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Treat-to-target in real-life psoriatic arthritis patients: achieving minimal disease activity with bDMARDs/tsDMARDs and potential barriers

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ABSTRACT

Objective: (1) to describe the frequency of minimal disease activity (MDA) in a real-life psoriatic arthritis (PsA) cohort, (2) to longitudinally explore predictors of MDA; (3) to examine frequency and predictors of low disease activity (LDA) in patients with axial involvement (axPsA).

Methods: consecutive PsA patients in stable biological/targeted-synthetic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs/tDMARDs) who attended our center were enrolled. Disease activity indices, including MDA and ankylosing spondylitis disease activity score-LDA (ASDAS-LDA) for axPsA, were evaluated at baseline and every 6 months, up to 36 months or bDMARDs/tsDMARDs discontinuation. Patients' history, BMI, comorbidities — including osteoarthritis (OA) and fibromyalgia — were collected. Variables were compared between patients who achieved 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 beta coefficient (95%CI).

Results: 104 patients were enrolled, 54% males, mean age 55.7 years; 52% had axPsA. Across all evaluations, 52–61% reached MDA, and 17–24% achieved ASDAS-LDA. AxPsA, fibromyalgia, OA and BMI≥35 were less frequently observed in patients with sustained MDA. The GEE model confirmed the following factors were significantly and independently associated with MDA: age (Beta=–0.05), bDMARDs/tsDMARDs duration (Beta=+0.31), axPsA (Beta=–1.07), fibromyalgia (Beta=–3.35), OA (Beta=–1.87), BMI≥35 (Beta=–2.53). Age (Beta=–0.01), fibromyalgia (Beta=–2.03) and OA (Beta=–1.30) were also independently associated with ASDAS-LDA.

Conclusions: MDA is an attainable target in real-life. AxPsA represents a difficult-to-treat subset. Sustained MDA depends on disease features (axPsA) as well as patients' characteristics (e.g. age, bDMARDs/tDMARDs duration, comorbidities).

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease with very heterogeneous manifestations, including (but not limited to) peripheral arthritis, axial involvement, tenosynovitis, enthesitis, dactylitis, psoriasis, nail disease [1]. Given the wide clinical spectrum of PsA, it has been difficult to develop a comprehensive disease activity index able to capture ongoing activity in all domains, and define remission [2]. Hence the importance of minimal disease activity (MDA), a commonly used goal in PsA treatment and management [3]. 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 [3]. Its clinical relevance become evident after the TIght Control in Psoriatic Arthritis (TICOPA) trial showed that applying a treat-to-target strategy aimed at achieving MDA could improve PsA outcomes [4]. Based on these findings, along with the

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increased availability of effective therapies, international recommendations were formulated to advocate that the target of treatment in PsA be remission or, alternatively, low disease activity [5,6]. In a randomised controlled trial (RCT) of golimumab, MDA was achieved by approximately half of the patients at least once over a 5-year period [7]. However, what really seems to matter for long-term outcomes is not only reaching MDA at a certain timepoint, but being in a stable MDA state. In fact, patients who sustained MDA throughout 3 or 4 consecutive follow-up visits, achieved better functional improvement, patient global assessment, and radiographic outcomes [7]. 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.

In addition, the impact of the axial component of PsA (axPsA) on MDA achievement has rarely been studied. This partly depends on the fact that a clear definition of axPsA is still lacking [8]. In fact, features of axPsA can be complex and different from axial spondyloarthritis (axSpA): they include spinal involvement with unilateral sacroiliitis, delayed appearance of radiographic sacroiliitis, and possible low level of symptoms indicative of spinal involvement [8]. Nonetheless, axPsA is currently evaluated using indices borrowed from axSpA, such as the ankylosing spondylitis disease activity score (ASDAS) [9]. States of inactive disease and low disease activity (ASDAS-ID, ASDAS-LDA) have also been defined for ASDAS [10,11], and are increasingly considered as desirable treatment targets for axSpA [12].

Therefore, the primary aims of our study were:

(1) to evaluate the frequency of MDA achievement in a real-life PsA population undergoing stable bDMARDs/tsDMARDs treatment, during a three-year follow up
(2) to ascertain characteristics associated with 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 undergoing stable bDMARDs/tsDMARDs treatment, during a three-year follow-up
(2) to find characteristics associated with sustained ASADAS-LDA and predictors of ASDAS-LDA over time in a longitudinal cohort

