Rheumatol Ther
https://doi.org/10.1007/s40744-023-00588-4

BRIEF REPORT

Identification of the Minimal Disease Activity Domains Achieved Based on Different Treatments in Psoriatic Arthritis

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Received: May 22, 2023 / Accepted: July 24, 2023

ABSTRACT

Introduction: The aim of this work is to characterize which Minimal Disease Activity (MDA) domains are mainly achieved, based on different treatments, in psoriatic arthritis (PsA) patients. Moreover, the association between MDA achievement and the different treatment groups was assessed.

Methods: We conducted a cross-sectional analysis of two longitudinal PsA groups. Inclusion criteria were: age $\geq$ 18 years, PsA diagnosis, stable treatment for at least 6 months. Patients were grouped depending on the therapy: group 1: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)/cyclooxygenase 2 inhibitors (COX2i)/steroids, group 2: conventional synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs), group 3: Tumor Necrosis Factor α inhibitors (TNFi), group 4: interleukin inhibitors (IL)12-23i or IL-23i, group 5: IL-17i, group 6: phosphodiesterase 4 inhibitors (PD4i). For each group, the achieved domains based on therapy were assessed. Multivariate logistic regression analysis was performed to assess the association between the treatment groups and the MDA achievement.

Prior Publication: The present manuscript is partially based on work that has been previously submitted at EULAR meeting 2023; it was accepted as a poster-abstract. Ref. Scriffignano S, Perrotta FM, Fatica M, et al. AB1135 CHARACTERIZING THE MINIMAL DISEASE ACTIVITY DOMAINS ACHIEVED BASED ON DIFFERENT TREATMENTS. Annals of the Rheumatic Diseases 2023;**82**:1798.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-023-00588-4.

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Published online: 16 September 2023

Results: A total of 220 patients were enrolled, and MDA was achieved in 45.8% of them. In all treatment groups, the first MDA domains achieved were: body surface area ≤ 3, swollen joint count ≤ 1 and Leeds Enthesitis Index ≤ 1, while MDA domains less frequently achieved were Patient Global Assessment (PtgA) ≤ 2 cm and pain on visual analogue scale ≤ 1.5 cm. The logistic regression analysis showed higher odds ratios for the achievement of the MDA in those patients in groups 3 and 4.
Conclusions: In each treatment group, MDA domains less frequently achieved were PtGA and pain, suggesting that "patient-driven domains" are still an unmet need.Due to the study design and the low number of patients in some groups, it is not possible to clearly define which MDA domain was achieved or not based on treatment; however, it seems that some differences could be present. If larger and prospective studies confirm our preliminary results, we could move toward a personalized/domain treatment approach in PsA.

Keywords: Psoriatic arthritis; Outcome measure; Minimal disease activity; Therapy

Key Summary Points

Why carry out this study?
The percentage of MDA achievement in PsA patients on bDMARDs ranges from 40 to 60% in clinical trials, registries, and in routine clinical practice.
Evaluating differences in the various MDA domains based on different treatments could be of significant interest for the rheumatologist.
The aim of the current study is to characterize MDA domains based on treatment. Moreover, the association between the treatment group and the achievement of a MDA status was analyzed.

What was learned from the study?
About 60% of PsA patients, after a stable treatment (for at least 6 months), did not achieve a PtGA $\leq$2 cm and a pain on VAS $\leq$1.5 cm. Analyzing each treatment group, the MDA domains less frequently achieved were PtGA $\leq$2 cm and pain on VAS $\leq$1.5 cm, suggesting that the patient-driven domains are still an unmet need.
Comparing patients in different treatment groups, it seems that (for the studied population) the association with the achievement of a MDA status was higher in some groups of patients (namely on TNFi and IL12-23i or IL23i) but, due to the limitations of this study, no definite and univocal conclusion can be proposed.
Larger and prospective studies are needed to better explore these preliminary results, including some other confounding factors and also the newest therapies recently adopted for PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous inflammatory disease characterized by multidomain involvement [1]. In fact, arthritis (peripheral and/or axial), enthesitis, and dactylitis could feature the PsA patient, beyond the skin, nail, and extra-articular involvement [2].

The primary goal of treating PsA patients is the achievement of a sustained good control of the disease activity, namely remission or minimal disease activity [3, 4].

