What are the main barriers to achieve minimal disease activity in psoriatic arthritis in real life?

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on behalf of PsArt-ID (Psoriatic Arthritis-International Database)

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Abstract

Objective

Minimal disease activity (MDA) is an important target in patients with psoriatic arthritis (PsA), however it is also criticised for having a low threshold for patient reported outcomes (PRO).The aim of the study was to assess the prevalence of MDA and its components in patients with PsA and to evaluate disease characteristics and patterns in patients with or without MDA (MDA^+ or MDA^-).

Methods

PsArt-ID (Psoriatic Arthritis-International Database) is a prospective, multicentre web-based registry. PsA patients who had at least 1 year of disease duration and had full data for MDA were included for this analysis (n=317). Patients were considered in MDA^+ when they met at least 5/7 of the MDA criteria.

Results

MDA was achieved in 46% patients. Within MDA^- patients, body surface area (51.2%) and swollen joint count (53.5%) domains could still be achieved in the majority and 93.5% of them had no enthesitis using the Leeds enthesitis index. Of 170 patients with MDA^-, 90 patients did not fulfill all 3 PROs of MDA. Mono-arthritis subtype (RR: 2.01), absence of enthesitis (RR: 1.570) and absence of distal interphalangeal (DIP) joint disease (RR: 1.1) were associated with higher probability of achieving MDA.

Conclusion

The MDA criteria provide an objective target for treatment in trials and clinical practice; however, in real life PROs are the most significant barriers to achieve MDA. The presence of DIP joints disease makes it difficult to reach MDA due to active PROs.

Key words
psoriatic arthritis, minimal disease activity, patient-reported outcomes

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease with complex musculoskeletal and extra-articular manifestations (1, 2). The target of treatment for PsA is to reach clinical remission or low disease activity to inhibit the structural damage and the improvement of patient reported outcomes (PROs) (3). In 2010, minimal disease activity (MDA) criteria were developed by Coates *et al*. (4) and have been used as an outcome measure in several studies (5-7). MDA is a composite measure developed specifically for PsA including seven outcome measures on arthritis, psoriasis, enthesitis, pain, patient-assessed global disease activity, and physical function (5). Despite the growing body of evidence addressing the impact of MDA on disease outcomes, there are some potential concerns associated with MDA domains. Three out of seven MDA domains are PROs, which may be affected by non-inflammatory conditions, such as osteoarthritis or fibromyalgia. In addition, damage related disease features can contribute to PROs although not being linked to disease activity. The others are the lack of acute phase reactants and the lack of the evaluation of spondylitis activity (8).
The objectives of the study were: 1. to determine how often MDA is achieved in real life and the contribution of PROs on MDA; 2. to evaluate the factors that can affect MDA status with a focus on disease subtypes; 3. to explore the overlaps between PROs and other MDA domains.

Material and methods

Patients, data collection and setting

PsArt-ID (Psoriatic Arthritis-International Database) is a prospective, multicentre registry in PsA, which was initially developed in Turkey in 2014, with participation of Canada since 2015. Ethics approval was obtained from both Hacettepe University Ethics Board, Ankara, Turkey (GO 14/578) and Ottawa Health Science Network Research Ethics Board, Ottawa, Canada (20160436-01H). All patients gave informed consent prior recruitment. Patients with a diagnosis of PsA have been consecutively recruited to the registry with the aim of investigating the real-life data using a web-based system (www.trials-network.org) and the registry have been previously explained in detail (9). For the purpose of this analysis, we aimed to exclude patients with new diagnosis. Therefore, only patients who fulfilled the Classification for Psoriatic Arthritis (CASPAR) criteria with at least 1 year of disease duration were included if they had all the domains of MDA being reported (10). The presence of joint tenderness and swelling was evaluated in 68 and 66 joints, respectively. The Leeds enthesitis index was used to assess enthesitis and body surface area (BSA) for psoriasis severity.
Patients were classified as being in MDA state (MDA^+) when they fulfilled at least five of the following seven criteria: Tender joint counts (TJC) ≤1, swollen joint counts (SJC) ≤1, BSA ≤3%, pain visual analogue scale (VAS) ≤15, patient global assessment (PtGA) ≤20, health assessment questionnaire (HAQ) ≤0.5 and tender entheseal points (TEP) ≤1. Otherwise, they were classified as not being in MDA (MDA^-) (5). In addition, DAPSA ((Disease Activity in PSoriatic Arthritis) Score) was analysed in 277 patients where CRP was available (11).

