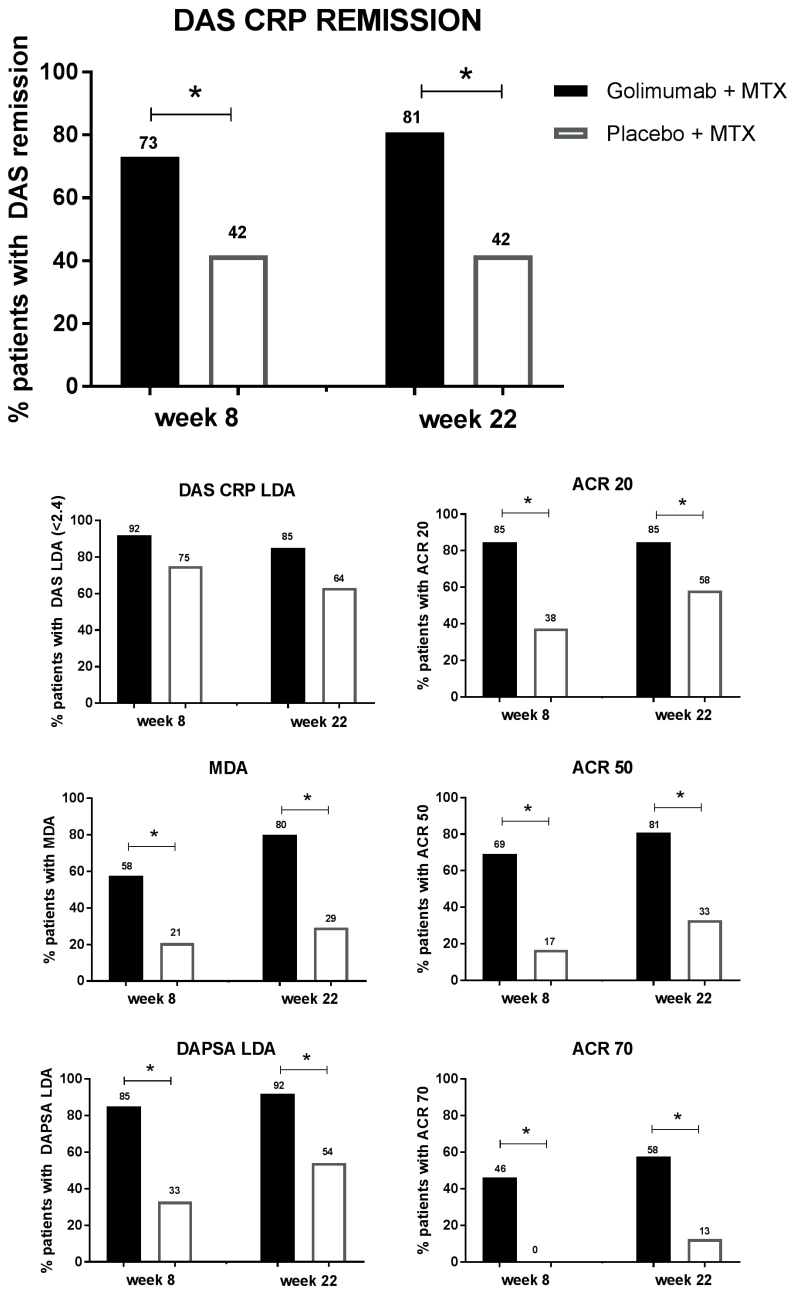

FIGURE 2. Primary and secondary response measures: Upper panel: Percentage of patients in DAS CRP remission after 8 and 22 weeks in the golimumab + MTX and the placebo + MTX arm, respectively. Other panels: percentage of patients reaching DAS CRP LDA, MDA, DAPSA LDA and ACR 20/50 and 70 responses.

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

	Baseline		Week 8			Week 22		
Efficacy measures	**Golimumab + MTX**	**Placebo + MTX**	**Golimumab + MTX**	**Placebo + MTX**	**P Value for group difference**	**Golimumab + MTX**	**Placebo + MTX**	**P Value for group difference**
DAS CRP	2.1(1.7-2.7)	2.4(1.9-2.9)	1.12(0.7-1.61)	1.8(1.31-2.34)	0.002	0.91(0.68-1.36)	1.8(1.18-2.19)	0.000
Swollen joint count	7(4-8.3)	5(4-10.3)	1(0-3)	4(1.5-8)	0.003	0(0-1.25)	2(0-4)	0.042
Tender joint count	9.5(4-15.3)	10(5.3-15.5)	1(0-4)	5(3-9.8)	0.019	0(0-4)	3(1-5)	0.019
PASI (in group with BSL PASI >2.5)	5.75(4.0-7.55)	4.95(3.5-8.45)	0.65(0-3.05)	2.7(0.75-4.25)	0.210	0.55(0-1.9)	0.5(0-1.95)	0.924
Number of patients with enthesitis	4	7	4	3	0.594	2	4	0.209
Number of patients with dactylitis	9	8	5	5	0.836	0	1	0.313
ESR (mm/hr)	20.5(6.5-33.3)	15.5(5-30.5)	2(2-5)	8(5-19)	0.003	2(2-18)	8(2-13)	0.566
CRP (mg/dl)	4.5(1.2-13)	7.1(2.2-16.6)	0.75(0.3-2.95)	2.9(1.25-7.75)	0.079	1.1(1.48-2.85)	3.6(1.2-7.0)	0.144
VAS patient global (mm)	48(26-59)	36(25-54)	21(6-36)	31(16-46)	0.184	9(4-32)	31(14-57)	0.038
VAS patient pain (mm)	44(29-64)	34(17-7)	11(3-24)	30(16-38)	0.003	6(2-18)	34(6-58)	0.001
VAS physician (mm)	48(37-53)	46(37-64)	10(6-25)	33(19-50)	0.000	4(1-20)	18(9-33)	0.047
BASDAI	40.5(29.9-56.3)	47.1(19.1-56.9)	36.5(16.3-59.6)	41.6(22.5-61.0)	0.287	18.1(4.9-23)	24.6(11.7-49.5)	0.022
HAQ	0.38(0.19-1.0)	0.63(0.19-1.47)	0(0-0.3)	0.43(0.03-0.84)	0.003	0(0-0.125)	0.25(0-0.5)	0.403
SF36 PCS	41.1(35.8-48.1)	43.6(36.1-48.5)	47.0(40.9-55.1)	48.8(45.3-53.0)	0.056	50.1(43.7-52.2)	50.7(44.5-52.1)	0.543
SF36MCS	47.9(40.7-55.4)	51.6(47.4-56.6)	51.7(40.7-56.8)	50.3(44.2-56.5)	0.041	50.7(40.0-55.5)	50.9(37.8-52.7)	0.125
DLQI	2(0-7)	2(0-5.75)	1(0-3.5)	1(0-5)	0.891	1(0-3)	0(0-3.5)	0.272

Values are median (p25, p75) or No of patients. PASI = psoriasis activity and severity index, ESR = Erythrocyte Sedimentation Rate, CRP = C-Reactive Protein, VAS = Visual Analogue Scale on a 0-100mm scale, BASDAI = Bath ankylosing spondylitis disease activity index, HAQ = Health Assessment Questionnaire, SF 36 PCS = Short form 36 Physical Component Score, SF36 MCS = Short form 36 Mental Component Score, DLQI = Dermatology Quality of Life Index.

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

Safety and adverse events

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

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

	Golimumab + MTX (n=26)	Placebo + MTX (n=25)
Subjects with SAE (non study-drug related)	0	1
Subjects with AE/event leading to lower or quit MTX		
Total	8	11
ALAT elevation	2	6
Nausea/vomiting	4	2
Infection	2	3
No of subjects with other treatment related AE	21	22
Liver toxicity	2	5
Upper airway infections	5	5
Other infections	3	8
Headaches	1	1
Malaise/tiredness around MTX intake	5	5
Nausea/vomiting	17	13
Other	8	8

AE = adverse event, SAE = Severe Adverse Event, MTX = methotrexate.

The incidence in adverse events was similar between arms. 43/50 patients experienced at least one adverse event (AE) during the trial period (range 1-7), all of which were graded mild to moderate. The most frequent AE involved nausea and occurred in similar incidences in both treatment arms and considered to likely to be treatment related. In eighteen patients an AE led to temporary halt and/or lowering of MTX dosage, and 4 AEs led to early withdrawal from the trial. No deaths occurred.

DISCUSSION

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

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

To assess the concept of early initiation of a TNFi the study used golimumab, where golimumab represents the total group of available TNFi. Whether this concept of high efficacy in early initiation could be translatable to other targeted therapies should be investigated in future trials.

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

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

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

The primary outcome measure could be argued since the ACR response criteria are widely used in clinical trials. The DAS remission was chosen as the primary endpoint as this reflects the actual disease activity status at the endpoint instead of a decrease of disease activity as measured by ACR response. As there is no consensus on 'the ideal target' to date, we included several secondary endpoints, including the traditional response measures, showing similar results.Ourdata raise a number of additional questions. First, clear effects were already seen at week 8 but most outcomes were even more pronounced at week 22. It remains unknown if the responses – in particular the stringent responses such as remission- have already plateaued at week 22 or could even further increase over time. Similarly, it remains to be determined if the combination of TNFi and MTX is only needed for the induction of remission or is also needed to maintain this state of remission over time. To this purpose, golimumab (or placebo) was stopped at week 22 in those patients achieving DAS CRP remission and an extension of the present study will explore if responses are maintained up to week 50 on MTX monotherapy.

Second, the improvement in outcome measurements was paralleled by significant improvement of single disease parameters such as SJC and TJC, but not enthesitis, dactylitis, and PASI. This could of course be due to the fact that only a fraction of the patients included in this PoC study had these disease manifestations (Table 1) and, accordingly, that the study was underpowered to detect potential differences. Alternatively, MTX could be more effective for these disease manifestations than for pure articular disease, as suggested for skin by the proven efficacy of MTX in psoriasis.[26]

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

fully explore this disconnect.Fourth, in this study we did not include assessments by radiography, MRI or ultrasound as these types of assessments require a much larger study population. Although interesting questions for future research with these modalities would be 1) if the observed clinical remission truly represents a resolution of inflammation without any sings of subclinical inflammation on imaging; 2) if the differences in achieved remission rates also protect from development of structural damage.

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

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

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PART III

IMMUNOLOGICAL AND SYSTEMIC EFFECTS OF IL-17A BLOCKADE

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Interleukin-17 blockade with secukinumab in peripheral spondyloarthritis impactssynovial immunopathology without compromising systemic immune responses

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Objective: Secukinumab(anti-Interleukin-17A) [anti-IL-17A] is an effective therapy for ankylosing spondylitis(AS) and psoriatic arthritis(PsA), the prototypical forms of spondyloarthritis(SpA). We undertook this study to determine if secukinumab modulates the immunopathology of target lesions without blunting systemic immune responses, using peripheral SpA as model.

Methods: Twenty patients with active peripheral SpA were included in a 12-week open-label trial with secukinumab (300mg once weekly from baseline to week 4 and then every 4 weeks thereafter). Outcomes included clinical response, cytokine production by peripheral blood cells using TruCulture™ technology, and histologic and real time quantitative polymerase chain reaction analysis of synovial biopsy samples before and after treatment.

Results: All patients completed the 12 week study, without severe adverse events (AEs) or severe treatment-related AEs. The efficacy endpoint, the number of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) at week 12, was achieved by 13 of the 20 patients, of whom 8 reached ACR50 response and 5 achieved an ACR70 response, with rapid and significant improvements in all clinical disease activity measurements. Clinical improvement in joint counts was associated with histologic decrease in synovial sublining macrophages ($P = 0.028$) and neutrophils ($P = 0.004$), both of which are sensitive synovial biomarkers of inflammatory response in peripheral SpA, as well as with decreased synovial expression of IL-17A messenger RNA (mRNA) ($p=0.010$) but not of tumor necrosis factor mRNA. Systemically, secukinumab treatment decreased the C-reactive protein level and the erythrocyte sedimentation rate (both $p<0.01$), and also decreased matrix metalloproteinase 3 production in the TruCulture system ($p<0.01$). However, with the exception of IL-17A itself, the capacity of peripheral blood cells to produce a broad panel of cytokines and chemokines upon stimulation with microbial antigens was not affected.

Conclusion: This mechanism-of-action study in peripheral SpA indicates that clinical improvement with secukinumab treatment is paralleled by immunomodulation of inflamed target tissues without compromising systemic immune responses.

