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TREAT-TO-TARGET IN REAL-LIFE IN PSORIATIC ARTHRITIS PATIENTS

IL TREAT-TO-TARGET NELLA REAL-LIFE IN PAZIENTI AFFETTI DA ARTRITE PSORIASICA

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Abstract

Objective: our study aimed at describing, in a real-life cohort of psoriatic arthritis (PsA) patients, the rates of minimal disease activity (MDA) achievement, and to longitudinally explore predictors of MDA. In patients with axial involvement (axPsA), we also examined the rates and predictors of low axial disease activity achievement.

Methods: consecutive PsA patients in stable biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) were enrolled. Disease activity indices, including MDA and Ankylosing spondylitis Disease Activity Score-Low Disease Activity (ASDAS-LDA) for axPsA, were evaluated at baseline and every 6 months, up to 36 months or bDMARDs permanent discontinuation. Patient history, BMI, comorbidities (including osteoarthritis (OA) and fibromyalgia) were collected. Characteristics of patients were compared between patients reaching sustained MDA and those who did not. Multivariable Generalized Estimating Equation (GEE) models were built to identify predictors of MDA and ASDAS-LDA over time. Data were expressed as coefficient β (95%CI).

Results: 104 patients were enrolled, 54% males, mean age 55.7$\pm$ 5.0 years; 52% had axPsA. Across all evaluations, 52%-61% reached MDA, and 17%-24% reached ASDAS-LDA. AxPsA, fibromyalgia, OA and BMI$\geq$35 were less frequently observed in patients with sustained MDA. The GEE model confirmed these factors were negatively and independently associated to MDA (axPsA β=–1.07, 95%CI –1.82/–0.33; fibromyalgia: β=–3.35, 95%CI–5.09/ –1.61; OA: β=–1.87, –3.07/0.66; BMI$\geq$35: β=–2.53; 95% –4.27/–0.79). Older age (β=–0.05; 95% CI –0.09/–0.02) and longer bDMARDs duration (β=0.31, 95%CI 0.00- 0.02) had a negative and positive association, respectively, with MDA. Older age (β=–0.01, 95%CI: –0.04- 0.01), fibromyalgia (β=–2.03, 95%CI –3.50/–0.56) and OA (β=–1.30; 95% –2.29/–0.31) were independently associated also to ASDAS-LDA.

Conclusion MDA is an attainable target in real-life patients. AxPsA represents a difficult-to-treat subset. Sustained MDA depends both on disease features (axSpA) and patients' characteristics (age, bDMARDs duration, comorbidities: OA, fibromyalgia).

Introduction

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory disease occurring in about 0.05-0.42% of the general population, with different estimates according to the different geographical regions (1). In patients affected with psoriasis, it occurs in a much higher percentage, ranging from 6% to 41% (1). PsA is a complex and multifaceted disease, belonging to the family of spondyloarthritis (SpA), with manifestations including much more than arthritis and psoriasis: in fact, it is characterized also by axial involvement, tenosynovitis, enthesitis, dactylitis, nail disease, and by a frequent association with inflammatory bowel disease (IBD), cardiovascular comorbidities, and uveitis (1-3). These clinical phenotypes share a common pathogenetic background: genetic, biomechanical, metabolic and microbial factors are responsible for mobilization of immune cells into the target tissue, with similar mechanisms regardless the target (e.g. joint, skin, enthesis) (3). The similarities in the pathogenesis of these conditions has brought to the definition of the term “psoriatic disease”, to refer to the whole spectrum of manifestations and comorbidities of psoriatic arthritis (4). The link between PsA and its comorbidities was also highlighted by observations suggesting that PsA treatment could be beneficial for comorbidities as well (5,6).

Since PsA is such a heterogeneous disease, it has been difficult to develop an index that can capture disease activity in all potentially involved domains, and most of all, an index that can detect true remission (7). This is even more complicated if remission is intended - as proposed by Kavanaugh et al.- as “*a complete absence of disease activity, with no signs or symptoms of active disease*” (8). Recognizing both the difficulty of defining remission with a gold standard measure, and of completely abolishing disease activity, a commonly used goal in PsA treatment and management has been minimal disease activity (MDA) (9). This criterion was developed as an attempt to describe a satisfactory state of

disease activity which could encompass all aspects of the disease, and it is a boolean indicator of low disease activity (9). Its clinical relevance become evident after the TIght Control in Psoratic Arthritis (TICOPA) trial showed that applying a treat-to-target strategy aimed at MDA could improve PsA outcomes (10). Based on these results, along with the increased availability of effective therapies, international recommendations were formulated advocating that the target of treatment in PsA should be remission or, alternatively, low disease activity (11). This appears an attainable goal as, in a randomized clinical trial (RCT) of the anti-tumor-necrosis factor (TNF) agent golimumab, it has been demonstrated that approximately half of the patients manage to reach MDA at least once over a 5-year observation period (12). However, what really seems to matter for patients is not only reaching MDA at a certain timepoint, but being in a stable MDA state. In fact, although a consensus definition of “sustained MDA” does not exist, patients who stayed in MDA for 3 or 4 consecutive visits in this study, reached better functional improvement, patient global assessment, and radiographic outcomes (12). Nonetheless, patients enrolled in clinical trials represent a very selected population of PsA patients, often with few comorbidities, and frequently naïve to previous biological treatment. Therefore, it would also be important to understand how frequently, in real-life clinical practice, patients can be expected to achieve a state of MDA and how frequently this is maintained over time. A relevant contribution towards this objective was made by Lubrano et al., who retrospectively analyzed patients treated with anti-TNF therapy and found that about 40% of patients who initiated a first-line anti-TNF therapy could indeed achieve a state of sustained MDA, defined in this case as MDA state maintained for at least 12 months (13). Yet, studies that have been published so far evaluated mostly naïve patients starting a new biological Disease Modifying Anti Rheumatic Drug (bDMARD) therapy. Besides, it is unknown, at present, whether a longer treatment duration or multiple previous treatment failures may increase the risk of losing a MDA state. This is why it would be important to

evaluate MDA achievement in real-life PsA patients, who could be more difficult-to-treat than the typical RCT patient, or than early PsA patients, due to multiple comorbidities, previous treatment failures, and adherence challenges.

In addition, the impact of the axial component of PsA (axPsA) in reaching MDA has rarely been studied. This partly depends on the fact that a clear definition of “axPsA” is still lacking (14), although the studies that have been conducted so far in PsA with axial symptoms and/or sacroliilitis seem to show a satisfactory response to bDMARDs (15–18). Therapeutic strategies for axPsA are usually derived from axSpA (19), but features of axPsA can be complex, and different from axSpA: they include spinal involvement without sacroiliitis, delayed appearance of radiographic sacroiliitis, and possible low level of symptoms indicative of spinal involvement (20). In addition, it has not been established yet whether axPsA simply follows PsA course, or if it can represent an additional burden with an independent disease trajectory. Nonetheless, disease activity at an axial level is so far normally evaluated with instruments that were borrowed from axSpA, like the Ankylosing Spondylitis Disease Activity Score (ASDAS) (21). Incidentally, also for ASDAS states of inactive disease and low disease activity (ASDAS-ID, ASDAS-LDA) have been defined (22,23), and are increasingly considered to be desirable treatment targets for axial spondyloarthritis, based on results of the strategy RCT TICOSPA in axSpA (24). Formally, TICOSPA failed its primary objective, which was to demonstrate a ≥30% improvement on the Assessment of SpondyloArthritis international Society-Health Index (ASDAS-HI), an index that measures overall health and function, in the treat-to target arm compared to usual care. However, many relevant secondary endopoints, such as efficacy and response outcomes, were met. In addition, the treat-to-target strategy was favorable in terms of economic evaluation, with reduced numbers of days of sick leave and of visits for physiotherapy and rehabilitation facilities in the treat-to-target arm. Thus, overall, the treat-

to-target strategy can be considered appropriate in axSpA. Naturally, we do not know whether these observations can be extended to axPsA as well.