Materials and methods

Design of the study

We conducted a longitudinal study in a cohort of consecutive adult PsA patients (aged≥18 years), diagnosed by a rheumatologist and fulfilling classification criteria for psoriatic arthritis (CASPAR) [13], attending the SpA Clinic of the Rheumatology Unit of Padova University Hospital between January and December 2018. At baseline, to be eligible for the study, patients had to be undergoing stable therapy with bDMARDs/tsDMARDs for at least 6 months, regardless of drug choice. Combination treatment with csDMARDs at a stable dose in the last 12 months was not an exclusion criteria. We excluded all patients treated with only csDMARDs or NSAIDs. Approval for the study was obtained from our institutional Ethics Committee [Azienda Ospedaliera di Padova (n. 52,723)], and all participants provided informed consent according to the principles of the Declaration of Helsinki. Our entire cohort was prospectively followed up every 6 months, for up to 36 months (T 0, 1,2, 3,4,5,6), or until bDMARDs/tsDMARDs 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/tsDMARDs therapy, they continued to be followed up and we recorded the number of following switches.

Variables of interest

At baseline, the following variables were collected:

- Demographic and lifestyle variables such as age, sex, smoking status (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 axPsA, nail disease ever), previous csDMARDs and bDMARDs/tsDMARDs therapies
- Axial involvement; this was considered to be present if all of the following conditions were met: (1) positive rheumatologist opinion (2) history of inflammatory back pain lasting at least 3 months, (3) recorded signs of Inflammation or structural changes at MRI and/or X-rays of the pelvis and of the spine (e.g. bone marrow edema at vertebral corner or SIJ; syndesmophytes/ pseudo-syndesmophytes or radiographic sacroiliitis)
- Comorbidities, including chronic comorbidities comprised in the modified Rheumatic Disease Comorbidity Index (mRDCI) [14], 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 time-points, 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) [15].
- Axial disease activity: ASDAS, calculated with the preferred version using C-Reactive Protein (CRP) [16,17].
- Skin disease activity: Body Surface Area (BSA), Psoriasis Area and Severity Index (PASI) [18].
- Enthesitis scores: Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada score (SPARCC) [19,20].
- Quality of life: Health Assessment Questionnaire (HAQ) [21].
- Low disease activity/remission criteria: MDA and very low disease activity (VLDA); ASDAS-LDA if axPsA was present [7,10,11].

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

Statistical analysis

Baseline disease characteristics of patients in different MDA states were compared using descriptive statistics: Chi square or Fisher's 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 achieving sustained MDA or not; (2) patients never achieving MDA vs. patients achieving MDA at least once; (3) patients always achieving MDA vs. patients not achieving MDA at least once; (4) patients achieving 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 time-point. 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) [22–24]. Results were expressed as beta coefficient and 95% confidence intervals (95%CI)

Analyses were conducted with STATA v.17 (Copyright 1985–2019 StataCorp LLC, College Station, Texas 77,845 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. All patients were treated with bDMARDs or tsDMARDs, 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-IL12/23 (10%), while a minority were treated with tsDMARDs (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.

Table 1
Baseline patients' characteristics.

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)	0.4±0.5
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)	0.2 ± 0.7
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index	0.9±2.3
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.

Targets of treatment over time

Across all evaluations, a percentage of patients ranging from 52% to 61% reached MDA (Fig. 1A), while a percentage between 12 and 20% reached VLDA (Fig. 1B). The less frequently fulfilled domains of MDA to were VASp, PGA and, to a lesser extent, HAQ (Supplementary Table 1).

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. In order to understand whether the differences between sustained MDA and non-sustained MDA were real and consistent, we also compared patients reaching MDA at least once with those never reaching MDA, and patients reaching MDA in all evaluations with those not reaching MDA at least once (*Supplementary Tables 2,3*).

These sub-analyses confirmed the differences seen in gender, baseline disease activity score (higher proportion of males, lower disease activity indices, lower frequency of axPsA, obesity, fibromyalgia and OA in those with a favourable MDA status).

In the multivariable GEE model having MDA as outcome (Table 3), we found that age, PsA, fibromyalgia, OA, BMI^{3}35 were independent negative predictors of MDA. On the contrary, bDMARDs/tsDMARDs therapy duration was positively associated with the outcome.

Axial involvement

Among 54 patients who had axPsA, an estimated 17% to 24% across all time-points managed to achieve ASDAS-LDA (Fig. 1C). From baseline to T6, a proportion of axPsA patients between 13% and 15% was also in MDA.

We analysed the difference between patients who achieved sustained ASDAS-LDA, and those who did not (Table 4). 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^{3}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. The multivariable model having ASDAS-LDA as an outcome (Table 5) showed that fibromyalgia, and OA were independent negative predictors of MDA. On the contrary, bDMARDs/tsDMARDs therapy duration was positively associated with the outcome, like in the model for MDA.