Abstract

INTRODUCTION

Targeting the interleukin (IL-17) cytokine axis has emerged as an effective therapeutic approach beyond TNF inhibitors (TNFi) in psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS).[1,2] In psoriasis, the blockade of IL-17A even yielded clinical efficacy superior to that of TNFi.[3] These clinical observations were confirmed by a unique impact of IL-17A blockade on the histologic and molecular features of psoriatic skin.[4] In contrast to psoriasis, the impact of IL-17A blockade on local tissue pathology in spondyloarthritis (SpA), the rheumatic syndrome to which AS and PsA belong, remains unknown, as clinical and imaging studies were not yet complemented by direct histologic and molecular analysis of target tissues before and after treatment. Moreover, it has not yet been assessed if a potential effect of IL-17A blockade on local tissue pathology is associated with systemic immunosuppression. Finally, the efficacy of IL-17A blockade had not been tested in other SpA subtypes beyond AS and PsA. In contrast to this scarcity of data with IL-17A blockade, a large number of studies with TNFi have shown their impact on tissue pathology, their efficacy in the different subtypes of the disease including peripheral SpA, and their long-term safety profile.[5,6] To be able to better position both therapeutic strategies, the present study aimed to evaluate the impact of secukinumab, a monoclonal anti-IL-17A antibody, on the immunopathology of one of the key target tissues in peripheral SpA, the synovial membrane, and relate this to suppression of signs and symptoms of disease as well as systemic immunosuppression.

PATIENTS AND METHODS

Study design

Twenty patients with a clinical diagnosis of peripheral SpA fulfilling the Assessment of Spondyloarthritis International Society criteria[7] for peripheral SpA were included in a single-center, open-label, investigator-initiated clinical trial with secukinumab (300 mg once weekly from baseline to week 4 and then every 4 weeks thereafter), consisting of a 12-week core mechanism-of-action study followed by a 2-year observational extension study. All patients provided written informed consent before enrollment in the study as approved by the Ethics Committee of the Amsterdam Medical Center.

Patients

The 20 with peripheral SpA included 13 with PsA, 3 with undifferentiated SpA, 2 with AS with peripheral arthritis, 1 with reactive arthritis and 1 with SpA with associated inflammatory bowel disease (IBD) (without active disease at screening and baseline). These different subtypes of peripheral SpA were pooled for analysis based on previous

studies showing no difference among them in synovial histopathology.[8–10] Patients were ages 18-70 years and had active peripheral joint disease defined by at least 1 swollen ankle or knee joint despite optimal treatment with non steroidal antiinflammatory drugs (NSAIDs).

The mean +/- SD age of the patients was 45.8 +/- 13.1 years, and 15 were male; their median symptom duration was 5.5 years (Inter quartile range 1-9 years). Stable doses of NSAIDs or oral corticosteroids (up to 10 mg daily prednisone equivalent) for at least 2 weeks, or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) on a stable dose for at least 4 weeks prior to baseline were allowed. Concomitant medication used were NSAIDs in 10 patients(50%), oral corticosteroids (max of 10 mg daily) in 3 patients (15%); methotrexate in 2 patients (10%); leflunomide in 2 patients (10%). Patients for whom not more than 1 TNFi had failed prior to the study could enroll after an appropriate washout. Nine patients (45%) had previously been treated with a TNFi.

Key exclusion criteria were use of any biologic agent other than TNFi, use of subcutaneous or intraarticular steroids within 4 weeks, active ongoing inflammatory diseases other than SpA (including active uveitis or active IBD), active or recent infections, clinically significant liver disease, history of malignancy within 5 years of baseline, and pregnancy.

Clinical assessments

The primary efficacy endpoint was the number of patients meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response)[11] at 12 weeks, representing response in the peripheral domain. The following secondary efficacy parameters were evaluated every 4 weeks in the core study and every 3 months in the extension study: 76 swollen joint count (SJC) and 78 tender joint count (TJC), patient's global assessment of disease activity (PtGA) on a 0-100mm visual analogue scale (VAS), patient's assessment of pain (PtP) on a 0-100mm VAS, physician's global assessment of disease activity (PGA) on a 0-100mm VAS, Bath Ankylosing Spondylitis Activity Disease Index (BASDAI)[12], Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[13], Dactylitis count (Dc), resolution of swelling of the target joint in which the arthroscopy was performed, Psoriatic Arthritis Severity Index (PASI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). At each visit, patients were asked about side effects, and physical examination and routine laboratory testing for safety were performed.

Arthroscopic synovial tissue biopsy

Synovial biopsy samples were obtained from the same inflamed ankle or knee joint by mini-arthroscopy at baseline and week 12 as described previously.[14] Samples (an average of 8 per patient from each of the 2 time points) were either snap frozen en-bloc in Tissue-Tek (Sakura Finetek USA) for histological evaluation or immediately stored in liquid nitrogen for subsequent RNA extraction.

Immunohistochemistry

Cryostat sections (4 µm) were fixed and endogenous peroxidase was blocked, after which the sections were incubated overnight at 4°C with the primary antibody. Primary antibodies used were directed towards macrophages (CD68; EBM-11, Dako), alternatively activated macrophages (CD163; 5cFAT, BMA Biomedicals), mast cells (tryptase, AA1, Abcam),T cells (CD3, UCHT1, Dako), Neutrophils (CD15, C3D1 Acris), B cells (CD20, L26, Dako), Plasma cells (CD138, MI15, Dako), transmembrane TNF (52B83, Hycult Biotech), vascularity (von Willebrand factor [vWF], A0082, Dako). As a negative control, isotype- and concentration-matched monoclonal antibodies were applied to parallel sections. After rinsing, sections were sequentially incubated with a biotinylated secondary antibody, a streptavidin horseradish peroxidase link, aminoethylcarbazole substrate as chromogen (all Dako). Sections were scored by semi-quantitative analysis (SQA) by two independent observers (L.vM, M.vdS) who were blinded with regard to patient coding and time of biopsy sampling. The expression of immunohistochemical markers was scored on a 5-point scale. CD68 positivity was scored for the lining layer and the synovial sublining separately.

Real time quantitative polymerase chain reaction (qPCR).

A set of snap-frozen biopsies were homogenized in STAT-60 (Amsbio). Total RNA was isolated from synovial tissue biopsy samples using RNA easy microkit (Qiagen), including treatment with DNase I, and reverse transcribed using RevertAid H Minus First-Strand cDNA synthesis kit (Thermo scientific). Real-time q PCR (qPCR) was performed using StepOnePlus real-time PCR system (Applied Biosystems). Predesigned TaqMan probe and primer sets for CCL20 (Hs00355476_m1), IL-6 (Hs00174131_m1), IL-8 (Hs00174103_m1), IL-17A (Hs00174383_m1), IL-17F (Hs00369400_m1), matrix metalloproteinase 3 (MMP-3) (Hs00968305_m1),TNFalpha (Hs00174128_m1) and GAPDH (4310884E) were purchased and assayed in duplex according to the protocol of the manufacturer (Applied Biosystems).

TruCulture

In the TruCulture system (Rules-Based Medicine) whole blood cells are incubated under stimulating conditions mimicking the presence of a (bacterial/fungal) infection. One mililiter of whole blood was drawn using standard phlebotomy techniques and incubated in a bench-top dry heat block at 37°C. Tube conditions were unstimulated (null), zymosan, which activates the innate immune system (granulocytes/monocytes) and staphylococcal enterotoxin B (SEB) which activates T-lymphocytes in an antigen-specific manner.[15] After 24 hours, supernatant was collected and stored at -80°C until analysis. Supernatants were analyzed by multianalyte profiling using TruCultureMAP® A and B (Rules Based Medicine)

Statistical analysis.

Data are presented as the median and interquartile range (IQR). Clinical disease activity parameters, real-time qPCR and immunohistochemistry were analyzed using nonparametric statistics with the Wilcoxon matchedpairs signed rank test. Correlations were evaluated with Spearman's rank correlation. P values less than 0.05 were considered significant.

RESULTS

Safety and clinical response to secukinumab in patients with peripheral SpA

All patients completed the 12-week core study period without any severe adverse events (AEs). In particular, there were no severe cases of fungal infections, severe infections requiring antibiotics or hospitalization, or episodes of inflammatory bowel disease. The most common AEs were common flu symptoms (n=6), worsening of skin psoriasis in the first weeks of treatment (n=3), throat infection (n=2), fungal skin infection of the feet (n=1). The primary clinical efficacy endpoint, an ACR20 response at week 12, was reached by 13 of the 20 patients, of whom 8 achieved an ACR50 response and 5 an ACR70 response. This was associated with a rapid and significant improvement in all clinical outcome measures as show in Table 1.

Analysis of the subgroups of patients with PsA those with non-PsA peripheral SpA revealed similar disease patterns (monoarticular/oligoarticular presentation) as well as similar ages, disease durations, VAS scores and TJCs. PsA patients did present with higher SJCs at baseline (1-2 IQR versus 0-1; p=0,006) but did not differ in either ACR responses, Disease activity Score in 28 joints (DAS 28) at baseline or change in the DAS28.[16] No

differences were observed in baseline histology or histologic response over time. Collectively, these data indicate a rapid, robust, and consistent clinical improvement upon secukinumab treatment in peripheral SpA.

TABLE 1. Clinical efficacy outcomes at baseline and at 4,8 and 12 weeks after initiation of treatment in the 20 study patients.

	Baseline	Week 4	Week 8	Week 12	P value *
DAS28	4.0(3.2-5.2)	3.2(1.8-3.8)	3.1(1.6-3.8)	2.5(1.5-3.0)	<0,001
Swollen joint count	2.5(1-4)	2(1-2.8)	1(0-2)	0.5(0-1)	<0,001
Tender joint count	6(2.3-8.8)	2(0.3-5.8)	1.5(0-4.8)	0.5(0-3)	<0,001
Enthesitis	0(0-1.8)	0(0-0.8)	0(0-0)	0(0-0)	<0,05
PASI score **	0(0-5.5)	N/A	N/A	0(0-0.6)	<0,01
BASDAI	53.4(25.5-63.3)	35(23.9-44.9)	21.9(12.4-40.2)	19.9(9.1-39.6)	<0,001
VAS patient global	45.5(28.3-65)	33.5(18.8-44.8)	24(9-40)	12.5(5.5-23.8)	<0.001
VAS patient pain	40.5(30.5-51)	32.5(17-42.3)	24(6-34)	17(2.5-27.8)	<0.001
Morning stiffness	56(10-83)	12.5(5-30)	8.5(1.3-27.5)	5(1.3-27.5)	<0,001
VAS physician	49.5(43.3-60)	32(17.3-48)	19(8-35)	18(8.5-27.8)	<0.001
CRP	3.9(1.4-16.6)	2.2(0.9-4.9)	2.4(1.4-5.7)	2.05(1.2-6.3)	<0,01
ESR	16(6-35)	8(2.8-23.3)	9.5(2.8-25.3)	7(2.8-16.3)	<0,01

Values are the median (IQR). * By Wilcoxon matched pairs signed rank test comparing baseline with week 12. ** thirteen patients DAS28 Disease activity score in 28 joints, PASI Psoriatic Arthritis Severity Index; NA not applicable, BASDAI bath ankylosing spondylitis activity index, PtGA patient's global assessment of disease activity, VAS visual analogue scale, PhGA physician's global assessment of disease activity, CRP c-reactive protein, ESR erythrocyte sedimentation rate.

Immunomodulation of synovial inflammation by secukinumab.

Using histopathologic examination, we next assessed whether the clinical response induced by secukinumab treatment was paralleled by a down-modulation of synovial tissue inflammation. As shown in Figure 1A, at week 12 there was a significant decrease in CD15+ neutrophils (p=0.004) and synovial sublining CD68+ macrophages (p=0.028), both of which are sensitive biomarkers of synovial inflammation in SpA.[17] No significant changes were noted for CD3+ T cells, CD20+ B cells, CD138+ plasma cells, tryptase-positive mast cells, and vWF+ blood vessels. Higher expression at baseline of several cells correlated with persistent swelling at week 12 of the joint that underwent the arthroscopy: CD68+ cells (macrophages) in both lining layer (r=0,561, p=0,015); and sublining layer (r=0,549, p=0,18), CD15+ cells (neutrophils) (r=0,508, p=0,037); and CD3+ cells (Tcells) (r=0,623,p=0,008). No correlation was found between changes in

clinical scores and changes in cellular infiltrate, only baseline scores of these cellular infiltrates correlated with clinical response, indicating the highly inflamed joints were less likely to show complete resolution of inflammation at week 12.