Different indices have been developed to measure PsA disease activity: Disease Activity for Psoriatic Arthritis (DAPSA) [5], Minimal Disease Activity (MDA) [6], Psoriatic Arthritis Disease Activity Score [7] and Composite Psoriatic Disease Activity Index [8]. All of these indices share some differences and similarities,

capturing the PsA disease activity, ranging from DAPSA, which mainly reflects the articular disease to a more comprehensive index that goes beyond the joints, like MDA. Each index showed its utility and validity for the PsA assessment, as well as, sometimes, even Patient Global Assessment (PtGA) could be a simple, quick and valid instrument to assess disease activity in routine clinical practice [9].

In particular, MDA is a dichotomous "multidimensional" index focused on more than a domain: a patient is in MDA status when achieved at list 5 of the following domains: tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, PtGA ≤ 2 cm, patient pain on Visual Analogue Scale (VAS pain) ≤ 1.5 cm, Leeds Enthesitis Index (LEI) ≤ 1, Body Surface Area (BSA) ≤ 3 or Psoriasis Area Severity Index (PASI) ≤ 1 and Health Assessment Questionnaire-Disability Index (HAQ-DI) ≤ 0.5. Therefore, the disease domains encompassed by MDA are: joints, enthesis, skin, function, and pain.

Fortunately, the opportunity to reach a state of MDA, due to the newest treatments introduced in the last 20 years, has been exponentially increasing for all PsA patients [10].

The achievement of MDA status earlier is desirable because a faster achievement after the diagnosis is associated with a better disease outcome, as shown in a recent study[11]. In fact, the failure to achieve MDA in the first year after PsA diagnosis was associated with worse Patient-Reported Outcome (PROs) that persisted over the years [11].

However, the choice of the "right treatment for the right patient" is still a challenge: data from registries, observational studies, and Randomized Clinical Trials (RCTs) showed a substantial unmet need when the achievement of a low disease activity state, by MDA, constitutes the treatment target [12]. Indeed, the percentage of MDA achievement in PsA patients treated with biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) ranges from 40 to 60%, both in RCTs and in routine clinical practice [12–17], as confirmed in a recent systematic review with meta-analysis [18]. Therefore, this means that approximately half of PsA patients did not achieve a state of MDA, despite the treatment potentially inducing some disease improvements.

The challenge in the achievement of MDA led the researchers to examine the domains less frequently achieved, and it has been shown that the "patient-driven ones" are those less likely achieved [13, 14]. Moreover, in clinical practice, it should be taken into account that the presence of other conditions (such as comorbidity/multimorbidity) may reduce the probability of achieving MDA [19, 20].

Other potential differences in the achievement of the MDA domains may depend on different treatment strategies. Therefore, the main aim of this study was to characterize which MDA domains are mainly achieved/not achieved, based on different treatments, in two groups of PsA patients. Moreover, we tried to understand the association between the MDA achievement and different treatment strategies.

METHODS

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was approved by the Institutional Review Board of the University of Molise (protocol n. 0001–017-2021).

This is a cross-sectional study of two longitudinal PsA groups of patients in which PsA clinical and treatment characteristics were analyzed. The Rheumatology Department of the University of Molise (Campobasso) and the Rheumatology Department of University of Tor Vergata (Rome) (tertiary centers devoted to PsA) were involved in this study; in particular, data collected from these two centers from January 1, 2022 to September 30, 2022 were analyzed.

The analysis included all those adult PsA patients (satisfying the Classification Criteria for Psoriatic Arthritis criteria) (CASPAR) [21] that were on stable treatment for at least 6 months.

Demographic and physical characteristics were collected, including: age, sex, height, weight, and Body Mass Index (BMI). Moreover, for each patient, disease duration, number of tender/68 and swollen/66 joints, C-reactive protein (CRP), LEI, dactylitis, BSA, PtGA, VAS pain, Physicians Global Assessment (PhGA) and related conditions (uveitis, ulcerative colitis, Crohn's disease) were collected. The disease activity and function were assessed by DAPSA, MDA, and HAQ-DI, respectively. As comorbidity, fibromyalgia and obesity (based on BMI) were also collected.

Patients were grouped into six groups depending on therapy (they had been taking from at least 6 months):

- Group 1: only Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)/cyclooxygenase 2 inhibitors (COXi) or oral steroids;
- Group 2: conventional synthetic DMARDs: methotrexate and/or salazopyrin;
- Group 3: Tumor Necrosis Factor-α inhibitors (TNFi);
- Group 4: interleukin 12–23 inhibitors (IL 12-23i) and IL23i;
- Group 5: IL-17i;
- Group 6: phosphodiesterase 4 inhibitors (PD4i).

