Comparison of Composite Indices Tailored for Psoriatic Arthritis Treated with csDMARD and bDMARD: A Cross-sectional Analysis of a Longitudinal Cohort

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ABSTRACT. ***Objective.*** In a complex disease such as psoriatic arthritis (PsA), several methods are available to define remission or low disease activity (LDA), including the assessment of different clinical features. The aim of this study was to compare the composite indices tailored for PsA in patients treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and biological DMARD (bDMARD).

Methods. Patients with PsA classified with the ClASsification criteria for Psoriatic ARthritis criteria and with > 6 months followup treated with first csDMARD and bDMARD were consecutively enrolled. To assess disease activity, composite indices tailored for PsA were used, such as the Disease Activity Index for Psoriatic Arthritis (DAPSA), clinical DAPSA (cDAPSA), Psoriatic Arthritis Disease Activity Score (PASDAS), minimal disease activity (MDA) 5/7, and MDA 7/7. DAPSA and cDAPSA score ≤ 4, MDA 7/7, and PASDAS ≤ 1.9 identified remission. MDA 5/7, DAPSA score ≤ 14, cDAPSA score ≤ 13, and PASDAS < 3.2 identified the MDA and LDA criteria.

Results. One hundred nine patients with PsA were enrolled: 79 patients were receiving stable treatment with bDMARD and 30 with csDMARD. Overall, 28 (25.6%), 23 (21.1%), 19 (17.4%), and 13 patients (11.9%) were in cDAPSA remission, DAPSA remission, MDA 7/7, and PASDAS ≤ 1.9, respectively. Moreover, 54 (49.5%), 80 (73.3%), 79 (72.3%), and 38 patients (34.8%) were in MDA 5/7, DAPSA LDA, cDAPSA LDA, and PASDAS LDA. Patients treated with bDMARD had significantly lower median DAPSA, cDAPSA, and PASDAS score than patients treated with csDMARD.

Conclusion. Patients with PsA receiving bDMARD are more likely to achieve a status of MDA and remission when compared with csDMARD. PASDAS ≤ 1.9 and MDA 7/7 seem to be stringent remission criteria. (J Rheumatol First Release June 1 2017; doi:10.3899/jrheum.170112)

Key Indexing Terms:
PSORIATIC ARTHRITIS | REMISSION | COMPOSITE INDICES
BIOLOGIC THERAPY | DMARD

Psoriatic arthritis (PsA) is a multifaceted chronic inflammatory disease characterized by association of psoriasis and arthritis[1]. The peripheral joint involvement of PsA seems to be progressive in the majority of patients, and the presence of enthesitis, dactylitis, axial disease, cutaneous involvement, and extraarticular manifestations reinforces the need for optimal management and treatment strategies[1,2]. Moreover, patients with PsA have functional impairment, reduced quality of life, and a significant increase in mortality compared with the general population[3]. In the context of the disease, there are still different unmet needs that should be addressed, mainly on treatment strategies to achieve the best possible disease control such as disease remission or low disease activity (LDA)[4]. Tumor necrosis factor-α (TNF-α) blockers showed to be effective in clinical trials and in real-life experiences, with the possibility to induce a state of remission or LDA[5,6,7,8,9]. More recently, new treatment strategies with biologic disease-modifying antirheumatic drugs (bDMARD) and targeted synthetic DMARD, such as the inhibitors of interleukin (IL)-12/23, IL-17A, and phosphodiesterase 4, have shown to be effective in clinical trials[10,11,12]. However, the latest Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)[13] and European League Against Rheumatism[14] recommendations still proposed conventional synthetic DMARD (csDMARD) such as methotrexate (MTX), sulfasalazine (SSZ), and leflunomide as a first step in treatment of peripheral joint involvement in PsA, although there are limited data on the possibility of inducing remission with