Another point of interest is the disagreement that seem to occur between patients and physicians about the global evaluation of the disease activity and the remission state (25,26). Although MDA, much like ASDAS, is both a patient- and physician-derived index, it would be important to know whether these patient-physician discrepancies occur in subjects considered to be in low disease activity, and if this can influence therapeutic choices.

Therefore, the primary aims of our study were:

1) to evaluate the frequency of MDA achievement in a real-life PsA population in stable bDMARD treatment, during a three-year follow up

2) to find characteristics associated to sustained MDA, and predictors of MDA over time, in a longitudinal cohort

The secondary aims of our study were:

1) to evaluate the frequency of ASDAS-LDA achievement in a real-life PsA population with axial involvement in stable bDMARD treatment, during a three-year follow up

2) to find characteristics associated to sustained ASADAS-LDA, and predictors of ASDAS-LDA over time, in a longitudinal cohort

3) to describe how frequent the discrepancy between patient and physician is among patients reaching sustained MDA or sustained ASDAS-LDA, and to explore if this has an influence on therapeutic management

Methods

Design of the study

This was a longitudinal cohort study of consecutive adult PsA patients (aged≥18 years), diagnosed by a rheumatologist and fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR criteria) (27), attending the Rheumatology Unit of Padova University, enrolled in the period January-December 2018. Patients with axial involvement were recruited within the international Spondyloarthritis Caught Early (SPACE) study, an ongoing longitudinal study that entails a standardized imaging evaluation for all patients (28,29). At baseline, in order to be eligible for the study, patients had to be in stable therapy with bDMARDs for at least 6 months, regardless of the treatment line. Combination treatment with conventional synthetic DMARDs (csDMARDs) was allowed, as long as this therapy had also been at a stable dose in the last 12 months. Patients treated with csDMARDs or NSAIDs only were excluded. Included subjects were then prospectively followed up every 6 months up to 36 months (t 0,1,2,3,4,5,6) or to bDMARDs permanent discontinuation (e.g in case of new onset of long-term contraindications to bDMARDs, such as neoplasm). On the other hand, if patients switched to another bDMARDs therapy, they continued to be followed up: the time-to-first switch, as well as the number of following switches, was collected.

Variables of interest

At baseline, the following variables were collected:

- Demographic and lifestyle variables such as age, gender, smoking habits (current/former or never smoker), Body Mass Index (BMI)
- Data regarding the disease history, such as disease duration, previously or currently involved domains (peripheral arthritis, enthesitis, tenosynovitis, dactylitis, axial involvement –i.e. axPsA-, nail disease ever), previous csDMARDs and

bDMARDs therapies; in this context, axial involvement was considered to be present if the patient ever complained of inflammatory back pain lasting≥3 months, in association with signs of Inflammation or structural changes at MRI and/or X-rays of the pelvis and of the spine (axpSA) (14)

- Comorbidities, including chronic comorbidities comprised in the modified Rheumatic Disease Comorbidity Index (mRDCI) (30), and other frequent rheumatic comorbidities, specifically physician-diagnosed fibromyalgia and symptomatic osteoarthritis (OA) of the hands, knee, spine or hips. The latter was defined as the presence of structural changes at plain X-rays of hands, knee, spine or hips, coherent with OA (e.g joint narrowing, osteophytes, seagull wing aspect at hand proximal inter-phalangeal joints, and so on) and responsible for pain according to the physician judgement.

Both at baseline and at each following timepoints, the following assessments were performed:

- Joint disease activity: 66/68 tender/swollen joint count, Visual Analogue Scale of pain (VASp) on a 0-10 scale, Patient and Physician Global Assessment of Disease Activity (PGA, PhGA) on a 0-10 scale, Disease Activity index for PsA (DAPSA) (31)
- Axial disease activity: ASDAS (32,33)
- Skin disease activity: Body Surface Area (BSA), Psoriasis Area and Severity Index (PASI) (34)
- Enthesitis scores: Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada score (SPARCC) (35,36)
- Quality of life: Health Assessment Questionnaire (HAQ) (37)
- Low disease activity/remission criteria: MDA and very low disease activity (VLDA); ASDAS-LDA if axPsA was present (9,22,23,38);

Throughout all evaluations, sustained MDA was defined as reaching an MDA state≥4 times out of the 7 evaluations, while sustained ASDAS-LDA was defined as reaching at least an ASDAS-LDA state (i.e. ASDAS-ID was also included) ≥4 times out of 7 evaluations.

In addition, we defined, for each evaluation, patient-physician discrepancy to be present if there was a difference between PGA and PhGA≥3 on a 0-10 scale. We distinguished negative discrepancy (physician rating higher than patient) from positive discrepancy (patient rating higher than physician). We then replied the analysis using a difference between PGA and PhGA≥2 to define a discrepant judgement.

Statistical analysis

Baseline disease characteristics of the patients in different MDA states were compared by descriptive statistics: Chi square or Fisher exact test were used for categorical variables, and Mann-Whitney U test was used for continuous variables. Specifically, a comparison was made between:

1) patients reaching sustained MDA or not

2) patients never reaching MDA vs patients reaching MDA at least once

3) patients always reaching MDA (persistent MDA) vs patients not reaching MDA at least once

4) patients reaching sustained ASDAS-LDA or not

Multivariable Generalized Estimating Equation (GEE) models were built to analyze predictors of MDA and ASDAS-LDA over time. GEE is a regression technique that is used for the analysis of longitudinal data, and has the advantage of making use of all collected data, at every timepoint. Besides, it is able to adjust for within-patient correlations. Independent variables for the multivariable models were selected

according to the factors that were considered potentially important, based on data from the literature, such as gender, BMI, mRDCI, fibromyalgia, axial involvement, and based on our hypothesis (tenosynovitis, OA) (14,30,39,40). Results were expressed as beta coefficient and 95% confidence intervals (95%CI)

A Cox regression model was built having time-to-switch as an outcome, and patient-physician positive discrepancy (yes/no) as the main independent variable. The model was corrected for age and gender. Results were expressed as hazard rate (HR) and 95% CI.

Analyses were conducted with STATA v.17 (Copyright 1985-2019 StataCorp LLC, College Station, Texas 77845 USA). $P<0.05$ were considered as significant

Results

Characteristics of patients

A total of 104 PsA patients were enrolled, 54% males, with a mean age of 55.7± 5.0 years and a disease duration of 16.4±9.6 years. Their baseline characteristics are depicted in *Table 1*.