For each treatment group, MDA domains were analyzed in order to assess which were more frequently achieved. Moreover, the association between the achievement of MDA and each treatment group was independently assessed, taking into account other confounding factors.

Statistical Analysis

Statistical analysis was performed using R [22] and R Studio [23]. All demographical and clinical characteristics were summarized by using descriptive statistics. Normally distributed variables were reported by mean ± standard deviation (SD), and non-normally distributed variables by median and inter-quartile range (IQR). Categorical data are shown as number and percentage. Patients reported missing data were not included in the analysis.

Kruskal–Wallis test and Fisher's exact test were used to assess the differences of the clinical/demographic characteristics among the six groups.

For each treatment group, MDA domains were assessed. Radar chart was used to illustrate the percentage of patients that reached each MDA domain based on the treatment group. Multivariate logistic regression analysis was performed to assess the association between the treatment groups (independent variable) and the achievement of the MDA (dependent variable), adjusted by other confounding factors such as age, sex, disease duration, BMI, and the presence of fibromyalgia.

Multicollinearity among independent factors was evaluated by the Pearson correlation coefficient, by tolerance and by variance inflation factor (VIF): factors with a Pearson correlation coefficient of more than 0.7, or tolerance < 0.1 or VIF ≥ 10, were not included in the multivariate model. Goodness-of-fit was estimated using the Cox & Snell R^2. Odds ratio (OR) was used as measure of association and a statistical significance was defined as a two-tailed p value ≤ 0.05.

RESULTS

We enrolled 220 patients. They had a median value (IQR) of disease duration of 90 (47.5–158.2) months, 54.5% were male and the mean (SD) age was 55.6 (± 12.5) years (Table 1).

The percentage of patients with uveitis (present or past), ulcerative colitis, and Crohn's disease was 2.7, 1.4, and 0.4%, respectively.

The mean BMI was 27.5 (± 4.84) and the obesity was present in 25.5% of patients. Fibromyalgia was present in 25 patients (11.4%) of whom five were males and 20 were females.

The majority of patients were on TNFi ($n = 89$, 40.5% of the total group), followed by IL17i ($n = 59$, 26.8%), csDMARDs ($n = 24$, 10.9%), NSAIDs/COXi or steroids ($n = 23$, 10.4%), IL12-23i or IL23i ($n = 14$, 6.4%) and PD4i ($n = 11$, 5%).

Table 1 Demographic and clinical characteristics of all patients

	All patients (n = 220)
Sex (M), n (%)	120 (54.5)
Age, (years) mean (± SD)	55.6 (± 12.5)
Smokers, n (%)	
Never smoked	126/201 (62.7)
Current smoker	43/201 (21.4)
Past smoker	32/201 (15.9)
Weight (kg), median (IQR)	75 (66–140)
Height (m), mean (SD)	1.67 (± 0.1)
BMI (kg/h^2), mean (SD)	27.50 (± 4.8)
PsA assessment	
Disease duration (months), median (IQR)	90 (47.7–158.2)
Tender joints/68, median (IQR)	1 (0–3)
Swollen joints/66, median (IQR)	0 (0–0)
CRP (mg/dl), median (IQR)	0.30 (0.2–0.5)
LEI, median (IQR)	0 (0–0)
Dactylitis, n (%)	
Never	160/215 (74.4)
Past	46/215 (21.4)
Present	9/215 (4.2)
BSA, median (IQR)	0 (0–1)
PtGA (0–10) (cm), median (IQR)	4 (2–6)
Pain on VAS (0–10) (cm), median (IQR)	3 (1–6)
PhGA (0–10) (cm), median (IQR)	3 (2–4)
Uveitis (present or past), n (%)	6/219 (2.7)
Ulcerative colitis, n (%)	3/219 (1.4)
Crohn's disease, n (%)	1/219 (0.4)
DAPSA, median (IQR)	9.3 (4.2–15.2)
MDA 5/7 n (%)	99/216 (45.8)
MDA 7/7, n (%)	39/216 (18.0)
HAQ-DI, median (IQR)	0.500 (0.125–1.250)
Fibromyalgia n (%)	25/220 (11.4)
Obesity (BMI ≥ 30), n (%)	55/216 (25.5)

BMI body mass index, *BSA* body surface area, *CRP* C-reactive protein, *DAPSA* Disease Activity for Psoriatic Arthritis, *IL* interleukin, *LEI* Leeds Enthesitis Index, *MDA* minimal disease activity, *PtGA* Patient Global Assessment, *VAS* visual analogue scale

Clinical and demographic characteristics based on the six treatment groups are shown in supplementary files. Even if there were some differences among groups, they were not statistically significant, except for MDA and fibromyalgia (supplementary file).