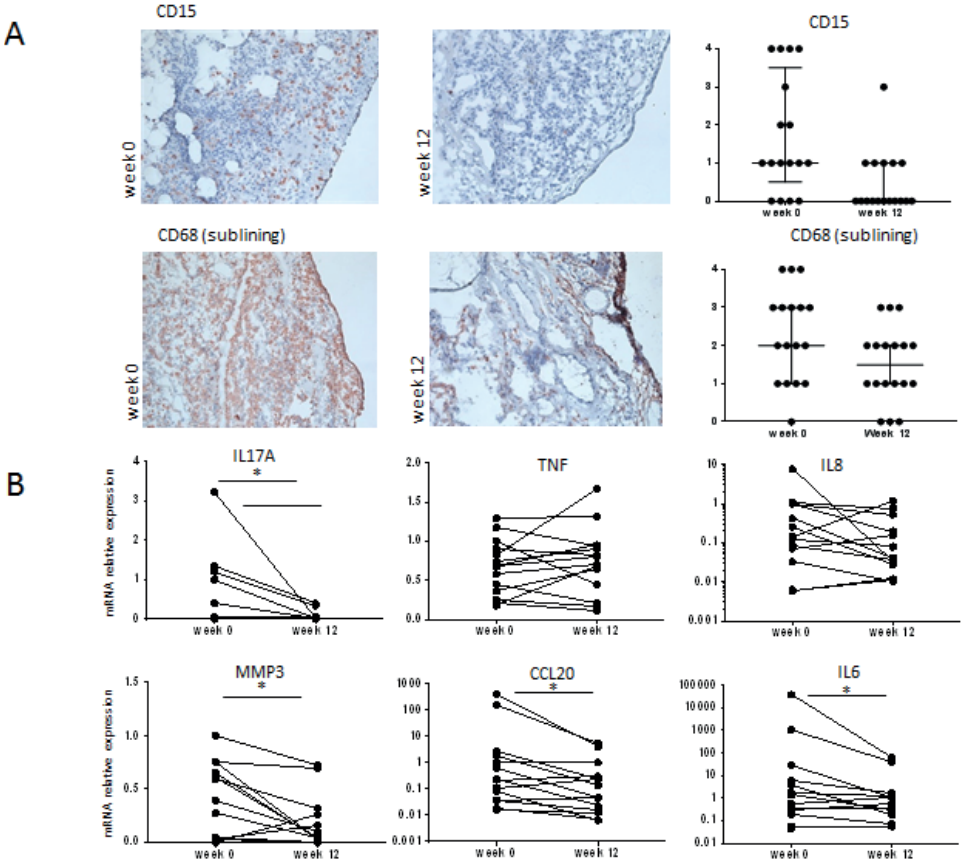

FIGURE 1. Immunomodulatory effect of secukinumab on synovial inflammation.
A, Left, representative paired sections of synovial biopsy tissue obtained at baseline (week 0) and 12 weeks after initiation of treatment. Original magnification 9 20. Right, Quantification of CD15+ neutrophils and synovial sublining CD68+ macrophages. Symbols represent individual samples (n = 17); bars show the median and interquartile range on a semiquantative scale.
B, Effect of secukinumab treatment on synovial tissue expression of mRNA for interleukin-17A (IL-17A), tumor necrosis factor (TNF), IL-8, matrix metalloproteinase 3 (MMP-3), CCL20, and IL-6 at week 0 and week 12, assessed by real-time quantitative polymerase chain reaction. Values are paired data points for each patient (n = 14). *=P < 0.05.

As these data indicated an improvement but not normalization of the synovial histology at 12 weeks, we aimed to confirm the impact of secukinumab on tissue inflammation by additional molecular analysis. Real-time qPCR analysis of a selected panel of key mediators of inflammation in peripheral synovitis revealed a significant decrease of synovial expression messenger RNA (mRNA) for IL-6 (p=0.042), MMP-3 (p=0.025), and CCL20 (p=0.042), but not IL-8 (p=0.241). As to the key pathogenic cytokines driving synovial inflammation in SpA, there was a significant decrease in expression of mRNA for IL-17A (p=0.010) while expression of mRNA for TNF was stable (p=0.426) (Figure 1B). The levels of Il-17A correlated highly with the presence of neutrophils (rs = 0.901, P < 0.0001 at baseline and rs =0.872, P = 0.0005 at week 12) and to a lesser extent with numbers of other cells in the infiltrate at baseline (for CD3+ T cells rs = 0.5906, p=0.04; CD68 sublining layer macrophages rs=0.6779 p=0.01). Collectively, the analysis of inflamed synovial tissue before and after treatment with secukinumab indicates a targeted modulation of local immunopathology.

Preservation of systemic immune responses upon secukinumab treatment

Finally, to further determine whether the effects observed in the inflamed target tissue, the synovial membrane, were due to specific immunomodulation rather than to global immune suppression, we assessed systemic inflammatory and immune responses. Consistent with published data,[1] secukinumab treatment induced a rapid and profound decrease of serum CRP levels (p <0,01) and ESR (p<0,01) (Table 1). In examining the capacity of peripheral blood cells to respond to microbial stimuli, using zymosan and SEB as prototypes stimulating innate immune cells and T cells, respectively, we observed a significant decrease in MMP-3 and IL-17A production, confirming the synovial tissue expression data. However, this analysis did not reveal any impact of secukinumab treatment on the capacity of peripheral blood cells to produce all 30 other cytokines and chemokines tested, including key host defense factors such as TNFalpha and IFNgamma (Table 2). These data indicate specific immunomodulation in the synovium rather than global immune suppression.

TABLE 2. Effect of secukinumab on the capacity of whole blood to produce several cytokines/chemokines under unstimulated and stimulated TruCulture system conditions (n = 18 patients)

	Unstimulated			Zymosan			SEB		
	Baseline	**Day 3**	**Wk 12**	**Baseline**	**Day 3**	**Wk 12**	**Baseline**	**Day 3**	**Wk 12**
BDNF	12(9,4-14)	13(9.6-15)	12(10-16)	12,5(8,8 – 13,3)	12,50(10.6-14)	**12(10,7-14)***	12,5(10,8-15)	12,5(1,8-15,3)	12,5(11,8-15,3)
Eotaxin-1	249(176-323)	221(187-298)	266(184-353)	188 (157-275)	227(179-290)	**245(161-307,8)***	201,5(139,8-258)	209,5(160,8-262,8)	218,5(176-319,3)
Factor VII	271(219-328)	285(254-333)	294(260-347)	266(212-305)	307(257-335)	312(256-349)	269(241-340)	285,5(252,3-322)	306(263-343)
GM-CSF	0(0-0)	0(0-0)	0(0-0)	52(0-76)	40(24-63)	59(49,7-82,3)	427(151-526)	299(142-574)	261(131-613)
ICAM-1	74(59-89)	67(62,3-92,5)	66(58-92)	68(59-82)	74,5(64.5-90.5)	72,5(57-8-92,5)	75,5(64,5-92,3)	67(62,5-90)	67(57,8-85)
IFN gamma	0(0-0)	0(0-0)	0(0-0)	177(77-367)	265,5(93-535)	315,5(57,3-634)	1180(840-3502)	**1255(847-3358)***	1115(469-4450)
IL-1 alpha	0,0013 (0-0,0017)	0,0012 (0-0,0016)	0 (0-0,0015)	0,155 (0,098-0,253)	0,17 (0,114-0,213)	0,18 (0,102-0,263)	0,0077 (0,0029-0,0253)	0,0068 (0,0023-0,0168)	0,0063 (0,0019-0,010)
IL-1 beta	0(0-10)	0(0-0)	0(0-0)	7625(5087-12175)	8000(5555-10295)	8450(6712-13850)	391(75-659)	310(112-586)	238(77-629)
IL-1 ra	156(90-262)	105(86-339)	116(86-153)	3565(2545-4717)	3200(2695-3987)	2935(2078-4855)	2570(1383-4370)	1650(1287-3935)	**1750(1061-2645)***
IL-2	0(0-0)	0(0-0)	0(0-0)	115(103-136)	122(103-140)	126,5(99,8-188)	4975(2208-8373)	3320(2252-8842)	3335(2328-6585)
IL-3	0 (0-0)	0 (0-0)	0 (0-0)	0,0175 (0,015-0,021)	0,0175 (0,014-0,01925)	0,0185 (0,0165-0,0245)	0,021 (0,011-0,028)	0,0165 (0,012-0,023)	0,0165 (0,00753-0,027)
IL-4	0(0-0)	0(0-0)	0(0-0)	141(110-168)	131(109-163)	151,5(114,3-203,5)	351(232,5-456,8)	245(214-486)	280(178-399)
IL-5	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-0)	0(0-1,175)	33(22,5-74,3)	28(18-57)	28,5(17,5-44,5)
IL-6	0(0-16)	0(0-4,6)	**0(0-0)***	40500(29325-56900	36150(27200-48150)	36250(25375-56300)	1212(229-2533)	591(126-1328)	419(166-1725)
IL-7	0(0-0)	0(0-0)	0(0-0)	47(39-54)	45(25,5-49,5)	**35,5(0-47,8)***	32(0-39)	39(126-1328)	31,5(0-40)
IL-8	109 (29-318)	50 (25-401)	**45 (32-92)***	204500 (150250-247500)	159000 (127000-197500)	189000 (159750-261500)	69800 (19750-176500)	64400 (15450-113000)	51800 (19700-88625)
IL-10	0(0-0)	0(0-0)	0(0-0)	660(554-1270)	534(406-874)	802(601-1217)	478(278-621)	484(251-618)	427(236-844)

TABLE 2. Continued

	Unstimulated			Zymosan			SEB		
	Baseline	**Day 3**	**Wk 12**	**Baseline**	**Day 3**	**Wk 12**	**Baseline**	**Day 3**	**Wk 12**
IL-12p40	0,52(0-0,73)	0,052(0-0,66)	0(0-54)	7,9(6-10)	8,7(6,3-11)	6,75(5,03-10,3)	0,8(0,59-0,96)	0,8(0,61-0,93)	0,66(0,52-0,87)
IL12-p70	0(0-0)	0(0-0)	0(0-0)	0(0-40)	0(0-48)	0(0-48,8)	20(0-54)	39(0-78)	43(0-71)
Il-15	0(0-0)	0(0-0)	0(0-0)	1,4(1,3-1,6)	1,55(1,27-1,6)	1,4(0-1,5)	0(0-0)	**0(0-1,2)***	0(0-0)
IL-17	0(0-0)	0(0-0)	0(0-0)	4,65(0-15)	**0(0-9,5)***	0(0-12)	168(85-261)	**24(17-34,8)***	**25(15-43)***
IL-18	119(94-207)	128(103-177)	119(99-189)	224(191-296)	234(202-297)	255(208-324)	185(121-244)	156(131-224)	160(16-230)
Il-23	3,6(0-4,4)	3,4(0-4,3)	**0(0-3,9)***	17(11-22)	18,5(12,7-22,5)	13,5(11,75-24,75)	3,9(3,4-4,8)	3,75(0-4,9)	**3,4(0-4,4)***
MIP-1 alpha	37(0-78)	28(0-118)	30(0-46)	75950(53925-115250)	58900(46925-90500)	75200(46975-104500)	22300(3023-28525)	11900(6115-26450)	11150(6732-20350)
MIP-1 beta	596 (251-1910)	424 (192-2755)	**490 (261-698)***	1415000 (903750-1900000)	1155000 (749250-1570000)	1305000 (617250-1822500)	227500 (100125-442750)	262500 (97325-344750)	186500 (102500-388000)
MMP-3	16(12-29)	16(11,3-26,5)	**9,4(7,1-24)***	15,5(9,9-27,5)	17,5(9,9-29,7)	**9,9(8,3-22,5)***	16(10,6-28,5)	17,5(12,8-27,3)	**9,8(7,7-21)***
MMP-9	0(0-36)	0(0-36)	0(0-36)	55(45-62)	57(47-71)	48(37-66)	17(0-44)	35(0-49)	0(0-44)
Mcp-1	432 (333-542)	455 (376-570)	475 (347-596)	72750 (33725-135250)	51850 (44175-79725)	59150 (47875-86950)	69100 (36600-133750)	**43700 (18550-92825)***	47650 (29025-81725)
SCF	0(0-252)	0(0-265)	0(0-292)	490(451-633)	561(462-662)	571(462-669)	252(0-321)	234(0-302,5)	115(0-305)
TNF alpha	0(0-0)	0(0-0)	0(0-0)	15750(8715-21275)	16650(8405-20425)	18300(10072-26850)	2900(1433-5912)	2990(1248-5580)	3555(2058-6423)
TNF beta	0(0-0)	0(0-0)	0(0-0)	53,5(49-68,5)	64,5(51,5-70)	59,5(51,8-78,5)	29(15-44,3)	22,5(0-42,8)	19(0-34)
VEGF	396(321-582)	372(263-559)	**313(238-404)***	596,5(463-709)	688,5(512,5-776,3)	633(439,8-724,8)	235(206-275)	258(214-313)	223(183-281)

* Values are the median (interquartile range) pg/ml. SEB = staphylococcal enterotoxin B; BDNF = brain-derived neurotrophic factor; GM-CSF = granulocyte–macrophage colony- stimulating factor; ICAM-1 = intercellular adhesion molecule 1; IFNc = interferon-c;IL-1a = interleukin-1a; IL-1Ra = IL-1 receptor antagonist; MIP-1a = macrophage inflammatory protein 1a; MMP-3 = matrix metalloproteinase 3; MCP-1 = monocyte chemotactic protein 1; SCF = stem cell factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

† $P < 0.05$ versus baseline, by Wilcoxon matched pairs signed rank test.

DISCUSSION

The primary aim of this study was to assess the impact of secukinumab treatment on synovial immunopathology in peripheral SpA to investigate whether an improvement in signs and symptoms of disease was associated with modulation of the underlying inflammatory processes. To this purpose, the study included specifically SpA patients with a clinically inflamed knee or ankle joint, and a 300 mg secukinumab dose was used in an open-label design. Within the limitations of this mechanistic trial design, we observed rapid and profound improvement of all clinical disease activity parameters, resulting in ACR20 response rate of 65%, without obvious differences between psoriatic and non-psoriatic peripheral SpA or between anti-TNF naïve and anti-TNF incomplete responders. While these clinical data support further investigation of the efficacy of secukinumab in SpA subtypes beyond AS and PsA[1,2], they mainly indicate that the study population provided the appropriate setting for the evaluation of local and systemic immunomodulation by IL-17A blockade.