Table 1. Baseline characteristics of the included patients

Variables	
Number of patients	104
Males	57 (54)
Age (years)	55.7±5.0
Disease characteristics:	
Disease duration (years)	16.4±9.6
Family history of psoriasis or PsA	38 (37)
Peripheral arthritis, ever	95 (91)
Dactylitis, ever	31 (30)
Enthesitis, ever	81 (77)
Axial involvement (axPsA), ever	54 (52)
DIP involvement, ever	48 (46)
Tenosynovitis, ever	72 (69)
Nail disease, ever	71 (68)
Body Surface Area (BSA) (1-100%)	0.7±1.6
Psoriasis Activity and Severity Index (PASI) (0-72)	1.0±1.7
Patient Global Assessment (PGA) (0-10)	3.8±2.3
Physician Global Assessment (PhGA) (0-10)	2.6±1.9
Visual Analogue Scale of pain (VASp) (0-10)	3.6± 2.4
Health Assessment Questionnaire (HAQ) (0-3)	0.42±0.49
C- Reactive Protein (CRP), mg/L	4.3±4.0
Disease Activity of Psoriatic Arthritis (DAPSA) score	13.2±7.8
Leeds enthesitis Index (LEI)	0.23 ±0.69
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index	0.86±2.31
Body Mass Index (cm/m2)	27.2 ± 5.1
Current smokers	11 (10)
Comorbidities:	
Inflammatory bowel disease	2 (2)
Fibromyalgia	12 (11)
Symptomatic OA of hands, knees, hip or spine	19 (18)
Modified Rheumatic Diseases Comorbidity Index (mRDCI)	1.4 ± 1.5
Concomitant csDMARDs at baseline	22 (21)
Biological therapy line at baseline	
First line	77 (74)
Second line	17 (16)
Third line	5 (5)
Fourth or more line	5 (5)

Legend. Continuous data are presented as mean±standard deviation or median (interquartile range) according to their distribution. Categorical data are presented as number (percentage)

DIP=distal interphalangeal; csDMARDs=conventional synthetic Disease Modifying Anti Rheumatic Drugs; OA=osteoarthritis

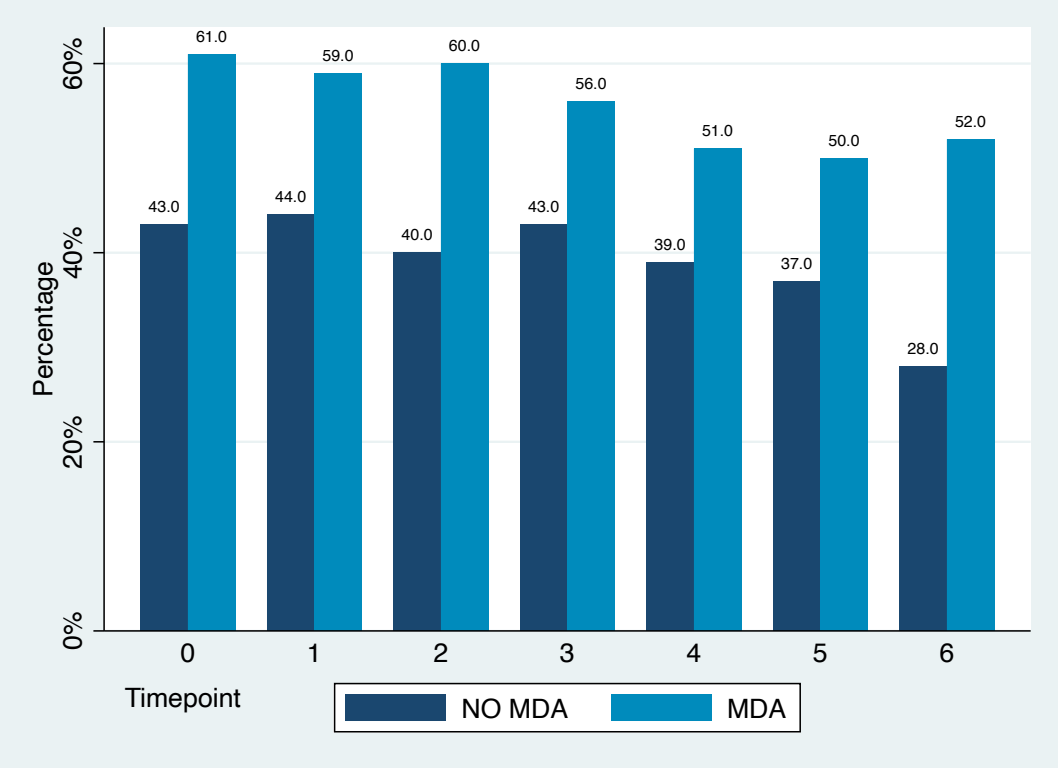
All patients were treated with bDMARDs, mostly first-line (74%), in combination with csDMARDs in 21% of cases. The bDMARDs at baseline were anti-TNF (66%), anti-IL17 (21%) and anti-IL23 (10%), while a minority were treated with apremilast (3%).

Mean therapy duration at baseline was 49.4 ± 50.1 months, with a minimum of 6 months (as per protocol) and a max of 191 months. Almost all patients (91%) had peripheral arthritis in their history, and about half (52%) had axPsA. Enthesitis and tenosynovitis were also very frequent, with 77% and 69% of patients respectively having these manifestations at least once in the disease course. At baseline, disease activity indices indicated a modest skin involvement and -on average- a moderate disease activity. Mean BMI was in the overweight range.

Targets of treatment over time

Across all evaluations, a percentage of patients ranging from 52% to 61% reached MDA (*Figure 1*), while a percentage between 12% and 20% reached VLDA (*Figure 2*).

Figure 1. Percentages of patients reaching MDA at each timepoint



Legend. MDA=Minimal Disease Activity; numbers above columns represent percentages

Figure 2. Percentages of patients reaching VLDA at each timepoint

Legend. VLDA=Very Low Disease Activity; numbers above columns represent percentages

Among all included patients, 17 (17%) switched therapy with a mean time to first switch of 18.0 ± 9.6 months, and 4 (4%) patients switched therapy twice. Reasons for switching were inefficacy (13/17) and adverse events (4/17).

Patients that could achieve sustained MDA were 54 (52%). The differences in disease characteristics between sustained and non-sustained MDA are shown in *Table 2.* Patients with sustained MDA, compared to those who did not achieve this target, were more frequently male (66% vs 42%), had less often axPsA (39% vs 66%) and tenosynovitis (59% vs 80%), and already at baseline had lower disease activity indices (VASp, PGA, PhGA, DAPSA, SPARCC). Physicians also classified these patients, at baseline, as having lower disease activity compared to those who did not reach sustained MDA. Interestingly, all patients with at least grade II obesity (BMI≥35), as well as all patients with fibromyalgia, were in the non-sustained MDA group. The percentage of patients with symptomatic OA of hands, knees, hip or spine was also significantly higher in the non-sustained MDA group.

