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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 closely as possible, acceptable disease state was not determined by predefined activity measures, but 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 fulfil MDA (MDA^-). The presence of tender joints 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% *vs* 7% ($P < 0.001$), enthesitis >1 in 14% *vs* 3% ($P = 0.002$) and Psoriasis Area and Severity Index >1 in 43% *vs* 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.

Conclusion. One-third of the PsA patients with acceptable disease state according to the treating rheumatologist did not fulfil 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.

Key words: psoriatic arthritis, minimal disease activity, outcomes research, residual disease activity

CLINICIAL SCIENCE

Rheumatology key messages

- The rheumatologist's opinion was discordant with minimal disease activity measurement in real-life PsA practice.
- Strategy trials in PsA should question if partial responders could benefit from treatment escalation.

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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 DMARDs (cDMARDs) and/or TNF inhibitors (TNFi) [1]. Obviously the question arises of whether 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 successfully 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 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 DAS and less radiographic progression [8–11]. 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 an 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 fulfil MDA, which factors contributed to residual disease activity, and to what extent the residual disease activity related to the patients' scores on quality of life and disability questionnaires.

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 20 rheumatologists and 10 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 $\geqslant 18$ years; (ii) had the clinical diagnosis of PsA and fulfilled the Classification Criteria for Psoriatic Arthritis [13]; and (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 for whom the treating rheumatologist had considered and/or performed treatment modifications in the past 6 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 78/76 joints [swollen joint count (SJC)/tender joint count (TJC)], Leeds Enthesitis Index (LEI) including the plantar fascii, 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 HAQ (HAQ DI) [14], the Short Form 36 (SF-36) health survey [15], the Dermatology Quality of Life Index (DLQI), the Hospital Anxiety and Depression Scale, the Bath Ankylosing Spondylitis Disease Activity 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 $\leqslant 1$; SJC $\leqslant 1$; PASI $\leqslant 1$; VASptPain $\leqslant 15$ mm; VASptGlobal $\leqslant 20$ mm; HAQ $\leqslant 0.5$; Leeds Enthesitis Index $\leqslant 1$ [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 fulfilment 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).

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 diagnosis, mean (S.D.)	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 <25 kg/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)
MTX, 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 DMARDs.

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.

Characteristics of MDA$^-$ patients

On average, MDA$^-$ patients were older than MDA$^+$ patients (Table 1), and had longer disease duration and a higher 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 (Fig. 2B).

A multivariate analysis model correcting for age, disease duration, gender, BMI, medication use and smoking status showed an effect of age (per 10 years) [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.

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).

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 the 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, available at *Rheumatology* Online).

Discussion

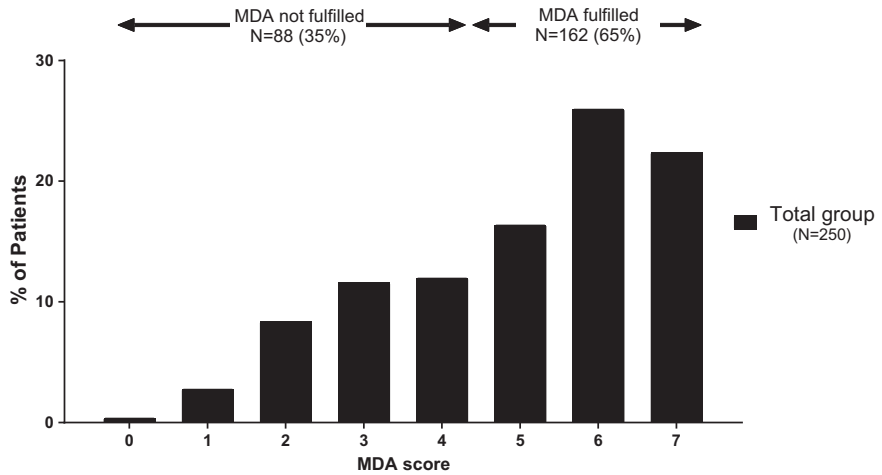
This study assessed the presence of residual disease activity in PsA patients considered to have an acceptable disease state according to their treating rheumatologist. One-third of the 250 patients did not meet the MDA

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)	0.000
Tender joint count	1 (0–5)	0 (0–2)	6 (2–10)	0.000
PASI	0.3 (0–1.5)	0 (0–1.2)	0.8 (0–2.4)	0.002
VASptGlobal	10 (3–29)	6 (1–11)	37 (23–56)	0.000
VASptPain	8 (2–23)	3 (0–8)	32 (20–53)	0.000
HAQ	0.25 (0–0.625)	0 (0–0.38)	0.75 (0.5–1.38)	0.000
Enthesitis: LEI	0 (0–0)	0 (0–0)	0 (0–0)	0.002
Patients with an enthesitis on the LEI, n	17	5	12	
Dactylitis, n	2	0	2	0.055
ESR, mm/h	6 (4–11)	5 (3–9)	8 (5–16)	0.000
BASDAI	14.6 (5.7–35.5)	9 (3–18.2)	41.4 (21–53.5)	0.000
VASphys	11 (4–26)	7 (3–17)	23 (9–42)	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.