Focusing on the modulation of tissue pathology, we observed that the baseline synovial biopsy samples showed the characteristics of inflamed SpA synovial tissue, with an increased lining layer thickness, hypervascularity, and increased inflammatory infiltrate consisting mainly of macrophages, T cells, mast cells, and neutrophils. The significant improvements in swollen and tender joint counts at 12 weeks of secukinumab treatment were paralleled by improvement of synovial immunopathology with a decrease in infiltrating neutrophils and macrophages and a downregulation of MMP-3 expression, all of which are biomarkers of successful response to therapy in SpA,[18–20] which confirms that secukinumab modulates local tissue pathology. These findings are consistent with previous studies with TNF inhibitors,[14,18] although direct comparison remains difficult.

Three observations deserve further attention. First, real-time qPCR analysis revealed a significant decrease mRNA for IL-17A, which suggests that secukinumab treatment not only blocks IL-17A protein but also targets cells producing IL-17A in inflamed synovium. The identity of cells producing IL-17A in SpA synovitis[21] and the impact of secukinumab on these cells remains to be defined. However, the rapid turn-over of neutrophils (which requires continued influx in inflamed tissue), the observed decrease of these cells at week 12, and the high correlation between neutrophil score and IL17A levels nominate them as candidates, although the capacity of neutrophils to produce IL-17A remains a subject of controversy.[22] Alternatively, neutrophils may drive IL-17A production by other cells in the inflamed synovial tissue.[23] Several groups, including our own, reported on the cellular source of IL-17A in SpA;[9,24,25] however, non of these studies was conclusive, and we still do not know the major cellular source of IL17A. Second, in contrast to IL-17A,

there was no decrease in synovial tissue expression of mRNA for TNF, indicating that the IL-17A pathway does not cross-regulate TNF. Third, despite clear clinical improvement, synovial histology was not normalized after 12 weeks of secukinumab treatment, which suggests that either longer treatment is needed or that other pathways – potentially including TNF – are still operative in the diseased tissues. Detailed RNA sequencing analysis of synovial biopsy samples before and after IL-17A blockade and after TNF blockade may provide more insights in the hierarchy of molecular pathways driving synovial immunopathology in SpA.

To determine whether the profound clinical and local immunopathologic impact of IL-17A blockade in peripheral SpA was associated with suppression of the immune system's response to microbial triggers, we used a novel technology allowing us to assess the functional responses of whole blood.[15] Consistent with the synovial findings, we observed treatment-induced decreases in MMP-3 (a biomarker of disease activity in SpA[18]) and IL-17A after treatment. However, we cannot exclude the possibility that the decreases in IL-17A may be explained by the presence of secukinumab in whole blood on day 3 and at week 12 binding IL17A, and thus decreases may not reflect a real impairment of IL-17A production. Further analyses at the mRNA level are needed to clarify this issue. More important, however, the TruCulture approach did not reveal other significant changes, thereby suggesting that the capacity of circulating immune cells to respond to microbial triggers is unaffected following IL-17A blockade. Interestingly, a similar TruCulture approach in patients with axial SpA revealed a profound impact of TNF blockade on the production of a variety of key mediators of inflammation, including IL-1beta, IL-8, MCP-1, MIP-1alpha and MIP-1beta.[26] Larger long term studies are needed to further establish how these distinct findings on systemic immune fitness relate to the overall safety profile of the different types of cytokine blockade in SpA.

In conclusion, this mechanism-of-action study indicates that IL-17A blockade with secukinumab has a profound clinical and immunopathologic impact on peripheral SpA without compromising systemic immune responses.

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Submitted

Secukinumab treatment decreases arterial wall inflammation in patients with peripheral spondyloarthritis

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Abstract

Objective: Patients with spondyloarthritis (SpA) have increased cardiovascular risk, partly attributed to arterial wall inflammation. Whereas secukinumab, an IL17A blocker, successfully attenuates disease activity in SpA, its effect on arterial wall inflammation is unknown.

Methods: 20 patients with peripheral SpA (pSpA) were treated with secukinumab (300 mg weekly during the first 4 weeks, followed by four-weekly administration up to 12 weeks). The ACR50 response criteria were used to define responder status. Carotid arterial wall inflammation was assessed as target-to-background ratio (TBR) using ^{18}-Fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT) at baseline and week 12.

Results: Scans were available in 16 patients. Secukinumab treatment tended to lower TBR_{mean} (1.50±0.3 to 1.41±0.2; p=0.069). In a post-hoc analysis, patients with a good clinical response showed a significant decrease in TBR after secukinumab treatment (TBR_{mean} 1.50±0.2 to 1.39±0.2, p=0.022), while there was no change observed in non-responders.

Conclusion: Secukinumab treatment showed a trend towards a decrease of arterial wall inflammation in pSpA patients, mainly in patients with a good clinical response. Larger, controlled trials are needed to assess the relationship with CV events.

INTRODUCTION

Spondyloarthritis (SpA) is an immune-mediated inflammatory disease, with ankylosing spondylitis (AS) and psoriatic arthritis (PsA) as the most prototypical sub-forms. Patients with SpA have an increased cardiovascular (CV) risk[1], which has been partly attributed to the chronic inflammatory state in these patients. In support, patients with PsA and AS were found to have increased arterial wall inflammation, assessed with ^{18}-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT)[2, 3], which is a predictor of adverse cardiovascular outcome[4]. ^{18}F-FDG is a glucose analogue, so it reflects metabolic activity. ^{18}F-FDG PET/CT has emerged as a validated method to quantify arterial wall inflammation[5], whereas ^{18}F-FDG uptake in plaques is associated with macrophage content and activity[6].

IL-17A has been identified as a crucial mediator of synovial inflammation and joint destruction in SpA[7]. More recently, IL-17A blockade using secukinumab has been introduced as an effective therapy in SpA patients[8]. However, the role of IL-17A in cardiovascular disease remains controversial, with data supporting pro- as well as anti-atherogenic effects in experimental models[9]. Consequently, the effect of anti-IL-17A treatment on arterial wall inflammation in patients is unknown.To evaluate the effect of anti-IL-17A therapy on arterial wall inflammation in humans, we conducted a pilot trial with ^{18}F-FDG PET-CT in SpA patients with peripheral disease (pSpA) treated with secukinumab, a monoclonal anti-IL-17A antibody.

MATERIALS AND METHODS

Study population and design

Twenty patients with a clinical diagnosis of peripheral spondyloarthritis, fulfilling the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis[10], were included in a single-center, open label, investigator-initiated clinical trial with secukinumab (300 mg once weekly from baseline to week 4 and then every 4 weeks thereafter)[11]. All patients provided written informed consent before enrollment in the study as approved by the Ethics Committee of the Amsterdam Medical Center. Clinical improvement was measured at week 12 by the ACR50 response criteria, which are commonly used in psoriatic arthritis and which we have recently validated for non-psoriatic pSpA[12]. Additional clinical and laboratory assessments included weight, height, lipid levels, BSE and CRP levels.

^{18}F-FDG PET/CT scan

To measure arterial wall inflammation, we performed ^{18}F-FDG PET/CT imaging on a Philips scanner (Philips, Best, the Netherlands) at baseline and after 12 weeks of treatment in 18 patients. For 2 patients, a PET/CT was not performed. Patients were fasted for at least 6 hours before infusion of ^{18}F-FDG. 90 minutes post-infusion, a PET scan was performed in combination with a low-dose, non-contrast enhanced CT for attenuation, correction and anatomic co-registration. Images were analyzed with dedicated software (OsiriX, Geneva, Switzerland; http://www.osirix-viewer.com) by experienced readers blinded for patient data and sequence of images. Arterial ^{18}F-FDG uptake was quantified by drawing regions of interest around both carotids on 5 slices of the co-registered transaxial images. Standardized uptake values (SUV) were averaged for each artery, and divided by the average venous background activity (SUV_{mean}) in the jugular vein to obtain the target-to-background-ratio (TBR). The SUV is the decay-corrected tissue concentration of ^{18}F-FDG in kBq/ml, adjusted for the injected dose. The mean and maximal target-to-background-ratio (TBR_{mean} and TBR_{max}) of the carotid with the highest mean ^{18}F-FDG uptake were determined[5].

Statistical analysis

All data were analyzed using SPSS version 23.0 (SPSS Inc, Chigago, Illinois). Data are presented as the mean ± standard deviation (SD) for normally distributed data, the median with interquartile range (IQR) for non-normally distributed data or as a number (percentage) for categorical variables. Differences in clinical parameters and TBR's before and after treatment were assessed by a paired student's T-tests or Wilcoxon signed-rank test, respectively, for normally and non-normally distributed data. In a post-hoc analysis, differences in baseline characteristics between patients with a good clinical response and patients with no clinical response were assessed by a student's T-test or Mann-Whitney U test for, respectively, normally and non-normally distributed data. A 2-sided P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

From the 18 pSpA patients, 2 patients were excluded due to insufficient image quality of the PET/CT. Baseline characteristics of the 16 patients are listed in table 1. Twelve patients had psoriatic arthritis and 4 non-psoriatic pSpA, patients were 45±12 years old, 75% male, 7 patients used disease-modifying antirheumatic drugs (DMARD's) at baseline (methotrexate (n=2), leflunomide (n=2), sulfasalazine (n=1), prednison (n=2)

and mesalazine (n=1)) and 6 patients had used TNF-a inhibitors before inclusion. None of the patients had diabetes or had experienced a previous CV event; three patients used statins and 3 patients used anti-hypertensive medication at baseline; all patients continued secukinumab treatment at the same dose.

TABLE 1. Baseline characteristics

Characteristics	pSpA patients (n=16)	Post-treatment (n=16)	P value
Gender, men/women	12/4	n/a	n/a
Age, years	45±12	n/a	n/a
BMI, kg/m^2	28±4	n/a	n/a
VAS_{pain} score	40[26-51]	15[2-37]	0.002
SJC	3[1.25-4]	0[0-1]	0.001
TJC	6[2-9]	1[0-3]	<0.001
CRP, mg/L	3.2[1.05-10.50]	1.8[0.9-5.10]	0.023
BSE, mm/U	11[4-29.50]	6[2-12.50]	0.046
LDL cholesterol, mmol/L	3.3±0.9	3.6±1.0	0.280

Values are n, mean ± SD or median [IQR] for non-normally distributed data.
BMI indicates body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, CRP; C-reactive protein, SJC; swollen joint count, TJC; tender joint count, VAS; visual analogue scale

Clinical response

Eight of the 16 patients were classified as clinical responders (ACR50 achieved), with baseline characteristics being comparable between the responders and non-responders (table S1). ACR50 responders showed a significant decrease of peripheral disease activity and systemic inflammation (CRP) after treatment, while only a decrease in peripheral disease activity (swollen and tender joint counts) was shown in non-responders (table S1).

Impact on arterial wall inflammation

Secukinumab treatment resulted in a trend towards a TBR decrease between baseline and week 12: ^{18}F-FDG uptake in the carotids was reduced by 6% (TBR_{mean} 1.50±0.3 to 1.41±0.2, p=0.069; TBR_{max} 1.84±0.4 to 1.73±0.3, p=0.081; table 2). There was no change in lipid levels or other traditional cardiovascular risk factors (table 1).

In a post-hoc analysis, comparing TBR change within ACR50 responders and within non-responders, only responders showed a significant decrease in TBR after secukinumab treatment (TBR_{mean} 1.50±0.2 to 1.39±0.2, p=0.022; TBR_{max} 1.87±0.4 to 1.74±0.4, p=0.032; table 2), whereas no change was observed in the non-responders.

TABLE 2. The effect of secukinumab treatment on arterial wall inflammation displayed as cohort and per responder and non-responder group

		TBR baseline	TBR wk12	p-value
Whole cohort	TBR_{mean}	1.50±0.3	1.41±0.2	0.069
(n=16)	TBR_{max}	1.84±0.4	1.73±0.3	0.081
Responders	TBR_{mean}	1.50±0.2	1.39±0.2	0.022
(n=8)	TBR_{max}	1.87±0.4	1.74±0.4	0.032
Non-responders	TBR_{mean}	1.49±0.3	1.42±0.2	0.460
(n=8)	TBR_{max}	1.81±0.5	1.73±0.3	0.462

Values are mean ± SD
TBR indicates target-to-background ratio, max: maximum

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DISCUSSION

The present study showed a trend towards decreased arterial wall inflammation in pSpA patients upon 12-week treatment with secukinumab. In a post-hoc analysis, pSpA patients with a good clinical response showed a significant decline in TBR following secukinumab treatment, whereas in non-responders no change upon secukinumab treatment was observed.