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these drugs[15]. The same concept of disease remission is still debated, and at present, there are different composite indices to assess remission[16]. Recently, the concept of minimal disease activity (MDA) has been introduced and validated for PsA. Concerning the latter point, Coates, *et al* developed a composite outcome measure as a target of treatment for patients with PsA that encompasses most of the disease domains[17]. Patients are considered in MDA when they satisfy 5/7 of the following criteria: tender joint count ≤ 1, swollen joint count ≤ 1, psoriasis activity and severity index ≤ 1 or body surface area (BSA) ≤ 3, patient pain visual analog scale (VAS) score of ≤ 15, patient's global disease activity VAS score of ≤ 20, Health Assessment Questionnaire (HAQ) score ≤ 0.5, and tender entheseal points ≤ 1. These criteria were validated using interventional trial data[17,18]. The importance of disease control with the lowest grade of disease activity is justified because achieving sustained MDA (defined as MDA for over 12 mos at consecutive clinic visits) reduced radiographic joint damage progression over a 3-year period[18]. In a more recent study, the same authors proposed a more stringent definition of remission in which all 7/7 criteria had to be satisfied[19]. The GRAPPA Composite Exercise project recently developed the Psoriatic Arthritis Disease Activity Score (PASDAS), and different thresholds to identify disease activity were provided[20,21], while Schoels, *et al* proposed the remission criteria for the Disease Activity Index for Psoriatic Arthritis (DAPSA)[22], which can be calculated with or without C-reactive protein [CRP; clinical DAPSA (cDAPSA)]. There are a limited number of reports that assessed the MDA and the remission rate in patients with PsA treated with csDMARD and bDMARD in a real-life setting using specific measures tailored for PsA[15,23]. The aim of our study was to evaluate the remission or MDA in a group of patients with PsA consecutively seen in an outpatient clinic and regardless of the treatment strategy by using the composite indices validated and tailored for PsA.

MATERIALS AND METHODS

Patient selection. In our cross-sectional analysis of a longitudinal cohort, patients were enrolled at the Rheumatology Unit, Department of Medicine and Health Science, University of Molise, Campobasso, Italy. During the period January 1, 2016, to December 31, 2016, all patients with PsA who were receiving at least a 6-month followup treatment were considered potentially eligible for our study. Inclusion criteria were PsA classified with the ClASsification criteria for Psoriatic ARthritis criteria[24], age > 18 years, at least 6 months of followup at the study visit, and stable treatment with a first csDMARD or bDMARD for at least 6 months. To assess MDA and remission, composite indices tailored for PsA [DAPSA, cDAPSA, PASDAS, MDA (5/7), and MDA (7/7)] were used. The subject's written consent was obtained according to the Declaration of Helsinki and the study was approved by our institution. Ethics approval was not required for this study, in accordance with the policy of our institution.

Data collection. Patient data collection included a medical history, physical examination, current use of medications, and laboratory assessment. Demographics and disease characteristics including age, sex, disease duration, and pattern of articular manifestation were taken into account. The clinical assessment documented the number of tender joints (of the 68 assessed joints) and swollen joints (total of 66 joints), enthesitis, and dactylitis. Enthesitis was measured using the Leeds Enthesitis Index (LEI)[25], and dactylitis as present/absent. Skin assessment included the Psoriasis Area Severity Index (PASI) score and the BSA[26]. The HAQ[27] and the Medical Outcomes Study Short Form-36[28] were used to assess function and quality of life. Patient's global assessment (PtGA) and pain assessment on visual analog scale (VAS) were performed by all patients[29]. Physician's global evaluation of disease on VAS was also recorded. Erythrocyte sedimentation rate and CRP were also collected.

Minimal disease activity and remission criteria. MDA was defined according to Coates, *et al*[17]. MDA 7/7 was satisfied when all 7 criteria were met[19]. DAPSA score was identified according to Nell-Duxneuner, *et al* and was calculated by adding the number of tender and swollen joints, VAS pain, PtGA, and CRP (mg/dl)[30]. The cDAPSA was calculated without the contribution of CRP[22]. PASDAS was calculated according to Helliwell, *et al*[20]. DAPSA and cDAPSA score ≤ 4, MDA 7/7, and PASDAS ≤ 1.9 identified remission, while MDA 5/7 was the minimal disease activity criterion, and PASDAS < 3.2, DAPSA ≤ 14, and cDAPSA ≤ 13 identified a condition of LDA[19,21,22].

Statistical analysis. Categorical variables were analyzed by chi-square test with Yates correction or Fisher's exact test. The significance of the differences was determined using the Mann–Whitney U test for unpaired samples. Correlations among the different variables were assessed using Spearman test for nonparametric variables. Concordance was assessed using Cohen κ and was considered as follows: < 0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, and 0.81–1.00 = very good. Sensitivity, specificity, and likelihood ratios were evaluated to assess the accuracy of the different criteria. P values < 0.05 were considered significant. Results were expressed as median (interquartile range).