Table 2. Comparison between patients fulfilling MDA criteria in at least 4 evaluations (sustained MDA) and those fulfilling MDA in less than 4 evaluations (non-sustained MDA)

Variables	Sustained MDA	Non-sustained MDA	p-value
Number of patients	54	50	
Males	**36 (66)**	**21 (42)**	**0.012**
Age (years)	53.7±16.4	57.8±13.2	0.10
Disease characteristics:			
Disease duration (years)	17.1±9.4	15.6±9.8	0.35
Family history of psoriasis or PsA	18 (33)	20 (41)	0.43
Peripheral arthritis, ever	48 (89)	47 (94)	0.35
Dactylitis, ever	16 (30)	15 (31)	0.91
Enthesitis, ever	39 (72)	42 (84)	0.14
Axial involvement (axPsA), ever	**21 (39)**	**33 (66)**	**0.007**
DIP involvement, ever	28 (51)	20 (40)	0.22
Tenosynovitis, ever	**32 (59)**	**40 (80)**	**0.022**
Nail disease, ever	41 (76)	30 (60)	0.08
Body Surface Area (BSA) (1-100%) at baseline	0.6±0.8	0.9±2.2	0.64
Psoriasis Activity and Severity Index (PASI) (0-72) at baseline	0.9±1.2	1.2±2.2	0.29
Patient Global Assessment (PGA) at baseline (0-10)	**2.8±1.9**	**4.9± 2.1**	**<0.0001**
Physician Global Assessment (PhGA) at baseline (0-10)	**1.6±1.2**	**3.7±1.9**	**<0.0001**

Visual Analogue Scale of pain (VASp) at baseline (0-10)	**2.3±1.8**	**5.0±2.2**	**<0.0001**
Health Assessment Questionnaire (HAQ) at baseline (0-3)	0.1± 0.25	0.7±0.5	0.051
C- Reactive Protein (CRP) at baseline, mg/L	3.5± 1.8	5.1±5.3	0.051
Disease Activity of Psoriatic Arthritis (DAPSA) score at baseline	**8.8±4.4**	**17.9±7.8**	**0.012**
Leeds enthesitis Index (LEI) at baseline	0.2±0.7	0.3±0.6	0.06
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at baseline	**0.33±1.28**	**1.44±2.97**	**0.025**
Body Mass Index (cm/m2)	26.2± 3.9	28.2± 5.9	0.64
Body Mass Index (cm/m2)≥35	**0 (0)**	**6 (12)**	**0.009**
Current smokers	5 (9)	6 (12)	0.79
Comorbidities:			
Inflammatory bowel disease	1 (2)	1 (2)	0.95
Fibromyalgia	**0 (0)**	**12 (24)**	**<0.0001**
Symptomatic OA of hands, knees, hip or spine	**3 (5)**	**16 (32)**	**<0.0001**
Modified Rheumatic Diseases Comorbidity Index (mRDCI)	1.1±1.3	1.7± 1.7	0.09
Concomitant csDMARDs at baseline	12 (22)	10 (20)	0.78

Legend. Continuous data are presented as mean±standard deviation or median (interquartile range) according to their distribution. Categorical data are presented as number (percentage). Significant results are indicated in bold. DIP=distal interphalangeal; csDMARDs=conventional synthetic Disease Modifying Anti Rheumatic Drugs; OA=osteoarthritis

In order to understand whether the differences between sustained MDA and non-sustained MDA were real, and not random, we also compared patients reaching MDA at least once with those never reaching MDA (*Table 3*), and patients reaching MDA in all evaluations with those not reaching MDA at least once (*Table 4*).

Table 3. Comparison between patients fulfilling MDA at least once and those never fulfilling MDA criteria

Variables	MDA ever	MDA never	p-value
Number of patients	79	25	
Males	45 (57)	12 (48)	0.43
Age (years)	54.3±15.9	59.9±10.8	0.13
Disease characteristics:			
Disease duration (years)	16.6±9.5	15.6±10.0	0.54
Family history of psoriasis or PsA	30 (37)	8 (33)	0.68
Peripheral arthritis, ever	71 (89)	24 (96)	0.34
Dactylitis, ever	26 (33)	5 (20)	0.20
Enthesitis, ever	**56 (71)**	**25 (100)**	**0.002**
Axial involvement (axPsA), ever	**36 (46)**	**18 (72)**	**0.024**
DIP involvement, ever	35 (44)	18 (52)	0.50
Tenosynovitis, ever	**35 (62)**	**13 (92)**	**0.005**
Nail disease, ever	55 (70)	16 (64)	0.59
Body Surface Area (BSA) (1-100%) at baseline	0.6±0.8	1.3±2.9	0.26
Psoriasis Activity and Severity Index (PASI) (0-72) at baseline	0.9±1.3	1.4±2.7	0.26
Patient Global Assessment (PGA) at baseline (0-10)	**3.0±2.0**	**6.3±1.4**	**<0.0001**
Physician Global Assessment (PhGA) at baseline (0-10)	**1.9±1.5**	**4.6±1.6**	**<0.0001**
Visual Analogue Scale of pain (VASp) at baseline (0-10)	**2.7±1.9**	**6.5±1.4**	**<0.0001**
Health Assessment Questionnaire (HAQ) at baseline (0-3)	**0.2±0.3**	**1.1±0.4**	**<0.0001**
C- Reactive Protein (CRP) at baseline, mg/L	4.1±4.2	4.7±3.4	0.30
Disease Activity of Psoriatic Arthritis (DAPSA) score at baseline	**10.5±6.4**	**21.5±5.8**	**<0.0001**
Leeds enthesitis Index (LEI) at baseline	0.2±0.6	0.4±0.8	0.19
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at baseline	0.38±1.23	2.40±3.86	0.008
Body Mass Index (cm/m2)	26.5± 4.1	29.3±6.9	0.10
Body Mass Index (cm/m2)≥35	**6 (2)**	**4 (16)**	**0.012**
Current smokers	10 (13)	1 (4)	0.21
Comorbidities:			
Inflammatory bowel disease	1 (1)	1 (4)	0.38
Fibromyalgia	**2 (2)**	**10 (40)**	**<0.0001**
Symptomatic OA of hands, knees, hip or spine	**10 (8)**	**44 (23)**	**<0.0001**
Modified Rheumatic Diseases Comorbidity Index (mRDCI)	**1.2±1.4**	**2.1±1.8**	**0.008**
Concomitant csDMARDs at baseline	16 (20)	6 (24)	0.68

Legend. Continuous data are presented as mean±standard deviation or median (interquartile range) according to their distribution. Categorical data are presented as number (percentage). Significant results are indicated in bold. DIP=distal interphalangeal; csDMARDs=conventional synthetic Disease Modifying Anti Rheumatic Drugs; OA=osteoarthritis.

In patients never reaching MDA (*Table 3*), the percentage of males was lower, albeit not significantly. Similarly, to the previous analysis, the percentage of patients with PsA was higher in the group never reaching MDA, and in addition these patients more frequently had enthesitis and tenosynovitis. The mRDCI was significantly higher in patients never reaching MDA, as well as baseline disease activity scores (PGA, PhGA, VASp, HAQ, DAPSA, SPARCC). Grade II obesity, fibromyalgia and OA were also more frequent in the patients never reaching MDA.

