Assessment of Response to Treatment, Remission, and Minimal Disease Activity in Axial Psoriatic Arthritis Treated with Tumor Necrosis Factor Inhibitors

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ABSTRACT. ***Objective.*** To assess the response to treatment, remission, and minimal disease activity (MDA) in a group of patients with predominant axial psoriatic arthritis (axPsA). Predictors of response were also evaluated.

Methods. Patients fulfilling the ClASsification of Psoriatic ARthritis (CASPAR) criteria and treated with anti-tumor necrosis factor (anti-TNF) agents adalimumab, etanercept, and golimumab were enrolled and prospectively followed every 4 months for 1 year in a clinical practice setting. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 was assessed as a set of response criteria to treatment; Composite Psoriatic Disease Activity Index (CPDAI) < 4, Disease Activity Index for Psoriatic Arthritis (DAPSA) score ≤ 3.3, and partial remission (PR) were also evaluated as remission criteria. Patients were considered in MDA when they met at least 5/7 of the criteria previously defined. Patients achieving BASDAI 50, PR, and MDA were compared to identify outcome predictor factors. Concordance between the outcome measures was also performed.

Results. Of the 58 patients treated with anti-TNF, at baseline no patients were in PR or MDA. No patients had a CPDAI < 4 or a DAPSA score ≤ 3.3. After 12 months, BASDAI 50 was achieved in 15/48 patients (31.2%). CPDAI < 4, DAPSA score ≤ 3.3, PR, and MDA were achieved, respectively, in 17/48 (35.4%), 11/48 (22.9%), 11/48 (22.9%), and 24/48 (50%) patients. No difference was found among the 3 anti-TNF. Predictors for MDA were male sex, young age, low disease duration, low Health Assessment Questionnaire score, and absence of enthesitis.

Conclusion. This longitudinal observational study, based on a clinical practice setting, showed that remission and MDA are achievable targets in axPsA treated with anti-TNF. Predictors of remission and MDA were also identified. (First Release March 15 2016; J Rheumatol 2016;43:918–23; doi:10.3899/jrheum.151404)

Key Indexing Terms:
PSORIATIC ARTHRITIS SPONDYLITIS LONGITUDINAL STUDIES
MINIMAL DISEASE ACTIVITY ANTI-TUMOR NECROSIS FACTOR REMISSION

Psoriatic arthritis (PsA) has been defined as a unique inflammatory arthritis associated with psoriasis[1] with a prevalence of about 56.6 cases per 100,000 adults and variable incidence[2,3]. PsA is a disease with a broad spectrum of clinical and radiological features, and among these different phenotypes, axial involvement is one of the most intriguing disease subsets. In fact, the definition and measurement of axial disease in PsA (axPsA) remain problematic[4]. AxPsA can be frequent, ranging between 25% (early disease and clinical assessment only) and 75% (late disease and sophisticated imaging)[5]. Most of the time, an asymmetrical peripheral arthritis, with or without enthesitis, associated with axial involvement is the commonest subset of the disease. Thus, this overlap of peripheral and axial manifestations could be identified as a single entity belonging to PsA disease or as a possible phenotypical expression of the axial spondyloarthritis (SpA) group.

The concept of different diseases among the group of SpA, sharing some clinical, functional, and radiological aspects, is supported by the identification of conditions such as PsA. Similarly, the concept of 1 broad disease called SpA, with predominant peripheral or axial involvement, is supported by others, as suggested by the ASAS (Assessment of Spondylo-Arthritis International Society) with the new classification criteria[6]. With regard to axPsA, this debate is more than merely academic because its main characteristics could be a predominant phenotypic expression of SpA, true ankylosing spondylitis (AS) in patients with coincidental psoriasis, or a subset of PsA[7].