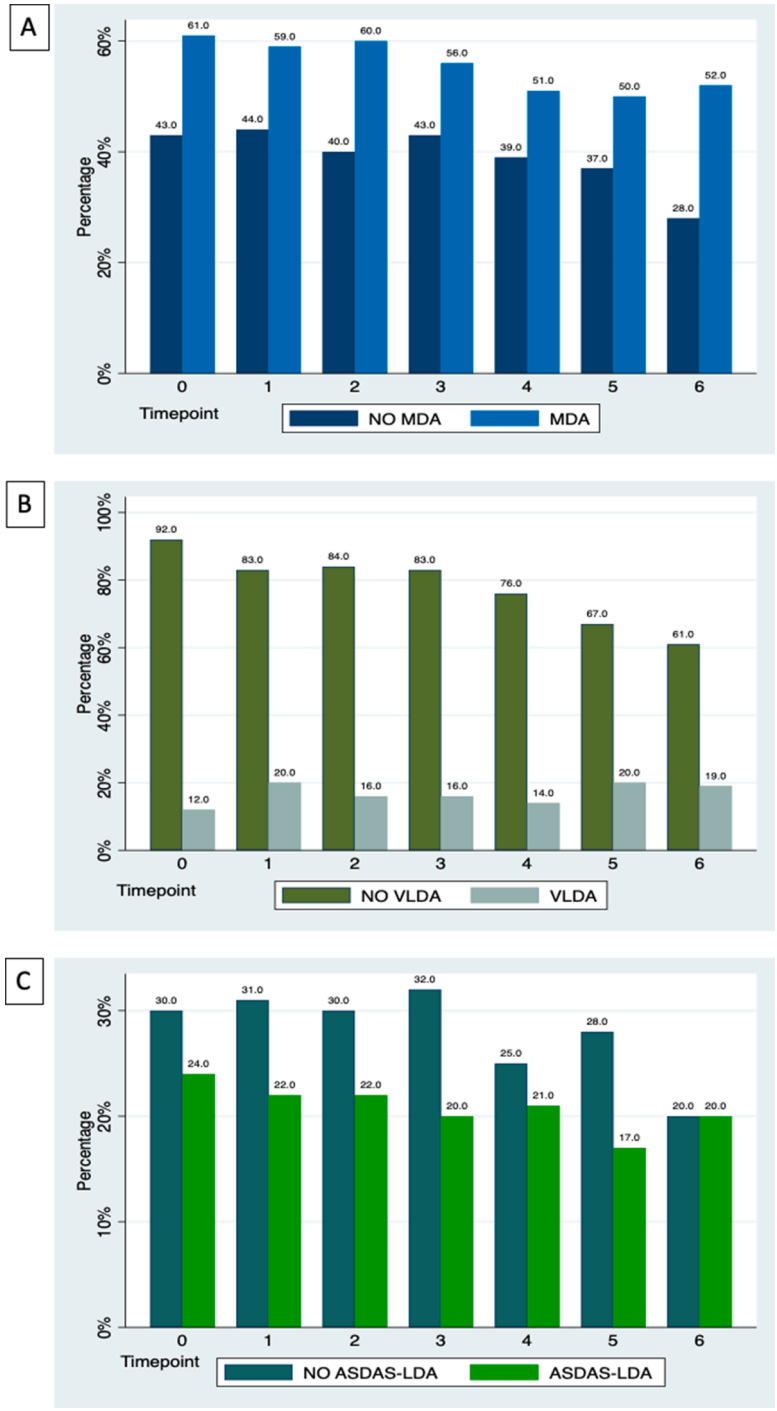

Fig. 1. Percentages of psoriatic arthritis ($n = 104$) patients who achieved minimal disease activity (MDA) (A) and very low disease activity (VLDA) (B) at each time-point. In patients with axial involvement ($n = 54$), percentages of patients who achieved ASDAS-LDA at each time-point are also shown (C).

Discussion

Our study showed that MDA is an attainable goal in a real-life cohort of PsA patients undergoing stable treatment with bDMARDs/tsDMARDs at baseline, with over 50% of patients achieving MDA across all evaluations during a three-year follow up. PsA patients with axial involvement less frequently experienced a state of low disease activity according to indices developed for axSpA (ASDAS-LDA). In addition, axial involvement is negatively associated with MDA achievement over time. Fibromyalgia and symptomatic OA of the spine, knee, hand or hip are negatively correlated with both MDA and ASDAS-LDA, whereas obesity appears to play an important role only when severe (BMI≥35), and more on MDA than ASDAS-LDA.

Recommendations about PsA management clearly state that treatment should be aimed at remission or, alternatively, low disease activity [5,6]. Although this would be an ideal outcome, true remission might be difficult to achieve and measure in clinical practice for the following reasons: i) there is no agreed definition of remission in PsA; ii) the multi-dimensionality of the disease may hamper the achievement of actual remission; iii) not all experts agree that current composite scores are the best way to assess PsA [25], as theoretically, a good response in one domain could compensate for a poor response in another domain.