Patients reaching MDA in all evaluations (persistent MDA, *Table 4*) were more frequently male and less frequently had axPsA and tenosynovitis. All of them had peripheral arthritis. Again, already at baseline disease activity indices were higher in the group with non-persistent MDA (PGA, PhGA, VASp, HAQ, CRP, DAPSA, SPARCC; LEI borderline significant). None of the patients with fibromyalgia or grade II obesity belonged to this group. Less patients with OA were included in the group with persistent MDA compared with patients that did not reach MDA at least once (non-persistent MDA): this difference was borderline significant.

Table 4. Comparison between patients fulfilling MDA in all evaluations and those that did not meet, at least once, criteria for MDA

Variables	Persistent MDA	Non-persistent MDA	p-value
Number of patients	30	74	
Males	**22 (73)**	**35 (47)**	**0.016**
Age (years)	53.1±11.6	56.7±16.2	0.25
Disease characteristics:			
Disease duration (years)	17.2±9.1	16.0±9.9	0.44
Family history of psoriasis or PsA	10 (33)	28 (38)	0.63
Peripheral arthritis, ever	**30 (100)**	**65 (87)**	**0.046**
Dactylitis, ever	9 (30)	22 (30)	0.99
Enthesitis, ever	21 (70)	60 (81)	0.21
Axial involvement (axPsA), ever	**11 (37)**	**43 (59)**	**0.04**
DIP involvement, ever	18 (60)	30 (40)	0.07
Tenosynovitis, ever	**16 (53)**	**56 (75)**	**0.025**
Nail disease, ever	24 (80)	47 (63)	0.10

Body Surface Area (BSA) (1-100%) at baseline	0.5±0.7	0.9±1.9	0.41
Psoriasis Activity and Severity Index (PASI) (0-72) at baseline	0.7±1.0	1.1±1.9	0.37
Patient Global Assessment (PGA) at baseline (0-10)	**2.4±1.8**	**4.4±2.2**	**<0.0001**
Physician Global Assessment (PGA) at baseline (0-10)	**1.2±1.0**	**3.1±1.9**	**<0.0001**
Visual Analogue Scale of pain (VASp) at baseline (0-10)	**2.0±1.6**	**4.3± 2.4**	**<0.0001**
Health Assessment Questionnaire (HAQ) at baseline (0-3)	**0.22±0.31**	**1.07±0.37**	**<0.0001**
C- Reactive Protein (CRP) at baseline, mg/L	**2.9±0.81**	**4.8±4.6**	**0.004**
Disease Activity of Psoriatic Arthritis (DAPSA) score at baseline	**7.4±3.4**	**15.5±7.9**	**<0.0001**
Leeds enthesitis Index (LEI) at baseline	***0.03±0.18***	***0.31±0.80***	***0.051***
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at baseline	**0.13±0.43**	**1.16±2.68**	**0.03**
Body Mass Index (cm/m2)	25.9±4.0	27.6±5.3	0.25
Body Mass Index (cm/m2)≥35	**0 (0)**	**6 (8)**	**0.10**
Current smokers	9 (7)	2 (12)	0.54
Comorbidities:			
Inflammatory bowel disease	0 (0)	2 (3)	0.36
Fibromyalgia	**0 (0)**	**12 (16)**	**0.019**
Symptomatic OA of hands, knees, hip or spine	***2 (7)***	***17 (23)***	***0.051***
Modified Rheumatic Diseases Comorbidity Index (mRDCI)	1.1±1.3	1.5±1.6	0.40
Concomitant csDMARDs at baseline	3 (10)	29 (25)	0.07

Legend. Continuous data are presented as mean±standard deviation or median (interquartile range) according to their distribution. Categorical data are presented as number (percentage). Significant results are highlighted in bold. Results close to statistical significance are indicated in bold and italics. DIP=distal interphalangeal; csDMARDs=conventional synthetic Disease Modifying Anti Rheumatic Drugs; OA=osteoarthritis

In the multivariable GEE model having MDA as outcome, we found that age, PsA, fibromyalgia, OA, BMI≥35 were negative independent predictors of MDA. On the contrary, bDMARDs therapy duration was positively associated to the outcome.

Table 5. Multivariable mixed model (Generalized Estimating Equations) of MDA predictors

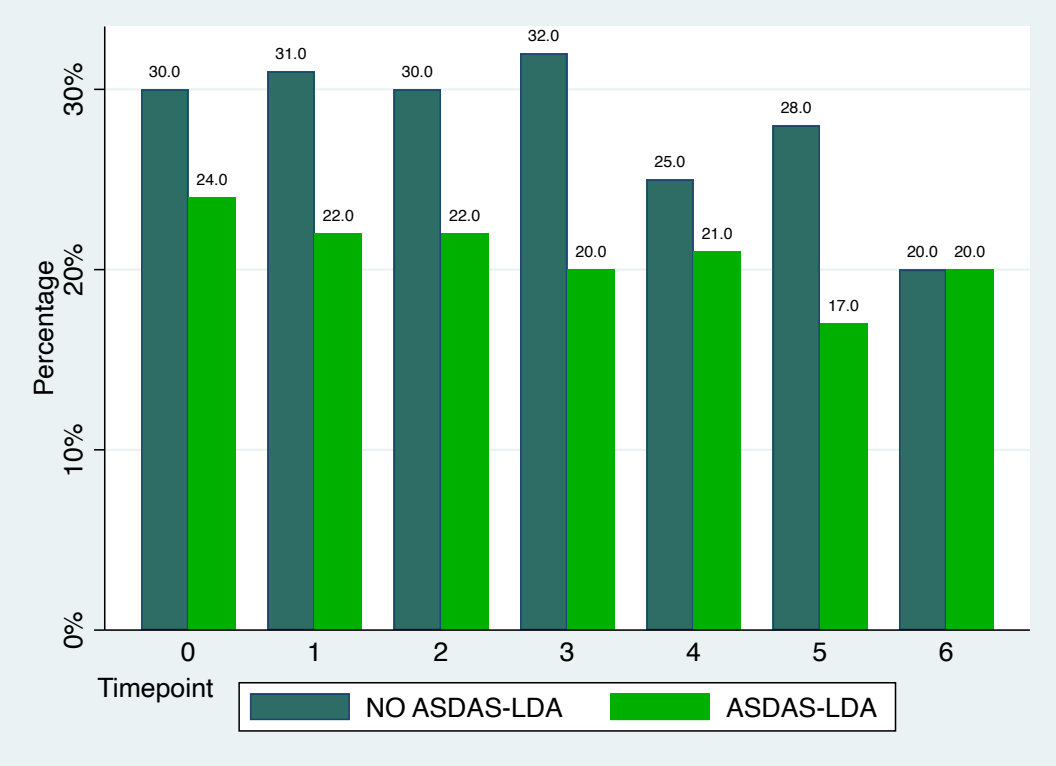
Independent Variables	Beta	Standard error	95% Confidence Interval	p-value
Male gender	0.11	0.41	–0.69 - –0.92	0.78
Age	**–0.05**	**0.01**	**–0.09- –0.02**	**0.001**
bDMARDs duration	**0.31**	**0.00**	**0.00- 0.02**	**0.007**
Axial involvement	**–1.07**	**0.38**	**–1.82 - –0.33**	**0.005**
Tenosynovitis	–0.82	0.51	–1.84 - –0.15	0.09
Fibromyalgia	**–3.35**	**0.89**	**–5.09 - –1.61**	**<0.001**
OA	**–1.87**	**0.61**	**–3.07 - 0.66**	**0.002**
BMI≥35	**–2.53**	**0.89**	**–4.27- –0.79**	**0.004**
mRDCI	0.02	0.16	–0.30 - 0.33	0.91

Legend. bDMARDs=biological Disease Modifying Anti Rheumatic Drugs; BMI= Body Mass Index; mRDCI=modified Rheumatic Diseases Comorbidity Index

Axial involvement

In the 54 patients who had axSpA, a percentage of patients ranging from 17% to 24% across all timepoints managed to reach ASDAS-LDA (*Figure 3*). From baseline to t6, a proportion of axPsA patients between 13% and 15% was also in MDA.