Effectiveness, defined as the effect of any intervention

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Accepted for publication January 29, 2016.

carried out in daily clinical practice and evaluated at the level of the community as well as the individual, was assessed in a group of patients with axPsA treated with etanercept in monotherapy and showing a good response to treatment[8]. However, remission in PsA has been deemed an important target and it is still considered an unmet need[9]. Treatment with anti-tumor necrosis factor-α (anti-TNF-α) has proven effective in clinical trials and in real-world settings, with a reduction in disease activity measures and radiographic progression[10], but it is still unclear whether anti-TNF therapy is effective in controlling all the different clinical features of PsA such as dactylitis, enthesitis, and axial involvement. In patients with PsA, a state of remission or low disease activity is the target of therapy. In this context, the definition of clinical response or remission must consider all disease domains. In 2010, minimal disease activity (MDA) criteria were proposed[11] and shown to be validated using interventional trial data[12] and a realistic target in real clinical practice[13,14,15]. However, the complexity of disease led to the development of a number of other disease activity measures and definitions of remission such as the Disease Activity Index for Psoriatic Arthritis (DAPSA), the Composite Psoriatic Disease Activity Index (CPDAI), and the Psoriatic Arthritis Disease Activity Score (PASDAS), which were used in clinical trials and in real-world settings[16,17]. To assess axPsA, most of the indices used in clinical practice are borrowed from AS: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and partial remission (PR) could be used, respectively, to assess disease activity/response to treatment and remission. The aim of our present study was to assess the response to treatment by using BASDAI 50, remission by using CPDAI, DAPSA, and PR, while MDA was assessed at 12 months in a group of patients with predominant axPsA receiving anti-TNF therapy. Predictors of response were also identified, and the relationship between these outcome measures was assessed.

MATERIALS AND METHODS

Study design. A single-center observational study was performed involving patients with PsA, satisfying the ClASsification of Psoriatic ARthritis (CASPAR) classification criteria[18]. The definition of axPsA was classified according to the criteria proposed by ASAS for inflammatory back pain and/or radiological axial involvement[8,19]. When present, radiographs of sacroiliac joints were scored according to the New York criteria[20].

Patients with PsA were recruited consecutively during their followup visits regardless of clinical subsets, according to Moll and Wright[21] and with predominant axial involvement. The study was carried out at the outpatient clinic for patients with PsA who were treated with biologic agents. In particular, anti-TNF were prescribed according to the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations[22].

During the observation period of enrollment (March 1, 2012, to August 31, 2014), all patients with predominant axPsA who were attending the outpatient clinic of the Academic Rheumatology Unit in Campobasso, Italy, were evaluated at baseline and then every 4 months for a 12-month followup. The study was approved by the local ethics committee and all patients gave their written informed consent. All patients with axPsA started taking adalimumab (40 mg every other week), etanercept (25 mg twice weekly or 50 mg weekly), or golimumab (50 mg monthly), and the choice of a specific agent was based on the patient and physician's preference. Exclusion criteria were age < 18 years, previous treatment with anti-TNF, and MDA or a state of remission before the initiation of anti-TNF therapy or at the baseline visit.

At baseline, BASDAI value ≥ 4 and a positive expert opinion for disease activity were chosen as criteria for starting the anti-TNF treatment.

Clinical and functional assessment. In all patients, a detailed clinical and functional assessment was performed. The American College of Rheumatology joint count (68 tender, 66 swollen joints) was used for peripheral joint evaluation as well as the BASDAI for the axial involvement[23].

Skin assessment included the Psoriasis Area and Severity Index (PASI) score and the body surface area[24]. Patients also completed questionnaires including the Health Assessment Questionnaire (HAQ)[25], patient global assessment (PtGA), and pain assessment on visual analog scale (VAS)[26]. Function was assessed using Bath Ankylosing Spondylitis Functional Index (BASFI)[27]. Physician global evaluation of disease on VAS was also recorded. Presence of dactylitis and enthesitis was clinically assessed. Enthesitis was measured using the Maastricht Ankylosing Spondylitis Enthesitis Score[28], while dactylitis was recorded as presence/absence in any digit at each visit. Drug treatment at time of recruitment was also recorded. Acute-phase reactants [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] were also tested to monitor disease activity. HLA-B27 typing was also performed.