Patients with SpA, similar to patients with rheumatoid arthritis[2], are characterized by an increased arterial wall inflammation compared with healthy controls[3], which is a predictor for adverse CV outcome[4]. Treatment with anti-inflammatory therapies such as TNF-a inhibitors and methotrexate in patients with SpA and rheumatoid arthritis has been shown to reduce CV risk[13]. Treatment with TNF-a inhibitors also displayed a reduction of disease activity and arterial wall inflammation in patients with PsA[14] as well as rheumatoid arthritis patients[15], supporting a common pathophysiological mechanism for the increased arterial wall inflammation and increased CV risk. In SpA patients, the IL-17A axis has proven to be instrumental in the pathogenesis of articular disease[7], however the potential effect of IL-17A inhibition on atherosclerosis remains equivocal as conflicting data exists on IL-17A mediated changes in the arterial wall. On one hand, IL-17A has been shown to support the production of pro-inflammatory

mediators, aggravating inflammatory activity in the arterial wall[9]. On the other hand, IL-17A may enhance plaque stability by promoting collagen production[9]. Moreover, IL-17A inhibits VCAM-1 expression on endothelial cells, reducing adhesion of immune cells to the endothelial layer[9]. The present study supports an overall atheroprotective effect of IL-17A inhibition: we report a trend towards decrease of arterial wall inflammation upon secukinumab treatment, especially in pSpA patients with a good clinical response. Our data are consistent with the positive effect of TNF-a inhibitors on arterial wall inflammation[14].

There are several limitations to the present study. First, a sample size of 16 patients has been proven to be of sufficient size to answer our main research question. However, the small sample size does limit the possibilities for the post-hoc analysis within this cohort. Therefore, we only assessed the TBR difference within the responder and non-responder groups and not between the two groups. Second, this pilot study is an open-label study, precluding a direct comparison with non-treated controls. Lastly, this pilot study covers only 12 weeks, which is not long enough to assess the potential relationship between the effect of secukinumab on arterial wall inflammation and CV events. However, since the effect on arterial wall inflammation is the primary outcome of this study, 3 months treatment should be sufficient to show effect on arterial wall inflammation, as treatment with TNF-a inhibitors for only 8 weeks was adequate to display reduction of arterial wall inflammation in patients with rheumatoid arthritis[15].

In conclusion, this pilot study in pSpA patients showed that treatment with secukinumab resulted in a trend towards decrease of arterial wall inflammation, mainly in patients a good clinical response to secukinumab. Larger, controlled trials are needed to confirm these findings and to assess the relationship with CV events.

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General Discussion and Summary

The therapeutic options for psoriatic arthritis vastly increased in recent years and resulted in improvements in outcome and quality of life. However, not only the availability of novel therapeutic options but also better understanding of when and how to use these treatments is important to improve disease outcome. This requires detailed understanding of remaining unmet needs in clinical practice combined with information from RCTs and strategy trials to assess how to implement treatments and address unmet needs. Therefore, the aim of this thesis was to investigate how we can address these issues to achieve clinical remission in PsA. In this final chapter we will summarize each chapter's main findings, discuss implications, and share our vision of research challenges in the field for the coming years.

New treatment options in PsA

In **Chapter 2** we describe how the growing therapeutic armentarium opened up new perspectives for PsA patients not responding or only partially responding to conventional DMARDs and/or TNFi. In short, new therapies that were approved in recent years include two anti-IL-17A[1,2], an anti-IL-12/IL-23 p40 subunit[3], CTLA-4 immunoglobulin[4], a phosphodiesterase inhibitor[5] and a JAK inhibitor[6]. Furthermore several agents are under development in phase III trials: a JAK inhibitor, anti-IL-23 p19 subunit[7], and an anti-IL-17A+anti-IL-17F[8]. The key question now arising is how to implement these treatments in clinical practice with an optimal benefit/risk balance and outcome for patients. To accomplish this there are several important questions to consider, including 1) timing and sequence of treatment as to date only limited amount of studies compare treatments directly or study optimal timing of intervention, and 2) treatment strategies as not only the treatment as such but also the treatment strategy itself is crucial to reach the full potential of treatment.

The importance of a good treatment strategy can be learned from the successful implementation of several treatment strategy concepts in RA. First, the earlier the start of treatment the higher the chances to reach remission.[9–11] The implementation of early arthritis clinics decreased the time from symptom to intervention vastly in recent years.[12] Studies exploring this concept in axial SpA and peripheral SpA show markedly higher remission rates in early disease, suggesting the same concept holds true in related SpA subtypes.[13,14] Second, the achievement of a low disease activity state (low disease activity and/or remission) in early disease showed to improve short and long term clinical outcomes and to prevent structural damage and disability. Therefore treatment guidelines for RA recommend to aim for remission.[15] Third, the implementation of tight control of disease activity, with regular monitoring of disease activity and subsequent treatment adjustment when the desired goal is not met (treat to target; T2T), has been

shown superior in improvement on disease activity, functioning and radiographic outcomes in comparison with usual care.[16–19] This concept was tested in PsA in the TICOPA study where superior clinical response was seen in the T2T arm of the study although with a higher rate of (non-severe) adverse events. In this study no impact on radiographic progression was seen, although overall radiographic progression was low. Future strategy studies in PsA should focus on these treatment strategies as we have learned from RA how much value they can add.

PART I: HOW CLINICAL PRACTICE DEFINES RESIDUAL DISEASE.

Although validation studies for MDA[20,21] and the TICOPA trial demonstrated that MDA is an achievable goal in PsA,[22] the few studies on disease activity in clinical practice of PsA indicate that only 20-40% of patients are in a minimal disease state despite treatment.[23,24] It is unknown which factors result in the sustainment of disease activity and if this disease activity is present due to lack of treatment options or other factors i.e. what clinical unmet needs remain.

Chapter 3 explored residual disease activity and unmet needs in clinical practice. We studied the relation of disease activity and subsequent treatment decisions made by the rheumatologist. This cross-sectional cohort recorded treatment use and disease activity in 142 consecutive patients visiting the outpatient clinic. We found that residual disease activity was present in almost two thirds of the patients. However, residual disease activity triggered treatment adjustment in only a quarter. The absence of treatment modification/intensification was not driven by the lack of therapeutic options or contraindications in a vast majority of patients. It suggests that rather subjective opinions of the rheumatologist and/or the patient drove the decision not to adjust treatment despite residual disease activity. Several factors could be driving this practice: 1) high costs of treatments, 2) lack of structural disease assessment in clinical practice, 3) poor implementation of guidelines, and 4) limited evidence to support the benefit of aggressive treatment in PsA. For future development and implementation of treatment strategies it is key to better understand why residual disease activity does not consequently lead to treatment adjustment in clinical practice and how to overcome these factors.

One of the big learnings of the RA field over the last decade is that objective measurement of disease activity – rather than subjective evaluation by the physician - contributes to the achievement of remission.[19] In contrast, measures such as DAS or MDA are not frequently used in PsA clinical practice. Coates et al showed that

PsA specific measurements were obtained in less than 50% of visits in an outpatient clinic[25]. The current driver of treatment decisions in PsA clinical practice is thus still the rheumatologist's opinion on disease activity. However, it remains unclear what the practicing rheumatologist considers an acceptable disease state and how this relates to a treatment target such as MDA. Therefore, the aim of **Chapter 4** was to answer the question: what is an acceptable disease state according to the treating rheumatologist when compared to MDA criteria. We conducted an observational cross-sectional cohort study of 250 patients all considered to have an acceptable disease state by their treating rheumatologist and assessed MDA and several patient reported outcomes. One third of these patients did not fulfill MDA criteria with disease activity shown across all MDA disease domains. Disease activity was present in all treatment categories, also in those on a csDMARD only, indicating that these patients were not only those without additional treatment options. Those not fulfilling MDA (1/3) would have been considered for escalation of therapy if following a treat to target approach, highlighting the discordance between a target steered approach and current clinical practice. This disconnect impacts patients as worse scores on all patient reported outcomes are seen in those not fulfilling MDA.

Collectively, the studies presented in **Chapter 3 and 4** indicate clearly that many PsA patients still display active disease with subjective and objective signs of inflammation and a clear impact on QoL measurements, despite the availability of additional treatment options.

These observations raise a number of questions. First, can these observations obtained in the Dutch health care system be generalized? Michelsen et al [26] show similar disease activity rates in a Norway-based real-life practice. Dutch clinical practice includes routine use of DAS28 and the Dutch healthcare system provides access to biological treatments for everyone when prescribed by a rheumatologist. Therefore, our findings are probably generalizable to countries with similar standards of care, and are most likely optimistic compared to countries with more restricted accede to the health care systems. Second, is there evidence that persistent mild-to-moderate disease activity leads to worse long-term outcome in PsA? Data from cohort studies suggest a link between persistent clinical disease activity and increased clinically damaged joint counts and radiographic progression.[27,28] RCTs with TNFi show a correlation between reduction of disease activity and reductions in radiographic damage.[29,30] Third, is there evidence that delay of initiation of targeted interventions leads to poorer responses over time in PsA? Although not as thoroughly studied and supported by evidence as in RA, several studies report worse outcomes in those patients with a long symptom duration at start of treatment compared to those treated earlier in the disease course.[24,31] In conclusion,

our observations need of course to be interpreted in the context of the specific study set-up but overall support the concept that earlier and more aggressive disease control remains an unmet need in PsA clinical practice.

Consensus on a treatment target

As discussed above, one potential reason for sub-optimal disease control in PsA is the lack of systematic disease monitoring with a well validated instrument. Since 2015 treatment guidelines recommend to aim for remission or the lowest possible disease activity. However, these guidelines do not define the specific target (remission, minimal disease activity, low disease activity) and do not specify how to measure it. **Chapter 5** therefore focused on the comparison of several composite scores proposed as target for remission and low disease activity(LDA) in PsA within the dataset from **Chapter 4**. We investigated which patients fulfill these criteria, the overlap between the different measures, and the presence of residual disease in the various domains in the different composite scores. We show that these different measures targeting the same conceptual definition (remission or low disease activity) result in different levels of residual disease. It is important to know which cut-off represents a disease activity with optimal outcome. Indeed, it can be questioned if the strictest targets always results in a better outcome, as they may require more intensive treatments that can be associated with increased side effects and/or costs. A study in RA, however, shows a relevant benefit of remission over LDA regarding physical functioning, quality of life, work capacity and costs.[32] Large longitudinal studies in PsA comparing LDA and remission as a target incorporating consequences on costs, side effects, and short and long term clinical outcomes are needed.

Part II: A strategy trial: early intensive treatment in PsA

In **Chapter 6**, we studied the effect of early intensive treatment in PsA. This double-blind placebo-controlled randomized study was initiated to investigate whether the combination of a TNF inhibitor(TNFi) plus methotrexate (MTX) as a first line treatment is superior in treatment with methotrexate alone in terms of reaching remission. We included 51 patients with early PsA who were naïve for MTX and TNFi and randomized them to treatment with either TNFi + MTX or MTX alone for a total of 22 weeks. The major finding of this study was that the combination therapy in this early PsA population doubled the number of patients achieving a DAS remission up to a rate of 81%. This was confirmed by additional outcome and disease activity measures and was well tolerated in terms of safety and adverse event rates. Our results extend the findings of the open label RESPOND study that early targeted intervention in PsA contributes to achieve remission in PsA. Response rates in several outcome measures are high when compared

with TNFi studies with PsA patients with longer standing disease, but this study was obviously not set-up to directly compare early versus late TNFi initiation. Several points for discussion remain. First, we did not investigate if the absence of clinical disease activity as measured by joint counts, inflammatory markers and patient reported outcomes really reflect a full resolution of inflammation, which could be assessed by ultrasound or MRI studies in the future. Second, the size of this study population made it difficult to analyze different subsets of disease domains, which would have required a much larger study population. Third, the success of the early intervention suggests a 'window of opportunity' where the early state of treatment result in a better outcome or even resolution of disease. Whether this successful combination of TNFi and MTX is only needed for the induction of remission or is also needed to maintain this state of remission over time was questioned in the follow up of this study. The TNFi was discontinued at week 22 in those patients achieving DAS CRP remission. Almost half of the TNFi treated patients retain remission up to week 50. These rates are comparable with a recently published study in early peripheral SpA where more than 50% maintain remission after TNFi withdrawal.[33] It is a higher success rate compared with previously reported high rebound rates in stop studies with longer standing PsA (around 30%).[34,35]

Part III: immunological and systemic effects of IL-17A blockade

When this thesis project started, the only available biological therapies for PsA were those inhibiting TNF. In recent years several new treatment options emerged. Among others, several target the IL-23/IL-17 axis including IL-17A inhibitors and IL-12/IL-23 p40 inhibitors. The first IL-17A blocking agent approved by FDA was secukinumab. Secukinumab demonstrated good clinical efficacy in PsA in several clinical domains (arthritis, enthesitis, dactylitis, skin and quality of life) in two phase III trials, and showed to inhibit structural progression both in TNFi naïve and TNFi non responder patients.[36,37] Soon after, ixekizumab became available with similar clinical and radiographic outcomes.[2,38] Interestingly, several studies showed superior clinical efficacy of these IL-23/IL-17 inhibitors over TNFi in skin psoriasis. A study with ixekizumab and etanercept (one of the TNFi) in psoriasis showed clinical superiority of IL-17A inhibition over TNFi, and secukinumab showed superior efficacy to ustekinumab in psoriasis.[39,40] Additionally, mechanism of action studies in psoriasis show a unique impact of IL-17A blockade on histological and molecular features of the psoriatic skin.[41]

To investigate if anti-IL-17A also has a deeper immunomodulatory effect than TNFi in peripheral SpA, we set up the mechanism of action study described in **Chapter 7.** We were the first to assess the effects of treatment with secukinumab, a monoclonal IL-17A antibody, on the immunopathology of the key target tissue in peripheral SpA, the

synovial membrane. We show that the blockade of IL-17A with secukinumab resulted in a profound clinical and immunopathological impact on pSpA with a decrease of the inflammatory infiltrate and downregulation of biomarkers known to be associated with successful therapy responses in earlier studies. Of interest, a decrease of IL-17A was observed on the mRNA level, suggesting that secukinumab treatment does not only block IL-17A protein but also target the cells producing IL-17A in the inflamed synovium.