Figure 3. Percentages of patients reaching ASDAS-LDA at each timepoint among patients with axial involvement



Legend. ASDAS-LDA=ASDAS Low Disease Activity; numbers above columns represent percentages

We analyzed difference between patients who reached sustained ASDAS-LDA, and those who did not (*Table 6*). The former was more frequently male, had less often a family history of psoriasis or psoriatic arthritis, and had, already at baseline, higher disease activity indices (PGA, PhGA, VASp, HAQ, CRP, DAPSA, SPARCC) than the latter. Fibromyalgia and OA were significantly more frequent in the group with non-sustained ASDAS-LDA: actually, none of the patients having these comorbidities belonged to the group with sustained ASDAS-LDA. The difference between the percentage of patients with BMI≥35 was not significant between the 2 groups, but only 3 of the patients with axial

involvement also had grade II obesity, and none of them was in the group with sustained MDA.

Table 6. Sub-analysis in patients with axial involvement; comparison between patients reaching sustained ASDAS-LDA (low disease activity in at least 4 evaluations), or not

Variables	Sustained ASDAS-LDA	Non-Sustained ASDAS-LDA	p-value
Number of patients	18	36	
Males	**14 (78)**	**14 (39)**	**0.007**
Age (years)	53.3±17.2	57.9±12.4	0.09
Disease characteristics:			
Disease duration (years)	16.8±9.5	16.0±9.8	0.63
Family history of psoriasis or PsA	**3 (17)**	**16 (44)**	**0.044**
Peripheral arthritis, ever	16 (89)	32 (89)	1.00
Dactylitis, ever	6 (33)	10 (28)	0.72
Enthesitis, ever	15 (83)	32 (89)	0.56
Axial involvement (axPsA), ever	18 (100)	36 (100)	N/A
DIP involvement, ever	12 (67)	16 (44)	0.12
Tenosynovitis, ever	15 (83)	30 (83)	1.00
Nail disease, ever	14 (77)	26 (72)	0.66
Body Surface Area (BSA) (1-100%) at baseline	0.7± 0.9	0.8±2.1	0.97
Psoriasis Activity and Severity Index (PASI) (0-72) at baseline	0.9±1.4	1.1±2.0	0.99
Patient Global Assessment (PGA) at baseline (0-10)	**2.3±1.6**	**5.3±1.9**	**<0.0001**
Physician Global Assessment (PGA) at baseline (0-10)	**1.4±1.1**	**3.7±1.8**	**<0.0001**
Visual Analogue Scale of pain (VASp) at baseline (0-10)	**2.0±1.5**	**5.1±2.1**	**<0.0001**
Health Assessment Questionnaire (HAQ) at baseline (0-3)	**0.1±0.2**	**0.7±0.5**	**<0.0001**
C- Reactive Protein (CRP) at baseline, mg/L	**3.5±1.9**	**5.0±5.2**	**0.018**
Disease Activity of Psoriatic Arthritis (DAPSA) score at baseline	**8.1±4.0**	**18.1±7.4**	**<0.0001**
Leeds enthesitis Index (LEI) at baseline	0.10±0.36	0.36±0.9	0.08
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at baseline	**0.17±0.47**	**1.55±3.10**	**0.01**
Body Mass Index (cm/m2)	26.5±4.1	27.8±5.8	0.36
Body Mass Index (cm/m2)≥35	0 (0)	3 (8)	0.20
Current smokers	3 (17)	3 (8)	0.30
Comorbidities:			
Inflammatory bowel disease	1 (5)	1 (3)	0.61
Fibromyalgia	**0 (0)**	**10 (28)**	**0.013**
Symptomatic OA of hands, knees, hip or spine	**0 (0)**	**11 (30)**	**0.009**
Modified Rheumatic Diseases Comorbidity Index (mRDCI)	1.2±1.3	1.6±1.7	0.21
Concomitant csDMARDs at baseline	4 (22)	8 (22)	1.00

Legend. Continuous data are presented as mean±standard deviation or median (interquartile range) according to their distribution. Categorical data are presented as number (percentage)
DIP=distal interphalangeal; csDMARDs=conventional synthetic Disease Modifying Anti Rheumatic Drugs

The multivariable model having ASDAS-LDA as an outcome showed that fibromyalgia, and OA were negative independent predictors of MDA. On the contrary, bDMARDs therapy duration was positively associated to the outcome, like in the model for MDA.

Table 7. Multivariable mixed model (Generalized Estimating Equations) of ASDAS-LDA predictors

Independent Variables	Beta	Standard error	95% Confidence Interval	p-value
Male gender	0.46	0.36	–0.25- 1.17	0.20
Age	–0.01	0.01	–0.04- 0.01	0.14
bDMARDs duration	**0.01**	**0.00**	**–0.00- 0.02**	**0.05**
Tenosynovitis	–0.37	0.41	–1.18- 0.43	0.36
Fibromyalgia	**–2.03**	**0.75**	**–3.50- –0.56**	**0.007**
OA	**–1.30**	**0.50**	**–2.29- –0.31**	**0.010**
BMI≥35	–1.51	0.84	–3.16- –0.12	0.07
mRDCI	0.02	0.15	–0.28- –0.33	0.89

Legend. bDMARDs=biological Disease Modifying Anti Rheumatic Drugs; BMI= Body Mass Index; mRDCI=modified Rheumatic Diseases Comorbidity Index