Looking at the total population, MDA was present in 45.8% of patients. In particular, the percentage of patients in which MDA was present was (ascending order): 30.0% in group 6, 31.8% in group 1, 37.9% in group 5, 39.1% in group 2, 55% in group 3, and 64.3% in group 4 (Table 2).

The radar chart in Fig. 1 shows the percentage of patients for each MDA domain based on treatment. In particular, in all treatment groups, the first three MDA domains more present were: BSA ≤ 3, ranged from 85.7% (patients on IL12-23i or IL23i) to 91.2% (patients on IL17i); SJC ≤ 1, ranged from 73.9% (patients on csDMARDs) to 93.0% (patients on IL17i); LEI ≤ 1, ranged from 76.2% (patients on NSAIDs/COXi/steroids) to 100% (patients on csDMARDs) (supplementary file).

Looking at the other domains in each treatment group, these are: HAQ-DI ≤ 0.5 ranged from 20% (patients on PD4i) to 64.3% (patients on IL12-23i or IL23i); TJC ≤ 1 ranged from 40% (patients on PD4i) to 64.3% (patients on IL12-23i or IL23i); PtGA ≤ 2 cm ranged from 28.6%

Table 2 Frequency distribution of patients among groups and frequencies of MDA 5/7 present among patents grouped by treatment

Treatment	Number of patients	MDA 5/7 (yes) Present
Group 1 (NSAIDs/COXi/steroids), *n* %)	23 (10.4)	7/22 (31.8)
Group 2 (csDMARDs), *n* (%)	24 (10.9)	9/23 (39.1)
Group 3 (TNFi), *n* (%)	89 (40.5)	49/89 (55.0)
Group 4 (IL 12-23i/IL 23i), *n* (%)	14 (6.4)	9/14 (64.3)
Group 5 (IL 17i), *n* (%)	59 (26.8)	22/58 (37.9)
Group 6 (PD4i), *n* (%)	11 (5)	3/10 (30.0)

COXi cyclooxygenase inhibitors, *csDMARDs* convention synthetic disease anti-rheumatic drugs, *IL* interleukin, *NSAIDs* non-steroidal anti-inflammatory drugs, *PD4i* phosphodiesterase 4 inhibitors, *TNFi* tumor necrosis factor alpha inhibitors

(patients on NSAID/CO2i/steroids) to 42.8% (patients on IL12-23i or IL23i); pain on VAS $\leq$ 1.5 cm ranged from 19% (patients on NSAID/CO2i/steroids) to 42.8% (patients on IL12-23i or IL23i) (supplementary file). These data confirm that PROs are the most difficult domains to reach in each treatment group.

Moreover, to assess, in general, the relationship between the achievement of MDA and treatment group, a logistic regression model was applied. This model (Table 3) showed a higher odds ratio (OR) for those patients in group 3 (TNFi), OR (CI 95%) = 3.58 (1.25–10.30), and in group 4 (IL 12-23i or IL 23i), OR = 4.94 (1.05–23.03), for the achievement of MDA, independently of age, sex, disease duration, BMI, and fibromyalgia (Table 3).

However, all the treatment groups had a positive value of OR (even if they did not reach statistical significance, probably linked to the sample size), suggesting that patients on csDMARDs, IL17i, and PD4i might have a higher probability of achieving MDA than NSAIDs/COXi/steroids.

Of note, it is necessary to specify that the results of the regression analysis do not show any causality link, but an association value that, due to the study design and the low number of patients in some groups, does not allow to conclude that the achievement of MDA is clearly different among these groups. However, an interesting aspect was the sex difference found in the regression model: male patients (compared with female), independently of treatment, fibromyalgia, and BMI (in addition to age and disease duration), had a positive association with MDA status, OR (CI 95%) = 3.25 (1.71–6.18) (Table 3). Therefore, female sex is confirmed as a negative prognostic factor for the achievement of MDA independently of therapy. In the same wavelength, fibromyalgia was a factor negatively associated with the MDA achievement, independently of treatment; in fact, in case of an absence of fibromyalgia, there was a significant and positive association with the achievement of MDA, OR (CI 95%) = 15.87 (1.95–142.85), p = 0.009.