Statistical analyses

Continuous data were described as median (first-third quartiles) or mean (SD) according to the distribution and categorical variables were expressed as frequencies and percentages (%). Chi-square test was performed to analyse categorical data. Comparisons for continuous variables between the two categories were made using the Mann-Whitney U-test. Relative risk was calculated for factors that can affect MDA status. Multivariate analysis was performed for prediction of MDA, using variables with a *p*-value less than 0.20 in univariate analyses. SPSS v. 22 was used for analysis (SPSS Inc., Chicago, IL, USA).

Results

In January 2018, 317 patients within the registry had MDA data, and 147 of them (46%) were MDA^+ at the recruitment.

Factors related with MDA status

Age, gender, disease duration, level of education, body mass index (BMI) and smoking status were similar in patients who were MDA$^+$ and MDA$^-$ (Table I). The MDA rates in Turkey and Canada were also similar. Disease phenotype had an impact on the MDA status as patients with mono-arthritis (RR 2.01; 95% CI: 1.579–2.559, $p<0.05$) and who never had any enthesitis (RR 1.570; 95% CI: 1.027–2.398, $p<0.05$) nor distal interphalangeal (DIP) joint disease at the disease course (RR 1.1; 95% CI: 1.001–1.25, $p<0.05$) achieved MDA more often. Patients with DIP joint disease had higher number of TJCs ($p=0.041$) and SJCs ($p=0.001$) if they have not achieved MDA, whereas the same difference could not be observed for patients in MDA (Supplementary Table I).

In multivariate analysis biologics increased the MDA rates whereas axial disease, DIP joint disease and family history was negative predictors, the latter 2 being borderline (Table II).

Mean DAPSA score was 14.8±11.1. The agreement rate between MDA and DAPSA remission was 76%. Patients with DIP joint disease also had more frequently moderate-high activity with DAPSA (p:0.008).

The distribution of MDA domains

MDA$^-$ patients had worse PROs, physician reported outcomes and inflammatory parameters than MDA$^+$ patients (Supplementary Table II). The less frequently achieved MDA criteria across patients who were MDA$^-$ were pain VAS (8.2%) and PtGA (12.9%) (Supplementary Table II). Those two parameters were also less frequently fulfilled among all PsA patients regardless of MDA state (30.6%, 41%, respectively) (Fig. 1).

On the other hand, the targets for BSA (51.2%) and SJC (53.5%) domains could be achieved in about half of the patients despite not achieving MDA and 93.5% of the same group had no enthesitis using the Leeds enthesitis index (Fig. 1, Suppl. Table I1). The TEP (96.2%) and SJC (72.9%) domains could be achieved by the majority of the patients regardless of MDA state (Fig. 1).

Amongst patients within MDA$^-$, the number of patients not fulfilling all 3 PROs (HAQ, pain VAS, PtGA) was higher than the number of patients not fulfilling 2 PROs or only one PRO (n=90, n=65, n=12, respectively) (Fig. 2). Those 90 patients who were MDA$^-$ had all 3 PROs exceeding the threshold, 17 (%19) had all physician-dependent MDA domains (TJC, SJC, TEP, BSA) fulfilled but still could not reach the MDA due to unmet PROs.

Amongst patients who achieved MDA, the cut-offs for TEP (99.3%) and SJC (95.2%) were still more frequently fulfilled than pain VAS (56.5%) and PtGA (73.5%) (Fig. 1).

Table I. The demographics, disease characteristics and patterns in patients with MDA$^-$ *vs.* MDA$^+$.