RESULTS

In the study period, 109 patients with PsA satisfied the inclusion criteria and were enrolled. Of these, 79 patients were in stable treatment with bDMARD (32 with etanercept, 24 with adalimumab, 18 with golimumab, and 5 with ustekinumab) and 30 with csDMARD (28 with MTX and 2 with SSZ, monotherapy). Of the 79 patients receiving bDMARD treatment, 14 were in combination therapy with MTX. Overall, median followup of our patients was 1.6 years. Overall, 28 (25.6%), 23 (21.1%), 19 (17.4%), and 13 patients (11.9%) with PsA were in cDAPSA remission, DAPSA remission, MDA 7/7, and PASDAS ≤ 1.9, respectively. On the other hand, 54 (49.5%), 80 (73.3%), 79 (72.3%), and 38 patients (34.8%) were in MDA 5/7, DAPSA LDA, cDAPSA LDA, and PASDAS LDA (Figure 1). As expected, patients receiving bDMARD had significantly lower median DAPSA, cDAPSA, and PASDAS scores than patients treated with csDMARD monotherapy (Table 1). Interestingly, the PASI score and enthesitis score (assessed by LEI) were also significantly lower in patients treated with bDMARD. A significant ($p < 0.001$) rate of patients receiving bDMARD treatment achieved a status of remission (cDAPSA score ≤ 4, DAPSA score ≤ 4), DAPSA LDA, MDA 5/7, and PASDAS LDA compared to csDMARD treatment. Although a higher rate of patients with PsA receiving bDMARD reached MDA 7/7 and PASDAS ≤ 1.9 compared to csDMARD, the differences were not significant (Table 2). Overall, the concordance between the indices ranged from poor to good. In particular, the

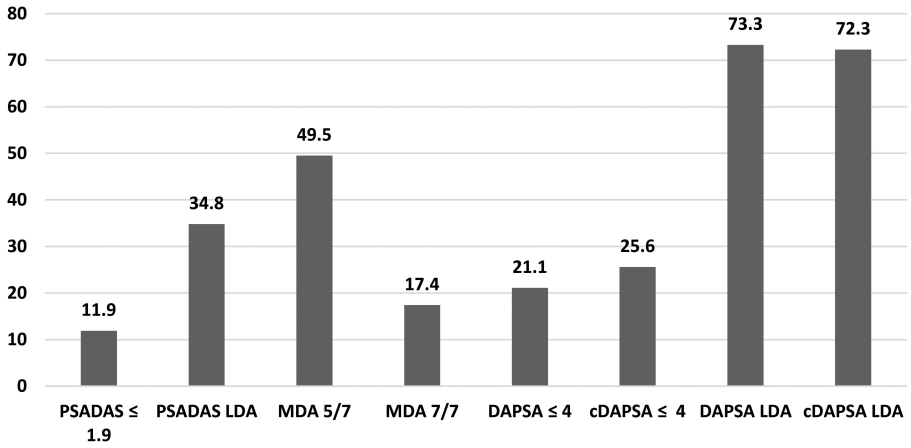

Figure 1. Overall rate (%) of PASDAS ≤ 1.9, PASDAS LDA, MDA 5/7, MDA 7/7, DAPSA remission, and DAPSA LDA in patients with psoriatic arthritis with > 6 months of followup treatment with bDMARD and csDMARD, according to the different definitions. PASDAS: Psoriatic Arthritis Disease Activity Score; LDA: low disease activity; MDA: minimal disease activity, DAPSA: Disease Activity Index for Psoriatic Arthritis; DMARD: disease-modifying antirheumatic drug; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD.

Table 1. Demographic and clinical disease activity characteristics in patients treated with bDMARD and csDMARD. Values are median (interquartile range) unless otherwise specified.

Characteristics	bDMARD, n = 79	csDMARD, n = 30	p
Female/male, n	38/41	16/14	NS
Age, yrs, mean (SD)	52.7 (12.4)	51.6 (12.3)	NS
Disease duration, yrs, mean (SD)	7.8 (9.3)	6.6 (8.2)	NS
TJC	1 (0–2)	5 (2–10.2)	0.0001
SJC	0 (0–1)	1 (0–3.2)	0.0001
PASI	0.3 (0–0.6)	1.5 (0–3.2)	0.02
Patients with axial involvement, n (%)	30 (37.9)	5 (16.6)	0.03
Patients with active enthesitis, n (%)	18 (22.7)	16 (53.3)	0.004
Patients with active dactylitis, n (%)	4 (5)	6 (20)	0.02
CRP, mg/dl	0.3 (0.16–0.49)	0.3 (0.2–0.76)	NS
PASDAS	3.28 (2.69–3.72)	4.43 (3.73–4.76)	< 0.01
MDA 5/7, n (%)	49 (62)	5 (16.6)	< 0.01
MDA 7/7, n (%)	16 (20.2)	3 (10)	NS
DAPSA	6.8 (3.7–9.57)	18.1 (16.5–31.5)	< 0.01
cDAPSA	6.5 (3.5–9.5)	17.5 (11.2–26.9)	< 0.01

DMARD: disease-modifying antirheumatic drug; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; TJC: tender joint count; SJC: swollen joint count; PASI: Psoriasis Area Severity Index; CRP: C-reactive protein; PASDAS: Psoriatic Arthritis Disease Activity Score; MDA: minimal disease activity; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; NS: not significant.

highest agreement was found between MDA 7/7 and DAPSA and cDAPSA remission ($\kappa = 0.63$ and 0.65, respectively) while poor agreement ($\kappa < 0.2$) was found between DAPSA LDA and MDA 7/7 and PASDAS ≤ 1.9.