Response criteria and assessment of remission. ASAS response criteria (BASDAI 50% relative change or absolute change of 20 mm and expert opinion in favor of continuation) was considered the main response criteria at the followup visits[29]. CPDAI was calculated based on the 68 tender joint counts (TJC), 66 swollen joint count (SJC), PASI, enthesitis scored from 0 to 4 (palpation of Achilles tendon and bilateral plantar fasciae insertion), dactylitis (a simple count of each digit involved), BASDAI, and Ankylosing Spondylitis Quality of Life score[30] at each visit.

A CPDAI score < 4 defined a state of low disease activity. Remission was also defined according to the composite index DAPSA, calculated as SJC of 66 joints + TJC of 68 joints + PtGA + pain VAS (cm) + CRP (mg/dl)[13]; it was also assessed at each visit. A DAPSA score ≤ 3.3 defined remission according to Husic, *et al*[31]. PR was reached when the score was < 20 mm (VAS 0-100 mm) in each of the following domains: (1) patient global assessment (in the last week); (2) pain (spinal); (3) function (measured by the BASFI); and inflammation (mean of intensity and duration of morning stiffness, from the BASDAI)[32].

MDA was identified according to Coates, *et al*[11] and assessed at 4 months (T4), 8 months (T8), and 12 months (T12) after the start of anti-TNF therapy.

Statistical analysis. Statistical analysis was carried out using the SPSS package (version 17.0). Descriptive analysis was performed, expressing variables such as mean ± SD, or median with 25th and 75th percentiles, according to data distribution.

Comparisons between baseline and 4-8-12 months were performed using the Wilcoxon signed-rank test for paired and Mann-Whitney U test for unpaired samples.

Categorical variables were analyzed by chi-squared test with Yates' correction or Fisher's exact test. The probabilities of achieving BASDAI 50, CPDAI < 4, DAPSA ≤ 3.3, PR, and MDA were explored using OR (lower and upper 95% CI) of outcome relative to the main variables. OR was interpreted as 1.5 to 1: weak association; 2.5 to 1: moderate association; 4 to 1: strong association; and 10 to 1: very strong association. Concordance was assessed using Cohen's κ coefficient and it was considered as follows: < 20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; 0.81–1.00, very good.

All statistical procedures were 2-sided; a significance level was set at $p < 0.05$.

RESULTS

Descriptive, clinical, and functional data. During the

recruitment time period, 137 patients with PsA were evaluated. Of those, 79 (57%) showed peripheral involvement without axial disease as defined for our study. Therefore, 58 patients with predominant axial disease [M/F: 25/33, median age (25th–75th percentiles): 51.5 (45.5–59) yrs, median disease duration: 8.05 (6-15) yrs] were enrolled. Peripheral joint involvement was present in 43/58 (74.1%) and the median (25th-75th percentiles) joint count was 2 (0–6) for tender and 0 (0–2) for swollen joints. Dactylitis was observed in 17/58 (29.3%) and enthesitis in 12/58 (20.6%). HLA-B27 positivity was found in 13/58 patients (22.4%).

All demographic, clinical, and functional data, as well as the outcome measures considered, are shown in Table 1.

At baseline, no patients reached a CPDAI score < 4, DAPSA score ≤ 3.3, or were in MDA or PR state. Of the 58 patients enrolled at baseline, 10 were lost during followup because of side effects (n = 4) and inefficacy (n = 6).