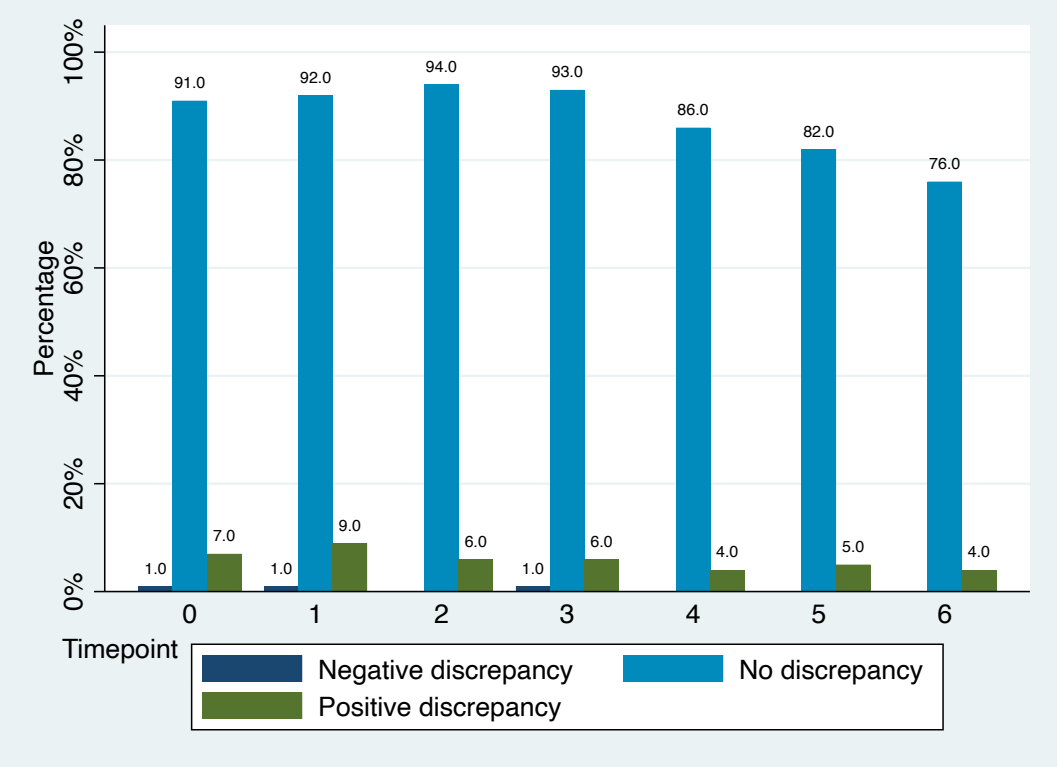
Patient-physician discrepancy

The difference (delta) between PGA and PhGA (both on a 0-10 scale) was calculated and, according to previous literature, a discrepancy was considered to be present if delta was≥3. The discrepancy was defined as positive if the patient rated higher than physician, and negative if the physician rated higher than patients. Based on this definition, we found that, across all patients and all evaluations (n=658 evaluations), in 1.2 % of cases there was a negative discrepancy, in 13.4% there was a positive discrepancy, while in 85.4% of cases patients rated approximately equal than their physicians.

When considering as discrepant a delta≥2, in 2.5 % of cases there was a negative discrepancy, in 32.2 % there was a positive discrepancy, while in 65.3 % of cases patients rated approximately equal than their physicians.

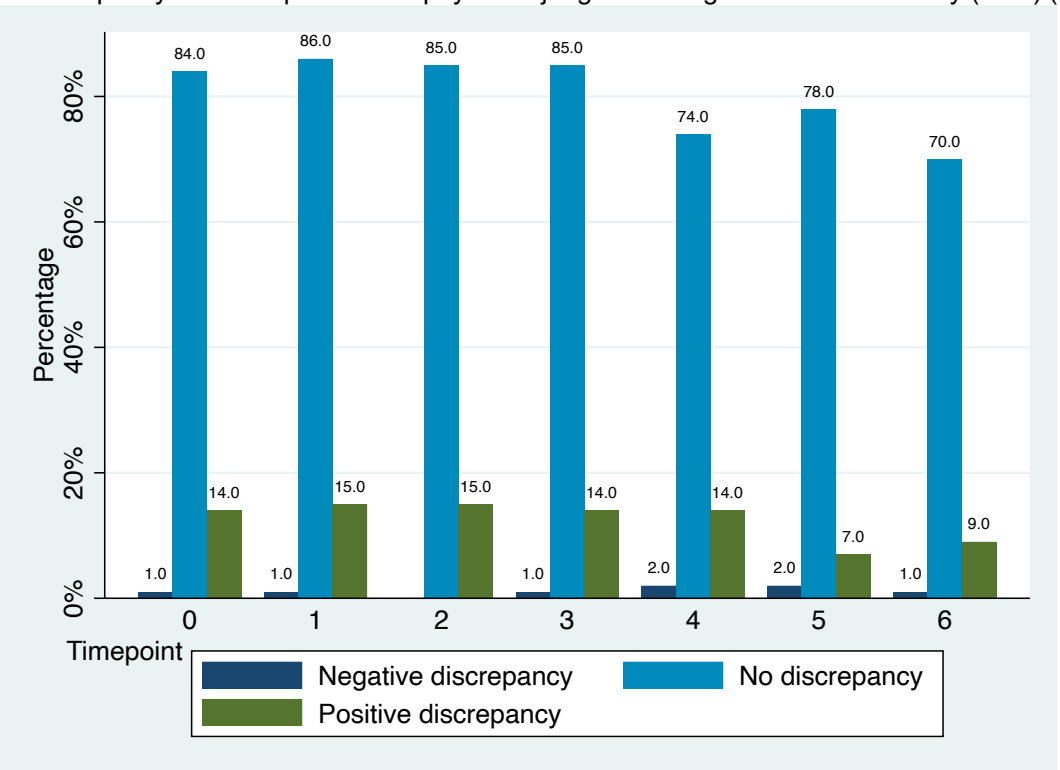
Across all evaluations, the prevalence of a positive discrepant judgement with a delta≥3 was very low, ranging between 4% and 7% (*Figure 4*)

Figure 4. Discrepancy between patient and physician judgement of global disease activity (0-10) (delta≥3)



The prevalence of discrepant judgement with a lower threshold was more frequent but still rather low, with a positive discrepancy regarding 9-14% of the patients (*Figure 5*).

Figure 5. Discrepancy between patient and physician judgement of global disease activity (0-10) (delta≥3)



Patient-physician positive discrepancy with a delta≥3 was significantly less frequent in patients with sustained vs non-sustained MDA (8% vs 21%, p<0.0001), as well as in patients with sustained ASDAS-LDA vs non-sustained ASDAS-LDA (5% vs 23%, p<0.0001). Besides, discrepancy was more frequent in patients with axPsA vs non-axPsA (62% vs 37%, p=0.033).

Patient-physician positive discrepancy with a delta≥2 was also less frequent in patients with sustained vs non-sustained MDA (25% vs 42%, p<0.0001), and in patients with sustained ASDAS-LDA vs non-sustained ASDAS-LDA (20% vs 47%, p<0.0001). Even in this case, discrepancy was more frequent in patients with axPsA vs non-axPsA (61% vs 38%, p=0.001).

In the multivariable Cox regression model with time-to-switch as outcome, a positive discrepancy with delta≥3 was associated to a higher hazard of switching (HR 1.44, 95%CI 1.12-1.85, corrected for age and gender). A positive discrepancy with delta≥2 was also associated to a higher hazard of switching albeit less strongly (HR 1.21, 95% CI 1.01-1.46, corrected for age and gender).

Discussion

This study showed that, in a real-life cohort of PsA patients in stable therapy with bDMARDs at baseline, MDA is an attainable goal, with more than half of the patients achieving this target across all evaluations. PsA patients with axial involvement experience less frequently a state of low disease activity according to indices developed for axSpA (ASDAS-LDA). In addition, axial involvement is negatively associated to MDA achievement over time. Fibromyalgia and symptomatic OA of the spine, knee, hand or hip are negatively associated to both MDA and ASDAS-LDA, while obesity seems to play an important role only when severe (BMI≥35), and more for MDA than ASDAS-LDA.