DISCUSSION

In this study, we assessed two Italian PsA groups of patients to describe how different treatments may impact all MDA domains. Patients were divided into six groups based on treatment and, generally, more than 90% of patients in each treatment group achieved BSA $\leq$ 3. This result could probably be related to the mild skin involvement that usually characterizes PsA patients in rheumatological clinical settings [24]. Moreover, SJC $\leq$ 1 and LEI $\leq$ 1 were achieved in more than 70% in all groups.

Of note, when analyzing those domains based on PROs, the achievement of good control for both PtGA and pain on VAS was never more than 43%. This means that about 60% of patients continue to have a higher burden of their disease, in each treatment group, representing an important unmet need in clinical practice.

When dealing with PsA patients, the lack of achievement of a good disease control could be

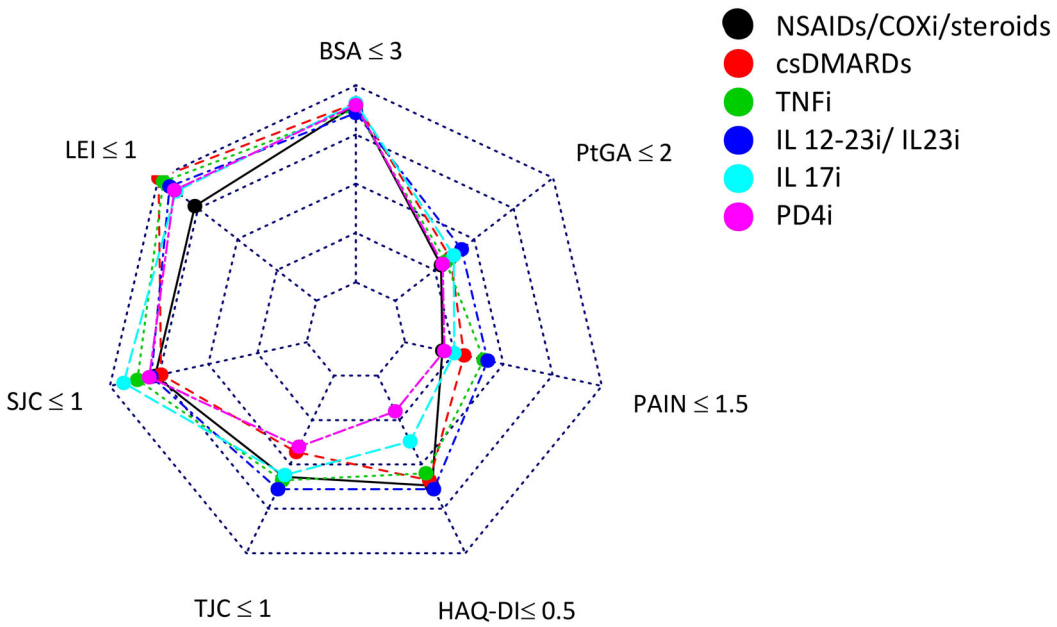

Fig. 1 Radar chart showing the percentage of achievement of each MDA domain based on treatment. "The inner dashed heptagon indicates a percentage prevlence of 20%, followed by 40%, 60%, 80%, up to the outer dashed heptagon which indicates 100%." *BSA:* body surface area, *COXi:* cyclooxygenase inhibitors, *csDMARDs:* convention synthetic Disease Anti-RheumaticDrugs, *HAQ-DI:* Health Assessment Questionnaire-Disability Index, *IL:* interleukin, *LEI:* Leeds Enthesitis Index, *NSAIDs:* Non-Steroidal Anti-Inflammatory Drugs, *PD4i:* Phosphodiesterase 4 inhibitors, *PtGA:* Patient Global Assessment, *SJC:* swollen joint count, *TJC:* tender joint count, *TNFi:* Tumor Necrosis Factor alpha inhibitors

linked to at least three different possibilities: the persistency of active disease (despite treatment), the lack of treatment response and/or the presence of some comorbidities that might influence the patient perception of her/his disease. Both the first and the second case could imply the need to change treatment by sequencing other treatment targets [25]. In the third case (presence of comorbidities), it would be appropriate to distinguish the burden that each comorbidity has on PROs [26]. In fact, as shown in our results, fibromyalgia was negatively associated with the achievement of MDA, independently of treatment. Indeed, we recently proposed the concept of multimorbidity in PsA to underline that some of comorbidities may have a different impact on the patients' perspective, such as fibromyalgia [27]. Therefore, it should be advisable to assess fibromyalgia burden by using specific instruments in routine clinical practice rather than solely relying on its presence being listed. In a wider spectrum, this factor could contribute to defining a patient as difficult to treat [28].