After 12 months, BASDAI 50 was achieved in 15/48 (31.2%) of patients with PsA. Moreover, CPDAI < 4, DAPSA score ≤ 3.3, PR, and MDA, were achieved respectively in 17/48 (35.4%), 11/48 (22.9%), 11/48 (22.9%), and 24/48 (50%) patients (Figure 1). The percentage of patients achieving BASDAI 50, CPDAI < 4, DAPSA ≤ 3.3, MDA, and PR remission increased significantly from baseline to T12. Moreover, the percentage of patients with PsA achieving MDA was higher ($p < 0.01$) than the percentage of patients achieving DAPSA remission and PR at T8 and T12 (Figure 1). No statistical differences were found among the 2 anti-TNF agents in relation to the index used to define remission, but the study was underpowered to detect differences.

The associations of BASDAI 50 response, PR, and MDA with the main variables were studied. For this purpose, these variables were categorized: sex, age (≤ or > 40 yrs), disease duration (≤ or > 10 yrs), enthesitis (absence vs presence), dactylitis (absence vs presence), HAQ (low ≤ 0.5, high > 0.5), ESR (low ≤ 15; high > 15 mm/h), and CRP (low ≤ 0.5, high > 0.5 mg/dl). In particular, these factors were independent predictors of MDA (Table 2): male sex (OR 3.4, 95% CI 1.02–11.25; p = 0.045), age (OR 21.0, 95% CI 1.12–392.39, p = 0.040), disease duration (OR 3.4, 95% CI 1.02–11.25; p = 0.045), and low HAQ score (OR 15.23, 95% CI 1.72–134.3; p = 0.01), while no predictors for achieving BASDAI 50 were found. Only low HAQ score was found as a predictor of PR (Table 3). Table 4 shows the concordance between BASDAI 50, CPDAI < 4, DAPSA ≤ 3.3, MDA, and PR.

Table 1. The main demographic and clinical features of PsA patients (n = 58) with axial involvement at baseline.

Male/female	25/33
Age, yrs, median (25th–75th percentile)	51.5 (45.5–59)
Disease duration, yrs, median (25th–75th percentile)	8.05 (6–15)
Articular manifestations, %	
Peripheral arthritis	74.1
Enthesitis	20.6
Dactylitis	29.3
Extraarticular manifestations, %	
Uveitis	8.6
IBD	1.7
HLA-B27	22.4
Indices and other measures, median (25th–75th percentile)	
DAPSA	24.7 (16.6–38.7)
Tender joint	2 (0–6)
Swollen joint	0 (0–2)
ESR, mm/h	19.5 (8.7–27.25)
CRP, mg/dl	0.55 (0.21–1.25)
VAS global	60 (45–70)
VAS pain	60 (45–76.25)
VAS back pain	47.5 (25–73.5)
VAS physician	45 (39.25–58.75)
BASDAI	5.95 (5–7.2)
HAQ	1 (0.62–1.5)
PASI	0 (0–1.9)
MASES	1 (0–3)
Concomitant treatment at baseline, n (%)	
DMARD	20 (34.4)
Prednisone intake	16 (27.5)
NSAID intake	40 (68.9)
Anti-TNF therapy, n (%)	
Adalimumab	15 (25.8)
Etanercept	30 (51.7)
Golimumab	13 (22.5)

PsA: psoriatic arthritis; IBD: inflammatory bowel disease; DAPSA: Disease Activity Index for Psoriatic Arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein, VAS: visual analog scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area Severity Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; TNF: tumor necrosis factor.

DISCUSSION

Our present study dealt with the assessment of response to treatment, remission, and MDA in a group of patients with predominant axPsA who were receiving anti-TNF therapy for 12 months. The results obtained showed that response to therapy using BASDAI 50, remission status using CPDAI, DAPSA, or PR, and a condition of MDA are possible achievable targets in this disease subset. The choice to measure response to therapy by using BASDAI is justified by the easy feasibility of this instrument in routine clinical practice and from a previous study measuring the effectiveness of anti-TNF treatment in axPsA[8]. Moreover, when BASDAI was compared to Ankylosing Spondylitis Disease Activity Score to measure disease activity in axial PsA, there were similar results in discriminative ability[33]. Measuring disease activity, severity, and response to treatment in PsA is still challenging for the rheumatologist, because of the complexity of the disease, and different proposals have been suggested to address this[9,34]. Although the BASDAI in PsA may be influenced by peripheral involvement[35], the changes observed should be consistent with a true effect of biologic agents on the axial component of the arthritis.