Recommendations about PsA management clearly state that treatment should be aimed at remission or, alternatively, low disease activity, and that this should be achieved by regular disease activity assessment and adjustment of therapy (11). However, although this is certainly an ideal situation, in clinical practice a true remission might be difficult to obtain. First of all, there is no agreed definition of “remission” for psoriatic arthritis: certainly one of the main difficulties lies in the multi-dimensionality of the disease, with several involved domains (joints, skin, enthesis, dactylitis, axial disease) (41). However, this is not the only problem that prevents remission definitions: composite scores do exist, but not all experts agree on the fact that these represent the best way to assess PsA (42). In fact, some argue that composite scores might miss non-response to therapy of a certain domain, as a good response in one dimension can ‘compensate’ for a bad one in another dimension. On the other hand, the risk of grading all domains separately is missing an overall picture of the disease (42). This being said, in our study we examined two multidimensional definitions (MDA and VLDA) that could reflect a state of low residual disease activity: while MDA was achieved fairly frequently, already using the VLDA criteria substantially lowered the percentage of patients (less than 20%) that could reach the

target. Yet none of the 2 definitions truly indicates remission, therefore the first observation is that probably, in clinical practice, MDA or VLDA represent a more realistic target than a complete absence of the disease in all domains. Our data are in line with those presented by Lubrano et al, indicating that sustained VLDA was achieved by 17% of patients, while at least once from 25% of patients (43). Thus, the ideal target could be VLDA, but since it is not achieved so frequently, we deemed important to focus on MDA, and especially sustained MDA, which has been proved to be associated to improved quality of life and possibly also less radiographic progression (12). In addition, MDA is associated to less disease burden than other low disease activity definition (44), so it seems an appropriate target.

Sustained MDA, in our study, was more frequent in males than females, although male gender did not represent *per se* and independent predictor for sustained MDA. This is in agreement with a previous real-life study in PsA by our group, where we demonstrated that male gender favored retention rate, but it was not an independent predictor of MDA in patients treated with secukinumab (45). A similar result was highlighted by another study in PsA, where female sex was an independent risk factor for switching (46). This is not surprising, as male patients have already been described to have a better response to treatment than females, even in RCTs, at least as far as peripheral PsA is concerned (47). Although the characteristics of the disease might be similar between men and women, it has been noted that female patients present with higher levels of pain, fatigue, and worse quality of life (47).

Independent negative predictors of MDA over time were instead age, axPsA, fibromyalgia, OA and BMI≥35. Among these, fibromyalgia is certainly well-known as a factor impairing response to treatment (40,48), while OA has less frequently been studied as an obstacle to MDA, despite being a frequent comorbidity (49). The challenge derives by the difficulty in discriminating OA from PsA long-term structural outcomes. In our study, we defined the

presence of symptomatic OA both based on the physician's diagnosis and on available X-rays that could demonstrate typical OA changes (e.g. osteophytes). Obviously, this method has some shortcomings: OA prevalence might have been over estimated by this method, e.g if physicians attributed to OA some of the PsA symptoms. However, the negative association shown between OA and MDA suggests that patients who are thought to have OA symptoms by their physicians are certainly at risk of not achieving MDA, and probably represent a specific population of interest where more efforts should be made to actually establish the causes of symptoms. As far as obesity is concerned, this condition is known to lower the response to bDMARDs and to be associated with a lower chance of sustained MDA with a dose-dependent response (50,51). In our analysis, we confirm a negative association with sustained MDA for BMI≥35, which represents grade II obesity, and indeed is more likely to represent a limiting factor than lower grades of obesity. A novelty of our study, that takes into consideration patients in stable therapy, differently from most studies in the literature, is that we found a positive association between length of bDMARDs therapy at baseline and sustained MDA. This is probably indication that patients who are in MDA from a long time (this is supposedly the reason why they maintained the same therapy) are not at a higher risk of flare, but on the contrary, are likely to maintain their state.

Axial disease deserves a separate consideration: the first observation is that it clearly represents an independent negative predictor for sustained MDA. Although it has been found that MDA is an achievable target also for axPsA patients (16), this does not exclude that axPsA patients might be a more difficult-to treat population. Already the fact that axPsA patients achieved MDA in a much lower percentage of cases (13-15% at each timepoints) compared to the whole group of PsA patients (50-61%) is an important indication. Furthermore, when looking at a specifically axial outcome such as ASDAS-LDA, this was reached only by about 20% of patients at each timepoint, underlining that this

manifestation might represent an important additional burden for patients. In fact, a study conducted within the Corevitas' Psoriatic Arthritis/Spondyloarthritis Registry, has found that Patients with self-reported axial symptoms had worse quality of life and higher disease activity than those without (52). In addition, in a previous study by our group, we found that patients with axSpA and psoriasis had a different phenotype than the typical axSpA patients, with less frequent HLA-B27+, radiographic sacroiliitis with a unilateral/asymmetric pattern, and more signs of spondylitis (28). These patients also presented with higher patient reported outcomes. However, since an official definition of axPsA and specific treatment paradigms, are still lacking, the treatment of this condition poses many challenges to the rheumatologist (53).

An interesting issue is also the discrepancy that can be sometimes detected between patient and physician judgement (25). When present, this discrepancy most frequently concerns patients rating higher their disease than physicians, as described in literature (54). The factors underlying this phenomenon seem to be mostly fatigue and pain, and to be more frequent for patients in remission than those in high disease activity (55). Also in our study, a positive discrepancy (patients rating higher than physicians) was seen more frequently in patients who did not manage to achieve the treatment targets (both MDA and ASDAS). Interestingly, a positive discrepancy was more frequent in axPsA, again suggesting that therapy does not entirely target patients' symptoms. Previous studies in rheumatoid arthritis found that a persistently high patient rating causes worse health related quality of life, work productivity and activity impairment over time (56). This is certainly concerning, but in addition to this, it would also be important to understand whether these discrepancies might cause patients to be undertreated. As an example, physicians might delay switch of an ineffective therapy because they rate the disease lower compared with the patients. However, in our study, a positive discrepancy was, on the contrary, associated to a higher risk of switching. This might simply indicate that

patients who have a discrepant judgement present with more pain, thus physicians could be more prone to change therapy, but at least suggests that a different score on global assessment does not necessarily mean undertreatment. The problem of patient-physician discrepancy is not, however, to be underestimated, as it can be a sign of active clinical issues that need attention.

The present study certainly has limitations concerning the physician-driven definition of some conditions, such as “symptomatic osteoarthritis” or “axPsA”, which could have caused to observe associations with the outcomes, that might not be reproducible if a different definition is applied. However, we do not have, at present, a consensus definition for axPsA, while OA is undoubtedly a frequent comorbidity in PsA and given the observed overall frequencies, it is unlikely it has been overestimated in this work. On the other hand, the strengths of this study are the inclusion of a real-life PsA patients, with a similar age, disease duration and comorbidity prevalence to the usual clinical practice, and the longitudinal observation up to 3 years.

In conclusion, MDA is an attainable target in PsA, and its achievement is influenced by both disease characteristics, such as axial involvement, and patient comorbidities, especially rheumatic concomitant conditions such as OA and fibromyalgia. Axial disease seems to represent a difficult-to-treat subset, with lower rates of target achievement and more frequent discrepancy between patient and physician evaluations.
Future studies are needed to confirm these results, and to better define axial involvement in psoriatic arthritis, in order to improve its detection and management.

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