However, the identity of the cellular source of IL-17A in SpA synovitis[42] and the impact of secukinumab on these cells remains to be defined. Neutrophils are nominated as possible candidates as their rapid turnover and high correlation between the numbers of neutrophils and IL-17A mRNA, although the capacity of neutrophils to produce IL-17A remains a subject of controversy.[43] Alternatively, neutrophils may attract other cells and/or drive IL-17A production by other cells in the inflamed synovial tissue.[44] Several cellular sources have been named in literature and the major cellular source of IL-17A remains a question to address in further studies.[45,46]

Another interesting finding was the lack of impact of IL-17A inhibition on TNF alpha mRNA expression and the absence of normalization of the synovial tissue after 12 weeks of treatment. This suggests that either longer treatment is necessary for complete normalization of the tissue on histologic and molecular levels, or that other pathways – potentially including TNF – are not affected by anti-IL-17A and thereby still operative in the diseased target tissues. These observations suggest that dual blockade of IL-17A and other relevant pathways may potentially result in greater efficacy in PsA. With the goal of dual blockade, Mease et al studied a dual antibody neutralizing TNF and IL-17A in psoriatic arthritis. This 12 weeks phase II study shows a similar safety and efficacy profile as adalimumab with a trend towards higher responses on PASI75, ACR50 and ACR70.[47] Nevertheless, this drug will not be developed further. Preclinical experiments showed that dual inhibition of IL-17A and IL-17F is highly effective in the suppression of in vitro cytokine response and neutrophil chemotaxis inhibition. A proof of concept trial shows rapid and profound effects of bimekizumab (a dual IL-17A and IL-17F inhibitor) on joint and skin in psoriatic arthritis patients.[48]

Currently our group is working on detailed molecular analysis of extracted RNA from synovial biopsies obtained pre- and post-treatment with secukinumab, adalimumab, and ustekinumab. Detailed RNA sequencing analysis of these synovial biopsies may provide more insights in the hierarchy and taxonomy of molecular pathways driving the synovial immunopathology in SpA.

Systemic effects

PsA is not limited to inflammation of joints and skin but also results in increased systemic inflammation. This systemic inflammation is linked to the higher prevalence of 'systemic' comorbid conditions in PsA and psoriasis patients, including impaired host defense, loss of bone density[50], increase in cardiovascular risk[51], associated diseases such as hypertension and diabetes, and increased prevalence of depression and anxiety.[52] Over half of PsA patients have two or more comorbidities with a significant impact on quality of life.[53–55] The link between these comorbidities and psoriatic disease is thought to be multifactorial with impact through shared genetic and environmental factors and inflammatory pathways. For the positioning of a new therapy in the expanding armentarium of treatment options not only clinical efficacy but insights in systemic effects and effects on comorbidities are of importance.

The impact of treatment on the different non-articular manifestations of PsA has been quite well studied for TNFi, showing a positive impact of TNFi on bone metabolism[56], cardiovascular risk[57] and even serotonin availability, which could be linked to decreased risk of depression.[58] However, data with other targeted treatments such as IL-17A blockade only start to emerge. To understand in more detail the overall impact of IL-17A blockade in PsA, in **Chapter 7** we additionally assessed whether the immunomodulating effects of IL-17A blockade did lead to global immune suppression. We assessed this by 1) systemic inflammatory markers in the serum, and 2) immune responses in the Truculture system. In the TruCulture system whole blood cells are activated by chosen stimuli, mimicking the presence of a (bacterial/fungal) infection ex vivo. We observed a significant decrease in serum CRP and levels of cytokines, MMP-3 and IL-17-A in the TruCulture system. These findings are in line with the clinical response and the synovial tissue expression data. However, no impact was observed on the capacity of peripheral blood cells to produce cytokines measured after stimulation, indicating that although anti IL-17A results in specific immunomodulation in the synovium, there is no global immune suppression. The IL-23/IL-17 axis is seen as a critical player in host defense against fungal, mycobacterial and bacterial infections.[59] However, clinical studies do not show evidence for increased risks on mycobacterial infection or severe bacterial infections.[60] Although vaccination studies with BCG a mycobacterium (bacilli Calmette-Guérin) show increased IL-17A responses, cytokine expression profiles did not correlate with protection.[61] IL-17A is important in the defense against fungal infections, as seen in both reports on patients with immune deficiencies involving IL-17A[62] and the safety reports of large phase III trials with secukinumab with fungal infection rates around 1% in patients treated with anti-IL-17A.[36,40] These infections were mild oropharyngeal and

vulvovaginal candida infections that were easily treated and did not need interruption of treatment. No cases of severe invasive candidiasis are reported in anti-IL-17A treated patients.

Another systemic impact of PsA is the increase in cardiovascular disease risk.[63,64] Patients with AS and PsA were found to have increased arterial wall inflammation when assessed by a 18-Fluorodeoxyglucose positron emission tomography with computed tomography (18F-FDG PET/CT), which is a predictor of adverse cardiovascular outcome. The effect of anti-IL-17A blocking treatment on arterial wall inflammation, and thereby cardiovascular risk, was not assessed previously. The role of IL-17A remains controversial with data supporting pro- and anti-atherogenic effects in experimental models. A reported pro-atherogenic effect of IL-17A is the positive impact on the production of pro-inflammatory mediators, aggravating inflammatory activity in the arterial wall. On the other hand, it is suggested that IL-17A enhances plaque stability by promoting collagen production and it results in an inhibition of VCAM-1 expression on endothelial cells, reducing adhesion of immune cells to the endothelial layer.[65] To evaluate the effect on arterial wall inflammation the cohort of patients of **Chapter 7** underwent a 18FDG-PET/CT before and after treatment. In **Chapter 8** we show that treatment results in a trend towards decrease of arterial wall inflammation, mainly in patients with a good clinical response to secukinumab. Larger, controlled trials are needed to confirm these findings and to assess the relationship with CV events.

9

Concluding remarks and future directions

Over the past years progress has been made in the development of treatment targets, the first strategy trial was conducted, and multiple novel therapeutics became available.

However, the three parts of this thesis also reveal questions worthy to address in future trials. The work done in part I of this thesis project highlights the current discrepancies between clinical practice and the target driven assessments recommended by treatment guidelines. The treat to target principle has not been implemented in clinical practice yet. Full understanding on the factors and/or unmet needs contributing to this is needed to take in account when new therapeutic and treatments strategies are implemented. A strategy trial assessing the benefits and costs of several levels of disease activity in a treat to target setting has to demonstrate how high we should raise the 'bar' with the lowest amount of consequences on safety and costs.

Part II of this thesis shows that the concept of early intervention is highly effective in PsA and supports the idea of a so called 'window of opportunity'. Additional questions to assess in future studies are 1) whether the same holds true for treatments with other

mechanism of action, 2) what the optimal steps are in the sequence of therapy, and 3) if this concepts benefits the prevention of structural damage. Clinical trials assessing different orders of treatments with different therapeutics in a head-to-head manner are important in answering these questions that are highly relevant for day to day practice.

Part III focused on the immunological and systemic effects of one of the new treatments, IL-17A blockade, that became available in recent years. Currently, the clinical outcomes on joints do not indicate a clear preference for TNFi or IL-17i, either on the overall population or in specific sub-populations. The choice between these treatments is still often based on personal experience or non-medical factors such as access or cost. A better understanding of how these and other emerging treatments impact PsA beyond the joints (skin, co-morbidities, …) may help to better personalize the treatment of PsA patients in the future.

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APPENDICES

NEDERLANDSE SAMENVATTING

Introductie

Artritis psoriatica (afgekort PsA) is een chronische ontstekingsziekte die ongeveer bij 1-2 per 1000 mensen voorkomt en gaat meestal samen met de huidziekte psoriasis. Het valt onder de overkoepelende ziektegroep spondyloarthritis (SpA), waarvan een deel met name door ontstekingen in de rug wordt gekarakteriseerd (axiale SpA en de klassieke 'ziekte van Bechterew') en het ander deel van het spectrum vooral door perifere gewrichts- en peesontstekingen wordt gekenmerkt (perifere SpA). PsA heeft een divers klinisch voorkomen: patiënten kunnen zich presenteren met ontstekingen van gewrichten (artritis), aanhechtingen van pees aan bot (enthesitis), ontsteking van een hele vinger of teen (dactylitis), van de huid en/of nagels (psoriasis) en van de wervelkolom (spondylitis) en/of het bekken (sacro-iliitis). Patiënten hebben hierdoor klachten van pijn, zwelling, stijfheid en/of bewegingsbeperking in gewrichten en/of de rug. In een deel van de patiënten zorgt de ontsteking voor gewrichtsschade (erosies of nieuwe bot aanmaak), en daarnaast heeft 80% van de patiënten huid psoriasis met roodheid, jeuk en zichtbare rode verheven plekken op de huid. De impact van PsA op het dagelijks leven van patiënten is aanzienlijk en doet niet onder voor andere gewrichtsontstekingsziektes zoals het meer bekende reumatoïde artritis. Bovendien hebben PsA patiënten ook vaker hart- en vaatziekten, depressies, obesitas en suikerziekte.

De klinische diagnose PsA is gebaseerd op het oordeel van de reumatoloog en niet op basis van specifieke regels of criteria. Voor de wetenschappelijke doeleinden zijn de CASPAR criteria ontwikkeld. Deze criteria maken het mogelijk om voor onderzoek een meer homogene patiëntengroep te verzamelen.

Het meten van de activiteit van de ziekte is een uitdaging voor de reumatoloog. Richtlijnen raden aan alle belangrijke ziekteverschijnselen te vervolgen, wat betekent dat zowel naar huid, gewrichten, peesaanhechtingen etc. gekeken moet worden. Hiervoor zijn diverse meetmethoden ontwikkeld (ziekteactiviteit maten). Ook zijn er scores ontwikkeld die een afwezigheid of lage hoeveelheid ziekteactiviteit kunnen vastleggen (zoals remissie of minimale ziekteactiviteit (minimal disease activity, MDA). Hiermee kan de reactie op een behandeling worden vervolgd en zo worden gestreefd naar een zo laag mogelijke aanwezigheid van de ziekte.

Tien jaar geleden waren de behandelopties voor PsA beperkt. Patiënten beginnen vaak met een zogeheten conventionele DMARD (disease modifying antireumatic drug) zoals methotrexaat, leflunomide of sulfasalazine, dit ondanks het feit dat het

wetenschappelijke bewijs voor sommige van deze middelen niet heel groot of zelfs bediscussieerbaar is. Als de patiënt niet op een of meerdere van deze middelen reageert, is de volgende stap een TNF blokker, wat een bewezen effectief middel is. Ondanks de aangetoonde effectiviteit waren er aanzienlijke aantallen patiënten die maar een beetje, tijdelijk of zelfs niet reageerden. De enige optie was dan te switchen naar een ander TNF blokkerend medicijn. Dit is nu veranderd.

De laatste jaren zijn er voor PsA veel nieuwe geneesmiddelen beschikbaar gekomen, waarmee voor meer patiënten verbetering kan worden bereikt in ziekteactiviteit en hun kwaliteit van leven. Ook de manier waaróp de middelen worden ingezet is belangrijk voor het verbeteren van de zorg en daarmee de uitkomsten voor patiënten. Om deze middelen optimaal in te zetten is het van belang inzicht te krijgen in de huidige praktijkvoering en actuele valkuilen/moeilijkheden en daarnaast onderzoek te doen naar strategieën hoe de verschillende medicijnen zo optimaal mogelijk ingezet kunnen worden.

Het doel van het proefschrift

Dit proefschrift heeft als doel om te onderzoeken hoe we het beste klinische remissie kunnen bereiken bij patiënten met artritis psoriatica. In **Hoofdstuk 1** wordt een algemene inleiding gegeven over het ziektebeeld.