Our results are also in keeping with the percentage of

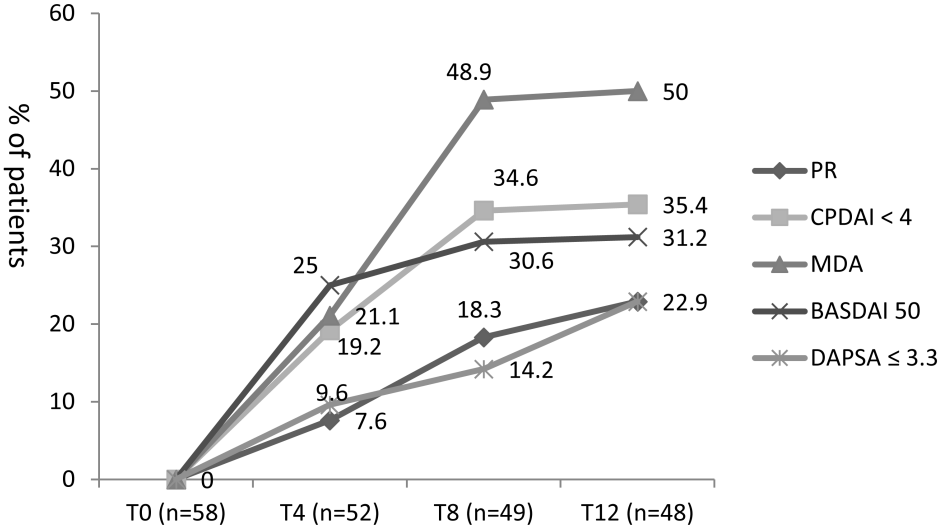

Figure 1. BASDAI 50, CPDAI < 4, DAPSA ≤ 3.3, PR, and MDA at the different followup timepoints (months) in patients with axial PsA who were treated with anti-TNF. All percentages among the 5 indices were not statistically different except MDA vs DAPSA (48.9% vs 14.2%, p < 0.01 at T8; 50% vs 22.9%, p < 0.01 at T12) and MDA vs PR (48.9% vs 18.3%, p < 0.01 at T8; 50% vs 22.9%, p < 0.01 at T12). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity Index for Psoriatic Arthritis; PR: partial remission, MDA: minimal disease activity.

Table 2. OR (95% CI) of achieving MDA according to the baseline variable values in patients with predominant axial PsA.

Variables	OR (95% CI)	p
Sex: male vs female	3.40 (1.02–11.25)	0.045
Age: ≤ 40 yrs vs > 40 yrs	21.00 (1.12–392.39)	0.040
Disease duration: ≤ 10 yrs vs > 10 yrs	3.40 (1.02–11.25)	0.045
Enthesitis: absence vs presence	1.18 (0.27–5.12)	NS
HAQ: low vs high	15.23 (1.72–134.30)	0.01
ESR: low vs high	1.00 (0.31–3.15)	NS
CRP: low vs high	1.00 (0.32–3.11)	NS
Dactylitis: absence vs presence	0.46 (0.086–2.4)	NS

MDA: minimal disease activity; PsA: psoriatic arthritis; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NS: not significant.

Table 3. OR (95% CI) of achieving PR according to the baseline variable values in patients with predominant axial PsA.