Accuracy of the criteria. Table 3 shows the sensitivity, specificity, and likelihood ratio of the different scores compared to physician's definition of remission (physician VAS < 10 mm). The composite indices with the most stringent criteria provide the high specificity for remission, although they lack sensitivity. Table 4 shows which disease domains were not satisfied by the different composite indices. In our analysis, a percentage of patients with PsA ranging from 18.5 to 33.7 that satisfied the different criteria had a PASI score > 1.

DISCUSSION

Remission or LDA status is the goal of therapy in chronic inflammatory arthritis. In patients with axial spondyloarthritis treated with anti-TNF-α, remission could be achieved in

Table 2. Percentage of PASDAS ≤ 1.9, PASDAS LDA, MDA 5/7, MDA 7/7, DAPSA ≤ 4, or DAPSA LDA in patients treated with bDMARD and csDMARD therapy. Values are n (%).

Variables	bDMARD	csDMARD	p
PASDAS ≤ 1.9	10 (12.6)	3 (10)	0.5
PASDAS LDA	33 (41.8)	5 (16.6)	0.02
MDA 5/7	49 (62)	5 (16.6)	0.001
MDA 7/7	16 (20.2)	3 (10)	0.22
DAPSA ≤ 4	20 (25.3)	3 (10)	0.02
cDAPSA ≤ 4	24 (30.4)	4 (13.3)	0.02
DAPSA LDA	71 (89.8)	9 (30)	0.0001
cDAPSA LDA	69 (87.3)	10 (33.3)	0.0001

PASDAS: Psoriatic Arthritis Disease Activity Score; LDA: low disease activity; MDA: minimal disease activity; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; DMARD: disease-modifying antirheumatic drug; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD.

Table 3. Sensitivity and specificity of the different indices regarding physician VAS < 10 mm.

Variables	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood Ratio
PASDAS ≤ 1.9	0.33 (0.17–0.51)	1 (0.95–1)	—
PASDAS LDA	0.93 (0.79–0.99)	0.93 (0.85–0.97)	14.6
MDA 5/7	0.9 (0.74–0.98)	0.69 (0.57–0.79)	2.9
MDA 7/7	0.46 (0.29–0.65)	0.96 (0.88–0.99)	11.72
DAPSA ≤ 4	0.65 (0.46–0.81)	0.98 (0.92–0.99)	49.22
cDAPSA ≤ 4	0.75 (0.56–0.88)	0.97 (0.9–0.99)	28.13
DAPSA LDA	1 (0.89–1)	0.36 (0.25–0.47)	1.56
cDAPSA LDA	1 (0.89–1)	0.36 (0.25–0.47)	1.56

VAS: visual analog scale; PASDAS: Psoriatic Arthritis Disease Activity Score; MDA: minimal disease activity; DAPSA: Disease Activity Index for Psoriatic Arthritis; cDAPSA: clinical DAPSA; LDA: low disease activity.

53.2% of the patients with the nonradiographic form and in 50.9% of the patients with ankylosing spondylitis in a setting of clinical practice[31,32]. In PsA, several tools could be used to assess disease activity and remission/LDA state[16]. Further, despite the wide use of bDMARD and their proven efficacy on all PsA manifestations, several patients in clinical practice still continue treatment with csDMARD for different reasons (good response to csDMARD, costs, contraindication/intolerance, or fear of biologic treatment). The need to achieve remission remains unmet in this group of patients. On the other hand, in recent years, the development of composite indices tailored for the assessment of PsA posed the question of which is the better tool to identify a state of real remission. Until a few years ago, the Disease Activity Score in 28 joints (DAS28) was still used to assess disease activity state and remission. In a previous study, we demonstrated that using this tool showed that about 69% of patients with PsA treated with anti-TNF achieved a DAS28 ≤ 2.6 after 12 months of therapy[8]. However, DAS28 is a measure tailored mainly for small joint involvement of the hands, while PsA is a real heterogeneous disease and this composite measure does not fully evaluate the multiple clinical domains of psoriatic disease (e.g., enthesitis, dactylitis, and axial and skin involvement).