	MDA$^-$ n / total n (%)	MDA$^+$ n / total n (%)	p-value
	170/317 (53.9)	147/317 (46.0)	
Female	109/188 (58)	79/188 (42)	0.061
Male	61/129 (47.3)	68/129 (52.7)	
Age (year)*	50 (40-59)	51.5 (37-60.5)	0.924
The duration of education (year)*	11 (5-15)	11 (5-14)	0.738
Disease duration (months)*	95 (66-155)	88 (59-155)	0.843
BMI (kg/m^2)*	28.20 (24.46-33.05)	27.53 (23.76-30.91)	0.166
Country of residence			
Turkey	128/232 (55.2)	104 /232 (44.8)	0.362
Canada	42/85 (49.4)	43/85 (50.6)	
Smoke			
Smoker	69/170 (40.8)	72/146 (49.3)	0.381
Never	100/169 (59.2)	74/146 (50.7)	
Family history (Psoriasis or PsA)	63/171 (36.8)	40/146 (27.4)	0.074
Nail involvement	92/171 (53.8)	73/146 (50)	0.500
Dactylitis	65/170 (38.2)	55/147 (37.4)	0.881
Enthesitis	35/170 (20.6)	16/147 (10.9)	**0.022**
PsA patterns			
Polyarthritis	78/170 (45.9)	70/146 (47.9)	0.714
Oligo/monoarthris	67/170 (39.4)	59/146 (40.4)	0.908
DIP joint disease	42/170 (24.7)	23/146 (15.8)	**0.050**
Axial disease	79/170 (46.5)	56/146 (38.4)	0.171
Arthritis mutilans	0/170 (0)	1/146 (0.7)	0.462
Biologic treatments§	51/150 (34)	63/134 (46)	**0.041**
Patients on first biologics	29/74 (39.2)	45/74 (60.8)	**0.009**

All data were given as n / total n (%) or *(median (first-third percentiles)). BMI: body mass index; PsA: psoriatic arthritis; DIP: distal interphalangeal; MDA: minimal disease activity. §anti-TNF and secukinumab.

Table II. Multivariate analysis for prediction of MDA.

Variables	Exp (B)	CI 95 %	p-value
Sex (men *vs.* women)	1.49	0.89-2.49	0.129
BMI	0.97	0.93-1.01	0.202
Family history (Psoriasis or PsA) (present *vs.* absent)	0.58	0.24-1.00	0.052
Axial disease (present *vs.* absent)	0.56	0.34-0.93	0.025
DIP joint disease (present *vs.* absent)	0.54	0.28-1.02	0.058
Enthesitis (ever) (present vs. absent)	0.59	0.29-1.21	0.154
Biologic treatment (present *vs.* absent)	1.72	1.04-2.85	0.033

DIP: distal interphalangeal, MDA: minimal disease activity.

The effects of treatments on MDA

Patients that were on biologics achieved MDA more often than other conventional disease-modifying antirheumatic drug (DMARD) therapies (46% *vs.* 34%, $p=0.041$). The percentage of patients who were MDA$^+$ was higher with first biologic (60.8%) compared to 1 switch (48.2%), 2 switches (42.9%) and 3 switches (25%) (Suppl. Fig. 1).

Comorbidities according to MDA status

The prevalence of cerebrovascular events was significantly higher in MDA$^-$ patients in comparison to MDA$^+$.

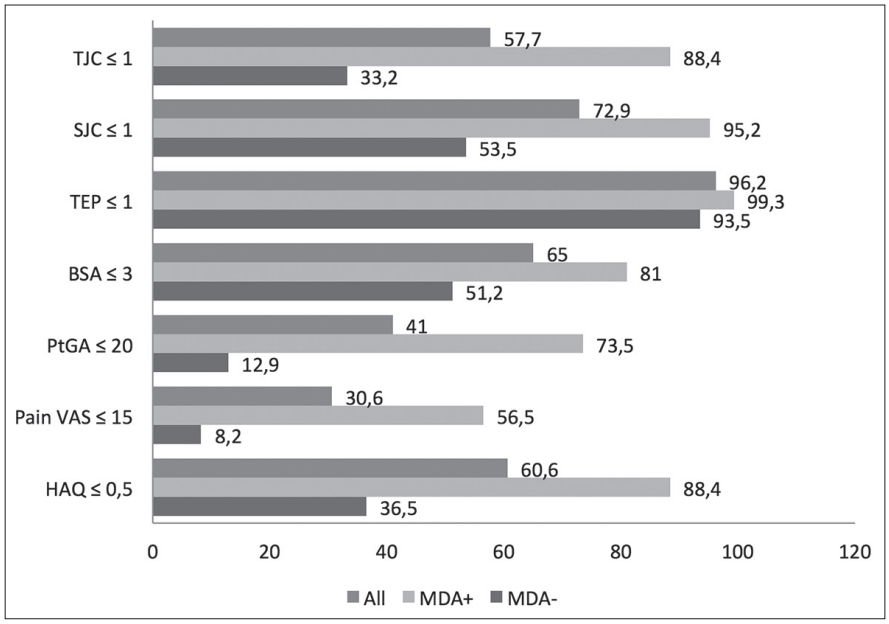

Fig. 1. The distribution of all fulfilled MDA domains in all patients, and in subtypes MDA$^+$ and MDA$^-$. Numbers are given as percentages.
TJC: tender joint counts; SJC: swollen joint counts; TEP: tender entheseal points; BSA: body surface area; PtGA: patient global activity; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire.