Het proefschrift begint met een review artikel in **Hoofdstuk 2** waarin nieuwe behandelingen en behandelstrategieën in PsA en het nauw verwante ziektebeeld SpA worden beschouwd. Diverse behandelingen met verschillende aangrijpingspunten/ werkingsmechanismes werden beschikbaar. Hoe deze middelen optimaal in te zetten in de kliniek moet bepaald worden aan de hand van onderzoek naar een aantal punten: 1) de beste timing om het middel in te zetten (juist vroeg of pas nadat andere middelen niet blijken te werken), 2) de volgorde: nadat patiënt op dit middel niet reageert, wat kan er dan het beste volgen, 3) het inzetten van een behandeldoel en een strategie om deze te bereiken (Treat to Target). In PsA bleken er maar weinig studies te zijn die hebben geprobeerd om dit soort vragen te beantwoorden.

Deel 1: Hoe wordt omgegaan met ziekteactiviteit in de kliniek

In **Hoofdstuk 3** kijken we naar behandelbeslissingen die de reumatoloog in de dagelijkse klinische praktijk neemt aan de hand van gemeten ziekteactiviteit.

Het blijkt dat meer dan 2/3 van de patiënten in de dagelijkse reumatologie kliniek nog enige (of vrij veel) ziekteactiviteit heeft. Opmerkelijk was dat deze ziekteactiviteit ook voorkwam in de groep patiënten waar nog volop onbenutte behandelmogelijkheden

waren, maar de reumatoloog ervoor koos om deze (nog) niet in te zetten. De precieze redenen achter deze behandelbeslissingen zijn moeilijk uit deze studie te achterhalen. Desalniettemin is het wel belangrijk om inzicht te verkrijgen in deze factoren zodat deze factoren in de overwegingen meegenomen kunnen worden bij het implementeren van behandelstrategieën.

In **Hoofdstuk 4** kijken we naar hoe de huidige standaard in het meten en opvolgen van ziekteactiviteit, namelijk het klinische oordeel van de reumatoloog, zich verhoudt tot een objectieve maat die ontwikkeld is voor het meten van ziekteactiviteit in onderzoeken, maar die nog niet is doorgedrongen in de dagelijkse praktijk.

We vroegen reumatologen om patiënten te verwijzen waarin ze de behandeling niet wijzigden, omdat de ziekte naar hun oordeel goed onder controle was. In deze groep patiënten keken we naar de ziekteactiviteit gemeten door middel van de MDA criteria (een specifieke maat voor ziekteactiviteit in PsA) en zagen we dat bij 1/3 van deze patiënten toch nog actieve ziekte was. Deze patiënten konden niet als in een lage ziekteactiviteit worden beschouwd. De ziekteactiviteit in deze patiënten was soms aanzienlijk en resulteerde in een beperking in het dagelijks functioneren en slechtere kwaliteit van leven. Als het treat to target principe zou worden toegepast in deze groep patiënten zou 1/3 in aanmerking komen voor een andere behandeling, wat aangeeft dat er een aanzienlijk verschil is tussen de huidige werkwijze in de dagelijkse praktijk en een eventuele treat to target strategie.

Hoofdstuk 5 analyseert en bediscussieert verschillende maten die ontworpen zijn om de ziekteactiviteit van PsA te meten. Er zijn meerdere maten waarmee ziekteactiviteit kan worden gemeten en die een afkapwaarde hebben voor remissie en/of lage ziekteactiviteit (low disease activity, LDA). Onze vergelijking van deze maten liet zien dat deze maten zeer verschillende niveaus van ziekteactiviteit aangeven, hoewel ze deze wel benoemen als remissie of LDA. Hoe laag of hoog de lat ligt is relevant, aangezien we streven naar een zo laag mogelijk ziekteactiviteit met het idee dat dat beschermt tegen het ontwikkelen van schade aan gewrichten en zorgt voor een zo goed mogelijke levenskwaliteit. Daartegenover staat het gevaar dat een zeer ambitieus doel kan leiden tot overbehandeling en daarmee meer bijwerkingen en hogere kosten.

Deel 2: Onderzoek naar een behandelstrategie; vroege intensieve behandeling

Wat we in het eerste hoofdstuk van het proefschrift al beschreven, is dat onderzoek naar behandelstrategieën van groot belang is. Antwoorden op vragen als a) wanneer moeten we welk middel inzetten? b) hoe moeten we de respons op een behandeling

meten? c) wanneer dan te switchen naar wat anders als een patiënt niet reageert op een medicijn? zijn belangrijk voor het goed inzetten van nieuwe geneesmiddelen in de klinische praktijk. **Hoofdstuk 6** kijkt naar zo een strategie: we vergelijken daar namelijk de huidige standaard behandeling methotrexaat met het vroeg opstarten van een TNF blokker samen met methotrexaat. TNF blokkers zijn bewezen effectief voor de behandeling van PsA, maar ook duur. Momenteel worden TNF blokkers vaak later in de behandeling ingezet, als blijkt dat conventionele middelen zoals methotrexaat niet voldoende werken. In deze studie komen we tot de conclusie dat wanneer een TNF blokker vroeg wordt ingezet er een veel hoger aantal patiënten in remissie komt dan bij de standaard behandeling. De patiënten in de studie die goed reageerden op de combinatie TNF blokker + methotrexaat zijn daarna nog vervolgd om te kijken of deze goede reactie op de behandeling ook aanhield, en dat was het geval bij ongeveer 50% van hen.

Deel 3: Immunologische en systemische effecten van behandeling met IL-17A blokkers

Zoals eerder besproken, zijn er de laatste jaren veel nieuwe geneesmiddelen voor de behandeling van PsA beschikbaar gekomen, waaronder medicijnen die interleukine-17A (IL-17A) blokkeren. Van IL-17A, een ontstekingseiwit, is inmiddels duidelijk dat het een belangrijke rol speelt in het ontstaan van psoriasis en de ziekteverschijnselen van SpA. Diverse grote studies hebben reeds aangetoond dat IL-17A blokkers heel effectieve geneesmiddelen zijn voor de behandeling van PsA en psoriasis. Onderzoek naar de moleculaire en cellulaire effecten in de psoriasis-laesies lieten een unieke impact zien. In **Hoofdstuk 7** hebben we, als eerste ter wereld, gekeken naar de klinische en immunologische effecten van IL-17A blokkade op het synovium (de ontstoken binnenbekleding van het gewricht in geval van artritis) bij patiënten met PsA en perifere SpA. Er wordt een aanzienlijke klinisch effect en immunologische impact gezien van het middel op het synovium), met een vermindering van de lokaal aanwezige immuuncellen en verlaging van stofjes in het bloed die correleerden met goede ziekteregulatie in eerdere studies. Een aantal bevindingen zijn interessant voor discussie. Ten eerste zagen we een daling van IL-17A RNA niveau, wat suggereert dat niet alleen het stofje zelf wordt geblokkeerd maar ook de cellen die het maken niet meer aanwezig zijn in het synovium na behandeling. Het lastige is dat we in deze setting niet goed kunnen zien welke cellen dat zijn, en ook is de wetenschap er nog niet uit welke cellen eigenlijk de hoofdrolspelers zijn bij het maken van IL-17A in SpA. Het tweede punt is dat IL-17A significant daalde, maar dat het niveau van TNF, een ander belangrijk

ontstekingseiwit, gelijk bleef. Ook zagen we dat na 12 weken behandeling de weefsels niet helemaal normaliseerden. Dit suggereert dat ofwel langere behandeling nodig is, of dat er andere belangrijke factoren voor ontsteking (zoals TNF) nog werkzaam zijn.

Een belangrijke tweede vraag in **Hoofdstuk 7** was of de lokale immuun suppressie, die ervoor zorgt dat de ontsteking in het gewrichtsweefsel verminderd, parallel verloopt met een verminderde afweer (immuun suppressie) in bredere zin. Met een systeem dat een infectie na kan bootsen buiten het lichaam (Truculture systeem) hebben we gekeken of behandeling met een IL-17A blokker ook effect heeft op de immuunreactie in het perifere bloed Er werden geen significante veranderingen gezien. Dit ondersteunt de bevindingen in grote studies waarin, behalve een iets hoger percentage schimmelinfecties, geen grote gezondheidsrisico's van de behandeling met IL-17A blokkade werden waargenomen.

In **Hoofdstuk 8** hebben we gekeken naar het effect van IL-17A blokkade op vaatwandinflammatie. Vaatwandinflammatie is een belangrijke factor in hart- en vaatziekten, welke vaker voorkomen in patiënten met PsA. Het effect van IL-17A op vaatwandinflammatie is niet volledig duidelijk in de literatuur. Basaal onderzoek toont dat de invloed van IL-17A op de vaatwand heel divers is en zowel pro- als anti-inflammatoir kan werken. Een methode om de effecten van behandeling op vaatwandinflammatie te onderzoeken is een PET-CT scan met gelabeld glucose. Deze scans, gemaakt in dezelfde groep patiënten als in **Hoofdstuk 7,** tonen een vermindering in de vaatwand inflammatie aan, vooral in dié patiënten die een goede reactie op de behandeling hadden.

Hoofdstuk 9 geeft een samenvatting van de hierboven genoemde hoofdstukken. Samenvattend hebben we met het onderzoek wat beschreven wordt in dit proefschrift proberen bij te dragen aan het optimaliseren van de behandelkansen van patiënten met artritis psoriatica. Onderzoek naar de verschillende facetten die we hebben onderzocht en hierboven beschreven zullen in de toekomst meer duidelijkheid bieden over de mechanismen achter de ziekte en behandelingen zodat er nog betere gerichte behandeling gegeven kan worden.

PHD PORTFOLIO

L.J.J. van Mens
Supervisors: Prof. D.L. Baeten, dr A.W.R. van Kuijk
PhD period: 2013-2017

PhD training: General Courses

The Academic Medical Center World of Science	2013	0.7 ECTS
Good Clinical Practice (GCP)	2013	0.1 ECTS
Basiscursus Regelgeving Klinisch Onderzoek	2013	1.0 ECTS
Practical Biostatistics	2013	1.1 ECTS
Educational Skills Training	2013	0.4 ECTS
Crash course: 'Chemistry, biochemistry and molecular biology for MD's (re)entering scientific research'	2013	0.8 ECTS
Clinical Data Management	2014	0.4 ECTS
Oral presentation in English	2015	0.8 ECTS
Entrepreneurship in medical health	2015	1.5 ECTS
Clinical Epidemiology: Randomized Clinical Trials	2015	0.8 ECTS
Evidence Based Searching	2015	0.1 ECTS
Scientific writing in English	2015	1.5 ECTS
Career development	2015	0.8 ECTS
Citation analysis and impact factors	2015	0.1 ECTS
AMC PhD Strategy Business Course	2016	0.8 ECTS
Clinical Epidemiology: Evaluation of Medical Tests	2016	0.8 ECTS
Basiscursus Regelgeving Klinisch Onderzoek herregistratie	2017	0.8 ECTS
Clinical Epidemiology 2; Observational Epidemiology	2017	0.5 ECTS
LEAN course, business school Nijenrode	2017	0.3 ECTS

Specific Courses

2nd Translational School of Immunology (COST), Potsdam	2013	0.75 ECTS
Federation of Clinical Immunology Societies (FOCIS) advanced Course in Basic & Clinical Immunology, Scottsdale, USA	2014	1.0 ECTS
GRAPPA Psoriatic Arthritis Assessments	2013	0.35 ECTS
Rheumatologic injection techniques	2015	0.4 ECTS
Postgraduate Advanced Immunology , Amsterdam	2015	2.9 ECTS

Seminars and Lecturing

Weekly department research seminars AMC, Reade, ARC	2013-2018	14 ECTS
Weekly department clinical education AMC	2013-2018	9 ECTS
Psoriatic Arthritis preceptorship Novartis	2014	1 ECTS
Dutch Arthrtis Foundation work visit	2014	0.35 ECTS
College, workshops en werkgroepen keuzevak studie Geneeskunde	2014-2017	1.5 ECTS

Scientific presentations

Annual European Congress of Rheumatology, London, England, Poster presentation	2016	0.5 ECTS
International Congress of Spondyloarthritis, Ghent, Belgium, Poster presentation	2016	0.5 ECTS
European Workshop on Immune-mediated inflammatory Diseases (ewIMID), Toulouse, France	2016	0.5 ECTS
Group for Reseearch and Assessment of Psoriasis and Psoriatic Arhtritis Annual Meeting, Miami USA, Poster presentation	2016	0.5 ECTS
Annual European Congress of Rheumatology (EULAR), Madrid, Spain, 3x poster presentation	2017	1.5 ECTS
Scientific Meeting of the American College of Rheumatology, San Diego, USA, Oral presentation	2017	0.5 ECTS
Scientific Meeting of the American College of Rheumatology, San Diego, USA, 3x poster presentation	2017	1.5 ECTS
Conference 'gender en gezondheid' gender inequalities in PsA, Oral presentation	2017	0.7 ECTS
Group for Reseearch and Assessment of Psoriasis and soriatic Arhtritis, Annual Meeting, Amsterdam, the Netherlands, Poster presentation	2017	0.5 ECTS
GRAPPA/OMERACT concensus meeting, London, UK	2017	0.5 ECTS
Group for Reseearch and Assessment of Psoriasis and Psoriatic Arhtritis Annual Meeting, Toronto, Canada, Poster presentation	2018	0.5 ECTS
Scientific Meeting of the American College of Rheumatology Chicago, USA, Poster presentation	2018	0.5 ECTS