In our present study of 109 patients with PsA, 28 (25.6%), 23 (21.1%), 19 (17.4%), and 13 patients (11.9%) with PsA were in cDAPSA remission, DAPSA remission, MDA 7/7, and PASDAS ≤ 1.9, respectively, while 54 (49.5%), 80 (73.3%), 79 (72.3%), and 38 patients (34.8%) were in MDA 5/7, DAPSA LDA, cDAPSA LDA, and PASDAS LDA. Further, MDA or remission was achieved at a higher rate in patients receiving bDMARD compared with csDMARD. While the rate of MDA or DAPSA remission in patients receiving bDMARD is very similar to that in other studies[8,33], the rate of MDA/remission in patients receiving csDMARD was quite low. In fact, in the Tight Control Of inflammation in early Psoriatic Arthritis study, 22.4% of 188

Table 4. No. and rate of patients with PsA who achieved PASDAS ≤ 1.9, PASDAS LDA, MDA 5/7, MDA 7/7, DAPSA ≤ 4, or DAPSA LDA with residual disease activity/functional impairment in the single domains. Values are n (%).

Variables	TJC > 1	SJC > 1	HAQ > 0.5	PASI > 1	LEI > 1
PASDAS ≤ 1.9	0	0	0	3 (23)	0
PASDAS LDA	2 (5)	1 (2.6)	4 (10.5)	8 (21.1)	0
MDA 5/7	8 (14.8)	1 (1.8)	3 (5.5)	10 (18.5)	1 (1.8)
MDA 7/7	0	0	0	0	0
DAPSA ≤ 4	0	0	2 (8.6)	7 (30.4)	0
cDAPSA ≤ 4	0	0	2 (7.1)	7 (25)	0
DAPSA LDA	24 (30)	6 (7.5)	22 (27.5)	17 (33.7)	6 (7.5)
cDAPSA LDA	23 (29.1)	4 (5.1)	21 (26.5)	17 (21.5)	5 (6.3)

PsA: psoriatic arthritis; PASDAS: Psoriatic Arthritis Disease Activity Score; LDA: low disease activity; MDA: minimal disease activity; DAPSA: Disease Activity Index for Psoriatic Arthritis; TJC: tender joint count; SJC: swollen joint count; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area Severity Index; LEI: Leeds Enthesitis Index; cDAPSA: clinical DAPSA.

patients with PsA treated with MTX achieved MDA after 12 months[34], and in a recent study of 167 patients with PsA treated with MTX, 29 (17.4%) achieved MDA[35]. In our study, the rate of patients with > 6 months of followup in MDA status was similar (16.6%), underlining the difficulty of using csDMARD to induce a state of complete control of the disease activity, even when assessed with less stringent criteria. Moreover, our study shows that MDA 7/7 criteria and PASDAS ≤ 1.9 are the most stringent criteria to assess a status of remission. These 2 composite indices consist of all clinical manifestations of the disease (in the PASDAS, even the assessment of objective inflammation such as CRP) and probably represent the most complete criteria, even if MDA is, overall, easier to perform during clinical evaluation.

The data obtained seem to show that MDA is a reliable instrument to assess a low disease status in patients with PsA during chronic treatment, as well as PASDAS LDA. On the other hand, MDA 7/7 and PASDAS ≤ 1.9 seem to be reliable in assessing a condition of disease remission and this, in turn in our study, was more evident in those patients receiving bDMARD therapy. The analysis of sensitivity and specificity provide further useful information; regarding physician's definition of remission, the composites indices with the most stringent criteria provide high specificity for remission, although they lack sensitivity. Although MDA 5/7 and DAPSA remission could not assess important domains, they provide good sensitivity and specificity. On this point, our results showed that a relatively high percentage of patients with PsA (ranging from 18.5 to 33.7) who satisfied the different criteria had a PASI score > 1, while a relatively low percentage of patients showed a residual disease activity in other domains such as enthesitis or had functional impairment (defined as both LEI > 1 and HAQ > 0.5; Table 4). Finally, DAPSA and cDAPSA LDA are good instruments to assess a low disease status, but their potential weakness is that they are instruments to evaluate only peripheral arthritis, with a risk of underestimating disease activity in important domains such as skin and enthesitis. In fact, a relatively high number of patients in DAPSA LDA still present active tender joints, enthesitis, or skin disease. Our present study could be of some interest because there are few reports on the rate of different ways to assess remission in PsA in real life.

Patients with PsA receiving bDMARD are more likely to achieve a status of MDA and remission compared to csDMARD. PASDAS ≤ 1.9 and MDA 7/7 seem to be stringent criteria.

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