Variables	OR (95% CI)	p
Sex: male vs female	4.20 (0.41–43.37)	NS
Age: ≤ 40 yrs vs > 40 yrs	9.6 (1.1–83.75)	NS
Disease duration: ≤ 10 yrs vs > 10 yrs	1.8 (0.39–8.8)	NS
Enthesitis: absence vs presence	1.7 (0.28–11.9)	NS
HAQ: low vs high	16.28 (1.47–179.97)	0.02
ESR: low vs high	0.69 (0.15–3.17)	NS
CRP: low vs high	1.71 (0.39–7.43)	NS
Dactylitis absence vs presence	0.18 (0.03–1.07)	NS

PR: partial remission; NS: not significant; HAQ: Health Assessment Questionnaire, ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 4. Concordance (Cohen's κ) between BASDAI 50, CPDAI < 4, DAPSA ≤ 3.3, PR, and MDA at months 4, 8, and 12 after the start of anti-TNF therapy.

Measures	T4	T8	T12
DAPSA vs MDA	0.57	0.29	0.63
DAPSA vs PR	0.39	0.40	0.18
DAPSA vs CPDAI	0.47	0.37	0.43
DAPSA vs BASDAI 50	0.29	0.19	0.15
MDA vs PR	0.47	0.20	0.30
MDA vs CPDAI	0.70	0.54	0.54
MDA vs BASDAI 50	0.57	0.31	0.28
PR vs CPDAI	0.51	0.28	0.20
PR vs BASDAI 50	0.38	0.46	0.52
CPDAI vs BASDAI 50	0.62	0.46	0.30

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity Index for Psoriatic Arthritis; PR: partial remission; MDA: minimal disease activity; TNF: tumor necrosis factor.

remission and MDA observed in various groups of patients[13,14,15,36] regardless of the predominant subset of the disease, and confirming that the achievement of remission in PsA is a possible target[37]. In our study, MDA was achieved in a lower percentage of patients compared to that seen in another study, in which the presence of axial disease was deemed a negative predictive factor to achieve MDA[38]. Further, the percentage of patients achieving MDA at T4 and T8 was higher than the percentage of patients achieving PR or DAPSA remission. This could be due to the different construction of composite indices: MDA criteria, in fact, do not contain items for the assessment of pain and function in

axial disease such as BASFI. The achievement of PR was already shown by 2 other studies in which we demonstrated a good proportion of patients with classic AS and nonradiographic axial SpA achieving a state of PR, confirming that in longitudinal observational studies the treatment with anti-TNF agents is effective[39,40]. Our present study also demonstrates a low disease activity status or remission, evaluated with different outcome measures, in a percentage of patients with predominant axPsA ranging from 22.9% to 50%; overall, a moderate to good concordance between the various measures was found. However, we found that the predictors for MDA were male sex, young age, low disease duration, low HAQ, and absence of enthesitis, while no predictors were found when the response was measured by BASDAI 50, and only low HAQ score was a predictor of PR. Our results reinforced that a good functional status when treatment starts could increase the probability of obtaining remission.

Therefore, these results showed that axial involvement, even if it represents an unmet clinical need for a better treatment strategy, could reach a condition of low disease activity when treated with anti-TNF in a setting of clinical practice. In fact, a possible novelty of our study is the overall assessment of remission and MDA in predominant axPsA, and to date, to our knowledge this is the first study showing these data.

There are a few limitations to our study: we did not evaluate the Medical Outcomes Study Short Form-36 questionnaire, meaning that it was not possible to calculate PASDAS. Moreover, no data were obtained from imaging assessment, so it was not possible to evaluate the presence of active/inactive lesions or the radiographic involvement of the spine and sacroiliac joints in our cohort of patients with PsA, and we could not evaluate the efficacy of anti-TNF on these aspects. However, all obtained data could be interpreted as just a low percentage of achievement of a good outcome, paving the way to a possible treatment modification, but the status of low disease activity or remission, measured by composite indices, is quite difficult to achieve, and probably only after a certain period of time.

Our study, based on clinical practice, showed that even though anti-TNF are effective in patients with predominant axial PsA, and the drugs contribute to achievement of remission or low disease activity in about 20%-50% of patients, there are still unmet needs for these patients, and further studies could contribute to this intriguing topic.

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