Moreover, from the regression analysis, we assessed how the association between treatment groups and the achievement of MDA varies among treatment classes: patients on TNFi and IL-23i or IL 12/23i had a higher OR value, but the study design, given the absence of any treatment stratification at baseline, does not allow to drawing any conclusion on the probability of achieving MDA based on treatment.

Beyond the therapy, it is very interesting to note that male sex is positively associated with the achievement of MDA, reinforcing the idea of a different impact of the disease in males and females [29].

However, our study has some limitations: the cross-sectional design does not allow to find any certain causal link between the results on MDA and the treatment group. Furthermore, in

Table 3 Multiple logistic regression analysis; dependent factor: MDA, independent factors: age, sex, disease duration, BMI, fibromyalgia, treatment groups

	Dependent variable	
	MDA	
Independent variables	**OR (CI 95%)**	***p* value**
Age (years)	0.98 (0.96–1.01)	0.159
Sex (male)	3.25 (1.71–6.18)	< 0.001
Disease duration (months)	0.99 (0.99–1.00)	0.588
BMI	1.01 (0.93–1.08)	0.855
Fibromyalgia (no)	15.87 (1.95–142.85)	0.009
Treatment group		
Group 2 (vs. group 1)	2.41 (0.63–9.19)	0.199
Group 3 (vs. group 1)	3.58 (1.25–10.30)	0.017
Group 4 (vs. group 1)	4.94 (1.05–23.30)	0.043
Group 5 (vs. group 1)	1.54 (0.50–4.72)	0.446
Group 6 (vs. group 1)	2.02 (0.29–13.70)	0.470

BMI body mass index, group 1: NSAIDs or COX2i or steroids, group 2: csDMARDs, group 3: TNFi, group 4: anti-IL 12–23 or anti-IL23, group 5: anti-IL17, group 6: PD4i; OR: odds ratio; CI 95%: confidence interval 95%

some groups, there was a limited number of patients, and a non-homogeneous patients' distribution among the treatment groups (mainly on TNFi); finally, some other comorbidities that showed a clear impact on PROs (like depression) [18] were not considered for the present study.

Beyond these limitations, the study showed that all the available therapies could be valid choices in the control of some domains, such as BSA, SJC, and LEI. However, when dealing with the "patient-driven domains" (such PROs), there is still an unmet need in clinical practice.

CONCLUSIONS

The characterization of the MDA domains based on treatment showed some practical issues: about 60% of PsA patients, after a stable treatment (for at least 6 months), in a routine clinical setting, did not achieve a PtGA $\leq$ 2 cm and a pain on VAS $\leq$ 1.5 cm. In fact, analyzing each treatment group, the MDA domains less frequently achieved were PtGA and pain, suggesting that the patient-driven domains are still an unmet need. Comparing patients in different treatment groups, it seems that (for the studied population) the association with the achievement of MDA status was higher in some groups of patients (namely on TNFi and IL12-23i or IL23i), but due to the limitations of this study, no definite and univocal conclusion can be proposed. Larger and prospective studies are needed to better explore these preliminary results, including some other confounding factors and also the newest therapies recently adopted for PsA, namely Janus kinase inhibitors.

ACKNOWLEDGEMENTS

We want to thank the participants of the study

Author Contribution. Silvia Scriffignano, Fabio Massimo Perrotta, Paola Conigliaro, Mario Ferraioli, Paola Triggianese, Maria Sole Chimenti, and Ennio Lubrano have made substantial contributions to all of these sections: conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.

Funding. No funding or sponsorship was received for this study or publication of this article. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Ennio Lubrano, Silvia Scriffignano, Mauro Fatica, Paola Triggianese, Paola Conigliaro, Fabio Massimo Perrotta and Maria Sole Chimenti have nothing to disclose.

Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was approved by the Institutional Review Board of the University of Molise (protocol n. 0001-017-2021).

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