Conferences

Scientific meeting of the American College of Rheumatology (ACR) San Francisco	2015	1.0 ECTS
Scientific meeting of the American College of Rheumatology (ACR) Washington	2016	1.0 ECTS
Scientific meeting of the American College of Rheumatology (ACR) San Diego	2017	1.0 ECTS
Scientific meeting of the American College of Rheumatology (ACR) Chicago	2018	1.0 ECTS (
Annual European Rheumatology Conference (EULAR) Paris, France	2014	1.0 ECTS
Annual European Rheumatology Conference (EULAR) London, UK	2016	1.0 ECTS
Annual European Rheumatology Conference (EULAR) Madrid, Spain	2017	1.0 ECTS
ewIMID 2014, Funchal, Madeira	2014	0.8 ECT
ewIMID, 2015, Amsterdam (organizing committee member)	2015	0.8 ECTS
ewIMID 2016, Florence (scientific committee member)	2016	0.8 ECTS
ewIMID 2017 Utrecht (scientific committee member)	2017	0.8 ECTS
GRAPPA annual conference 2016, Miami	2016	0.8 ECTS
GRAPPA annual conference 2017, Amsterdam	2017	0.8 ECTS
GRAPPA annual conference 2018, Toronto	2018	0.8 ECTS
Internation Congress on Spondyloarthritis, Ghent, Belgium	2016	0.8 ECTS

Grants

ewIMID tranvel grant	2014
ewIMID travel grant	2016
GRAPPA annual meeting travel grant	2016
GRAPPA annual meeting travel grant	2017
GRAPPA annual meeting travel grant	2018

CURRICULUM VITAE

Leonieke Johanna Jolanda van Mens is op 14 september 1987 geboren in Naarden en opgegroeid in hilversum. In 2006 behaalde zij haar VWO diploma aan het Willem de Zwijger College te Bussum. Aansluitend is zij gestart met de studie geneeskunde aan de Vrije Universiteit te Amsterdam. In 2007 is zij naast het reguliere geneeskunde curriculum gestart met het aanvullende Honours programma. Tevens heeft zij naast haar geneeskunde studie meerdere geneeskunde gerelateerde bijbaantjes gehad (histologie/pathologie en biochemie practica-assistent en verpleeghulp) en is zij penningmeester geweest bij de co-raad van de VU. Na het behalen van haar artsexamen eind 2012, is zij begonnen aan een promotieonderzoek op de afdeling Klinische Immunologie en Reumatologie van het Academisch Medisch Centrum/ Universiteit van Amsterdam, onder supervisie van haar promotor prof. dr. D.L.P. Baeten en co-promotor dr. A.W.R. van Kuijk. Naast het verrichten van vooral klinisch onderzoek in het AMC en op Reade heeft zij ook laboratorium onderzoek gedaan en heeft zij alle onderzoeksjaren als arts in het artroscopie team gefungeerd. Hiernaast heeft zij deelgenomen in de scientific committee van het European Workshop on Immune Mediated Inflammatory Diseases (EWIMID), het onderwijs voor geneeskunde studenten in het keuzevak van de immunologie/reumatologie en meerdere werkgroepjes in het kader van de fusie van de reumatologie onderzoekscentra in amsterdam (het ARC). In januari 2018 is zij begonnen met de vooropleiding Interne Geneeskunde (opleider prof. S.E. Geerlings) als onderdeel van haar opleiding tot reumatoloog (opleider Dr. N. de Vries) aan het Academisch Medisch Centrum in Amsterdam.

LIST OF PUBLICATIONS

J de Winter, LJJ van Mens, D van de Heijde, R Landewe, D Baeten Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. (Arthritis Research & Therapy, 2016)

LJJ Van Mens,C Turina, MGH van de Sande, MT Nurmohamed, A van Kuijk, D. Baeten. Residual disease activity in psoriatic arthritis: discordance between rheumatologists opinion and minimal disease activity measurement. (Rheumatology 2017)

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LJJ van Mens, M van de Sande, D Baeten. New treatment paradigms in Spondyloarthritis. Current Opinion of Rheumatology. (Current opinion in Rheumatology 2017)

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LJJ van Mens, M.G. van de Sande, D.L. Baeten, response to letter to the editor, Rheumatology 2017

LJJ van Mens, M van de Sande, A van Kuijk, D Baeten, L Coates. The ideal target for psoriatic arthritis? comparison of remission and inactive disease states in a real life cohort. (Annals of the Rheumatic Diseases, 2018)

LJJ van Mens, H.M. de Jong, M van de Sande, T Latuhihin, I. Blijdorp, N Yeremenko, D Baeten. Effects of anti-IL17A blockade with secukinumab on systemic and local immune responses: a mechanism-of-action study in peripheral spondyloarthritis. (Arthritis &Rheumatology 2018)

A.B. Gottlieb, L. Coates, L.J.J. van Mens, A. W. Armstrong,, J. F. Merola. Report of the Skin Research Working Groups from the GRAPPA 2017 Annual Meeting, (The Journal of Rheumatology, 2018)

LJJ van Mens, M. van de Sande, D. Baeten, L.C. Coates, "The ideal target for psoriatic arthrits: response to eLetter Schoels et al" Annals of the Rheumatic Disease, 2018

I Blijdrop, S Menegatti, L van Mens, M van de Sande, S Chen, H Hreggvidsdottir, T Noordenbos, T Latuhihin, J Bernink, H Spits, L Rogge, D Baeten, N Yeremenko: Expansion of Interleukin-22– and Granulocyte–Macrophage Colony-Stimulating Factor–Expressing, but Not Interleukin-17A–Expressing, Group 3 Innate Lymphoid Cells in the Inflamed Joints of Patients With Spondyloarthritis (A&R 2018)

S. Chen, T Noordenbos, I Blijdorp, LJJ van Mens, C A Ambarus, E Vogels, A te Velde, M Alsina, J Canete, N Yeremenko, D Baeten, Histologic evidence that mast cells contribute to local tissue inflammation in peripheral spondyloarthritis by regulating interleukin-17A content, (Rheumatology, 2018)

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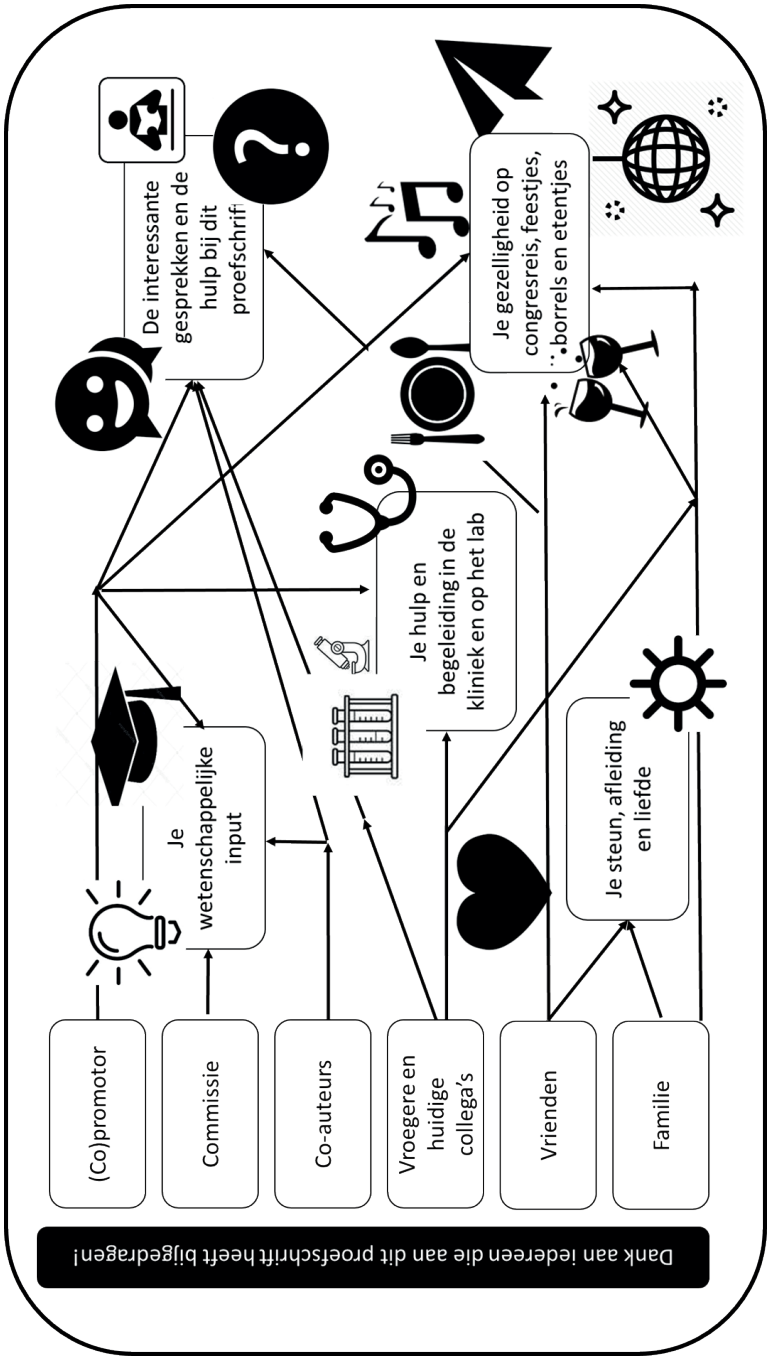
S. Verweij, LJJ van Mens, S Bernelot-Moens, D. Baeten, E. Stroes. Arterial wall inflammation is not affected by anti-IL17A treatment in patients with peripheral spondyloarthritis. (submitted)

Laura Coates, Laura Andreoli, Pavel V Ovseiko, Neelam Hassan, Uta Kiltz, Leonieke van Mens, Laure Gossec. Gender equity in clinical practice, research and training: Where do we stand in rheumatology? (submitted)

DANKWOORD


Dank aan iedereen die aan dit proefschrift heeft bijgedragen!
(Co)promotor
Commissie
Co-auteurs
Vroegere en huidige collega's
Vrienden
Familie
Je wetenschappelijke input
Je hulp en begeleiding in de kliniek en op het lab
Je steun, afleiding en liefde
De interessante gesprekken en de hulp bij dit proefschrift
Je gezelligheid op congresreis, feestjes, borrels en etentjes

Aangekomen bij het belangrijkste en misschien wel het spannendste hoofdstuk van het 'boekje' voor velen: het dankwoord. Alhoewel mijn poging een alternatief te vinden hiervoor ook in dit boekje is opgenomen (een figuur, lekker wetenschappelijk ;P) kon ik het toch niet laten om het dankwoord (lees: belangrijke pagina's vol lof en clichés en natuurlijk afsluitend met mijn grote liefde als climax) op te nemen in dit proefschrift. Want natuurlijk is ook dit proefschrift niet alleen tot stand gekomen door mij alleen, maar dankzij een jarenlange samenwerking met veel verschillende mensen met ieder hun eigen bijdrage. Zonder de hulp van hen allemaal was dit proefschrift niet tot stand gekomen. En al deze mensen wil ik toch heel graag bedanken.

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ik wens je veel succes binnen je nieuwe werkveld, de huisartsgeneeskunde. **Inka**, mijn redder in nood. Je bent een enthousiaste, lieve, vriendelijke collega die altijd voor mij klaar stond. Alhoewel soms de 1001 dingen die op de afdeling tegelijk liepen terecht je de pet te boven gingen is jouw bijdrage aan dit proefschrift onmisbaar geweest. Ik hoop dat we daar in toekomst nog vaak bij high tea's of andere culinaire gelegenheden op kunnen proosten. **Hugo**, lieve broer, wat ontzettend fijn dat we nu zo'n goede band hebben. Dank voor de discussies, vriendschap en gezellige momenten in het leven. En ontzettend fijn dat je zo'n lieve schoonzus voor me hebt gevonden!

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De onderzoeken van dit proefschrift hebben zich bijna allemaal op 2 locaties voorgedaan: in het AMC en op Reade. Dit biedt als voordeel dat ik wat extra pagina's dankwoord zal spenderen maar ook dat de studies én ik van meer patiënten en collega's konden leren in de afgelopen jaren. Er zijn heel wat collega's geweest op Reade die ik zeer erkentelijk ben.

Op de onderzoekerskamer zaten (gelukkig niet allemaal tegelijk, alhoewel de temperatuur in de zomer redelijk hoog op kon lopen**) Samina, Marian, Sjoerd, Anneke, Willem, Merel, Jill, Eva, Rabia, Lina, Maaike, Annelies, Renske, Milad, Mieke, Alper, Charlotte, Ingrid, Inge, Hennie** en ook **Serash, Nicole, Linda van de VU,** een groot deel van de nieuwe garde staat hier niet eens bij. Bedankt voor al jullie support, gezelligheid en humor op Reade en daarbuiten. Jullie hulp en gezelligheid heeft het promoveren een stuk leuker gemaakt.

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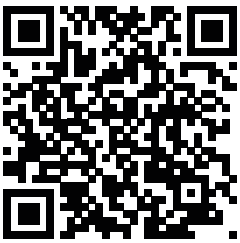

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