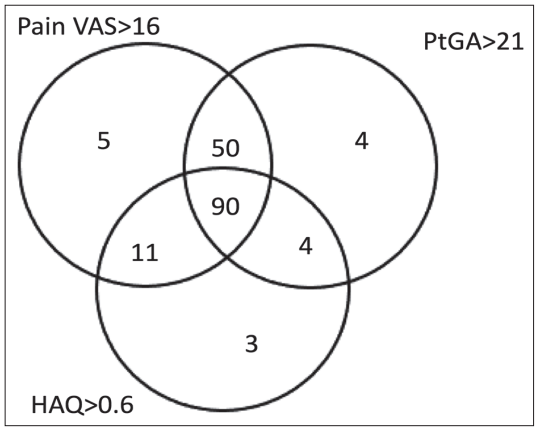

Fig. 2. The number of patients who did not meet MDA criteria in terms of PROs in patients with MDA.
PtGA: patient global activity; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire.

The other comorbidities were not significantly different between MDA$^-$ and MDA$^+$ groups.

Discussion

PROs are crucial for the physicians to understand the impact of PsA on patients, however there are significant overlaps among PROs and they can be affected by several conditions other than disease-related features. Our study showed that a greater magnitude of patients with MDA$^-$ could not meet all three PROs, then the probability of not meeting 2 or one PRO. The 3 PROs closely being linked to each other may be due to a redundancy and can all be negative despite all physician-based assessments being normal.

Some studies stressed that having different subtypes of PsA might affect the MDA status. In previous studies the presence of axial involvement and polyarthritis were related with a lower probability of achieving MDA and the presence of oligoarthritis was related to a higher probability (12). We have also found that having mono-arthritis (but not oligo-arthritis) increased the probability of achieving MDA, although the number of patients within this subtype was relatively low. Our study also showed that axial disease in PsA is a risk factor not to achieve MDA, similar to the observation by Perrotta *et al*. (12). This is in contrast to the observations by Theander *et al*., who had found the opposite, axial disease being a predictor of achieving MDA (13). All 3 studies were mainly based on the physicians' judgement with inflammatory back pain and/or physical examination features to define axial disease, radiographs not being a requirement in either of them. Axial PsA does not have a widely accepted definition and the differences between the studies may be due to the lack of agreed definitions and not including imaging to provide standardisation.

There is a gap in the literature on the effects of DIP joint disease on MDA. Our study confirmed that DIP joint disease is a risk factor not to achieve MDA, more frequently increasing all PROs at the same time. It is more straightforward to differentiate DIP joint subtype of PsA then osteoarthritis in younger patients, whereas this can be challenging in the elderly. As the onset of PsA has switched to the 5th decade of life-hood, the risk of these 2 conditions concomitantly being together is also increasing. The clinical pictures can be similar in both as well as shared imaging features (14). It is also challenging to understand to what extend the symptoms are due to Osteoarthritis or PsA activity. The risk of not achieving MDA in the group with DIP joint disease may be linked to the real effect of DIP involvement on PsA activity or may reflect the impact of osteoarthritis on MDA.

MDA status was linked to cerebrovascular events and patients that were not able to achieve MDA had more frequent cerebrovascular disease. This is of interest as PsA patients whose disease activity is poorly controlled have been shown to have more cardiovascular disease, in parallel to our observations (15).

There are some limitations of the study. Although the registry had around 1400 patients, only 317 of them had data that allowed us to calculate MDA status. The most frequent missing data within MDA was BSA, reflecting the lack of data collection on the skin psoriasis in rheumatology and may point out to one the biggest barriers of not being able to implement MDA in routine practice more often. Despite the lack of MDA data on the rest of the registry, we have observed similar MDA rates with the

previous randomised controlled trials (24–52%) and open label cohorts (44-64%) supporting the external validity of the registry and data collection (8). The data presented here only focuses on cross sectional data based on the recruitment date. The follow up is still ongoing and will be presented in future but at this stage the information on sustained MDA is not tested.

In conclusion, the MDA criteria provide an objective target for treatment in trials and clinical practice, however in real life; the overlap of PROs and DIP joint disease are the most significant barriers to achieve MDA within all domains.

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