Fig. 1 Minimal disease activity score

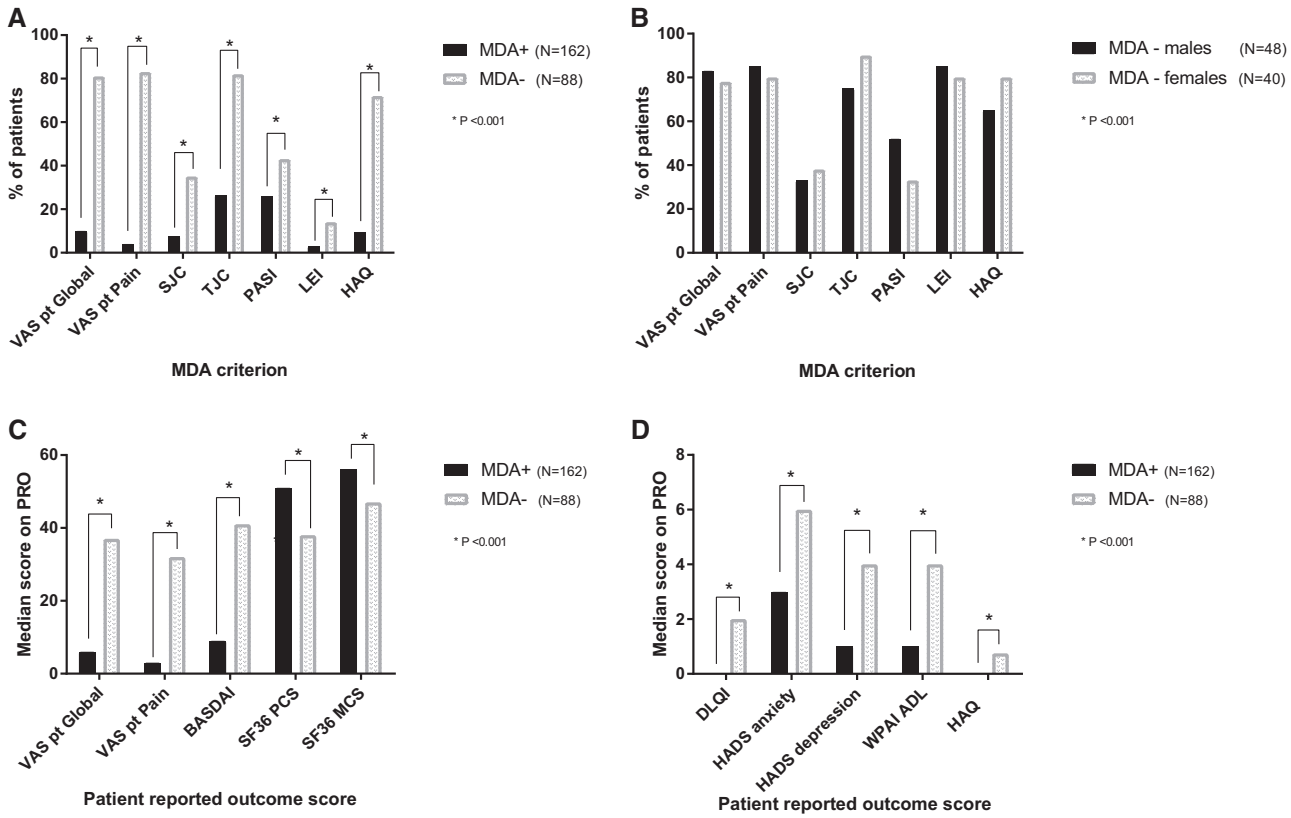


Patients were considered not in MDA (MDA$^-$) with a score of 0, 1, 2, 3 or 4 points and in MDA (MDA$^+$) with a score of 5, 6 or 7 points. MDA: minimal disease activity.

criteria, with residual disease activity across all MDA disease domains. Patients not in MDA were more frequently female and had 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] reported only 24% treated with 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

FIG. 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 non-normally 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.

present in MDA$^-$ patients was reflected both by 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 due only 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

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

Disease activity measures	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)	
Patients with a dactylitis, n	0	1	1	NS
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.

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 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. This study showed that tight control resulted in higher ACR20 responses (62 *vs* 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 Functional Index scores [11]. 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 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 centre 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 centres and we did not assess what percentage of the total PsA population did fulfil 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 determination of whether 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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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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