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	0.3±1.3	1.4±3.0	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.

Table 3
Multivariable mixed model (Generalized Estimating Equations) of predictors of MDA over time.

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 (axPsA)	–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.

Table 4
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	0.1±0.4	0.4±0.9	0.08
Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index at baseline	0.2±0.5	1.5±3.1	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.

Table 5
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.

On the other hand, grading all domains separately runs the risk of failing to capture the overall picture of the disease [25]. In our study, we examined two multidimensional definitions (MDA and VLDA) that reflect a state of low 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. Neither definition truly indicates remission, therefore suggesting that in clinical practice, MDA or VLDA may represent a more realistic target than complete absence of disease in all domains. Our findings are in line with a previous study by Lubrano et al., wherein sustained VLDA was achieved by 17% of patients, and at least once by 25% of patients [26]. Since VLDA is not achieved so frequently, we opted to focus on MDA, and especially sustained MDA which has been associated with improved quality of life and possibly less radiographic progression [7].

We found that sustained MDA was more frequent in males than females, although male sex did not represent *per se* an independent predictor of sustained MDA. This finding corroborates previous real-life studies in PsA and axSpA, which demonstrated that male participants showed a higher drug retention rate and better treatment response [27–32]. Previous works have already underlined how female patients usually present with higher levels of pain, fatigue, and worse quality of life [28,33]. Furthermore, radiographic and MRI features of axial disease might be different between men and women, possibly accounting for at least part of the observed differences [33].

Independent negative predictors of MDA over time were instead age, axPsA, fibromyalgia, OA and BMI≥35. It is well known that fibromyalgia hampers response to treatment in PsA patients [23,34], whereas OA has been studied less frequently as an obstacle to MDA, despite being a frequent comorbidity [35]. The challenge derives from the difficulty to discern OA from PsA as regards long-term structural damage [36]. In our study, we defined the presence of symptomatic OA based on the physician's diagnosis and available X-rays with typical OA findings (e.g. osteophytes). Obviously, this method has some shortcomings: the prevalence of OA might be overestimated (e.g. physicians may attribute some of the PsA symptoms to OA). However, the negative association 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 ascertain the root causes of the symptoms. Obesity is known to lower the response to bDMARDs and is associated with a lower likelihood of achieving sustained MDA with a dose-dependent response [37,38]. Our study confirmed a negative association between BMI≥35 — grade II obesity — and sustained MDA. Unlike most studies in the literature, we evaluated patients in stable therapy and highlighted a positive association between duration of bDMARDs therapy at baseline and sustained MDA. This is probably an indication that patients who are in MDA for a long time (presumably the reason why they did not switch therapy) are not at a higher risk of flare, but on the contrary, are more likely to achieve sustained MDA over time.

Axial disease deserves a separate consideration. Although it clearly constitutes an independent negative predictor for sustained MDA, it has been reported that MDA may be an achievable target in axPsA patients as well [39]; nevertheless, axPsA patients remains a more difficult-to-treat population. In fact, it bears noting that axPsA patients in our cohort achieved MDA in fewer cases (13–15% at each time-point) as compared to the whole group of PsA patients (50–61%). Furthermore, a specific index for axial involvement such as ASDAS-LDA was reached by only ~20% of patients at each time-point, underlining that this manifestation might represent an important additional burden for patients. In fact, a study conducted using 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 [40]. In addition, we previously found that patients with axSpA and psoriasis had a different phenotype than the typical axSpA patient, with less frequent HLA-B27+, radiographic sacroiliitis with a unilateral/asymmetric pattern, and more signs of spondylitis [41]. These patients also presented with worse patient-reported outcomes. However, there is currently no consensus among experts on the definition of axPsA and specific treatment regimens, thus making it challenging for rheumatologists [42].

We would remiss not to mention some of the limitations of our study. Namely, the physician-driven definition of some conditions such as axPsA or symptomatic osteoarthritis, which may result in associations with certain outcomes that might not be reproducible when applying a different definition. 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. Some of the strengths of our study lie in the inclusion of real-life PsA patients, with similar characteristics — age, disease duration and comorbidity prevalence — and the longitudinal observation of up to 3 years.

In conclusion, MDA is an attainable target in PsA, and its achievement may be influenced by both disease characteristics (e.g. axial involvement) and comorbidities (especially rheumatic concomitant conditions such as OA and fibromyalgia). Axial disease appears to be a difficult-to-treat subset, with lower rates of target achievement and more frequent discrepancy between patient-reported outcomes and physician evaluations.

Future studies are needed to confirm our results, and to better define axial involvement in PsA, toward improving its detection and management, as well as patients' quality of life.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

De-identified data are available on reasonable request by contacting the corresponding author via email.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152237.

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