

Predictors of Early Minimal Disease Activity in Patients with Psoriatic Arthritis Treated with Tumor Necrosis Factor- α Blockers

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ABSTRACT. *Objective.* To identify predictors of early minimal disease activity in patients with psoriatic arthritis (PsA) receiving tumor necrosis factor- α (TNF- α) antagonists.

Methods. In total 146 consecutive patients with PsA eligible for anti-TNF- α therapy were enrolled. At baseline (T0) information about age, sex, PsA subset, disease duration, comorbidities, and treatments was collected. All subjects were tested for metabolic syndrome (MetS) and/or liver steatosis. A clinical and laboratory evaluation was performed at T0 and at 3 months (T3). Changes in all these variables were compared in subjects achieving minimal disease activity (MDA) and those who did not.

Results. Among 146 PsA subjects, 10 discontinued therapy before 3-month followup because of adverse events; thus 136 concluded the study. All clinical outcome measures changed significantly from T0 to T3. Erythrocyte sedimentation rate showed a significant reduction ($p < 0.001$). C-reactive protein (CRP), serum cholesterol, and triglycerides showed no significant variation ($p > 0.05$). The prevalence of MetS and liver steatosis showed no significant differences between subjects achieving MDA and those who did not ($p = 0.347$ and 0.053 , respectively). Patients achieving MDA at T3 were younger than those not achieving MDA ($p = 0.001$). A lower baseline tender joint count ($p = 0.001$), swollen joint count ($p = 0.013$), Bath Ankylosing Spondylitis Disease Activity Index ($p = 0.021$), and Ritchie index ($p = 0.006$) were found in subjects achieving MDA. Age (OR 0.896, $p = 0.003$) and Bath Ankylosing Spondylitis Functional Index (BASFI) (OR 0.479, $p = 0.007$) inversely predicted, whereas CRP (OR 1.78, $p = 0.018$) directly predicted, achievement of MDA at T3.

Conclusion. In patients with PsA, age, CRP, and BASFI at the beginning of treatment were found to be reliable predictors of MDA after 3 months of TNF- α blocker therapy. (First Release Jan 15 2012; J Rheumatol 2012;39:568–73; doi:10.3899/jrheum.110763)

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Psoriatic arthritis (PsA) is a chronic inflammatory joint disease, usually seronegative for rheumatoid factors, associated with psoriasis^{1,2}. A “sine psoriasis” PsA subgroup, significantly associated with HLA-CW6, has been described in subjects without overt psoriasis and with a first- or second-degree family history of psoriasis³. Although PsA has been considered less erosive as compared with rheumatoid arthritis (RA)⁴, Gladman, *et al* showed that, even when disease is actively treated, patients may have significant joint damage⁵. Further, similar to other rheumatic diseases^{6,7,8}, an increased mortality is also evident in patients with PsA, especially because of cardiovascular events^{9,10,11}. These findings have led to the introduction of the new concept of “psoriatic disease,” which better describes this complex association of clinical disorders¹².

New therapies, such as the tumor necrosis factor- α blockers (anti-TNF- α), have been shown to reduce disease activity and radiographic progression of joint damage^{13,14,15}. Thus clinical remission is a possible target in PsA¹⁶, but the complexity of the disease makes it difficult to identify criteria that can predict achievement of low disease activity. Many groups

have attempted to address this issue, by using modified American College of Rheumatology criteria for RA¹⁷ or the presence/absence of actively inflamed joints¹⁸, but there is still no agreement in the definition of low disease activity and in the identification of predictors of treatment response. In particular, in an observational study of 344 patients with PsA, Coates, *et al*¹⁹ evaluated potential features that may be associated with achievement of minimal disease activity (MDA), finding a prognostic role for the degree of inflammation and for the pattern of articular disease.

Although composite disease activity measures for PsA, including those derived from RA²⁰ and reactive arthritis²¹, have been proposed, there is no agreed “gold standard.” We have chosen the definition of MDA according to Coates and Helliwell²² because it includes evaluation of joints, skin, entheses, and patient-reported outcomes, all useful criteria in real clinical practice.

In recent studies, baseline Health Assessment Questionnaire (HAQ)²³, higher swollen joint count (SJC), and no previous use of TNF blockers²⁴ were predictors of 12 months’ remission. The British Society of Rheumatology states that patients with PsA receiving TNF- α antagonists but not achieving a good clinical response after 3 months’ treatment should discontinue the therapy²⁵; thus early identification (i.e., within 3 months) of predictors of achievement of low disease activity in patients treated with anti-TNF- α is a major issue for investigation.

The aim of our study was to evaluate the influence of baseline demographic and clinical features on early response to anti-TNF- α treatment in PsA patients who did not respond to traditional therapies.

MATERIALS AND METHODS

In a period of 16 months (January 2009 to May 2010), we enrolled a cohort of 146 consecutive patients diagnosed with PsA according to the CIASSification criteria for Psoriatic ARthritis study group criteria (CASPAR)²⁶, who were classified as nonresponders to traditional therapies and who were eligible for anti-TNF- α therapy, attending our regional reference center for biologic treatment of rheumatic diseases. After a baseline evaluation, patients were followed for a period of 12 months. We collected information about age, sex, PsA clinical subset, disease duration, current comorbidities, and previous or current treatments; then all subjects underwent a complete clinical rheumatologic and laboratory evaluation at baseline (T0) and at 3 months (T3), including tender joint count (TJC), SJC, tender enthesal count, Psoriasis Area and Severity Index (PASI), HAQ, visual analog scale (VAS) for pain, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), Ritchie articular index, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

In order to evaluate the achievement of sustained MDA, the same clinical data were also collected after 6 months of treatment.

The BASDAI was performed only in subjects with axial involvement as defined by Rudwaleit, *et al*²⁷, while the Ritchie articular index was done only in subjects with peripheral disease. In addition, metabolic syndrome (MetS) and its main features (obesity, hypertension, hypercholesterolemia, hypertriglyceridemia, impaired fasting glucose) were evaluated at baseline and during the followup according to established criteria²⁸. An abdominal ultrasound was performed in all subjects (MyLab 25 Gold, 3.5 MHz convex probe; Esaote, Genova, Italy) in order to identify liver steatosis (“bright liver”) as an expression of metabolic impairment²⁹.

In order to evaluate disease activity, subjects were classified as having MDA when they fulfilled 5 of 7 outcome measures, as follows: TJC \leq 1, SJC \leq 1, PASI \leq 1 or body surface area \leq 3, VAS score for pain \leq 15, VAS score for global disease activity \leq 20, HAQ score \leq 0.5, and tender enthesal count \leq 1²².

The exclusion criteria were previous treatment with a TNF- α blocker, current minimal disease activity, or failure to provide informed consent.

Statistical analysis. Statistical analysis was performed with SPSS 16 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as means \pm SD and categorical variables as percentages. To compare continuous variables, independent-sample T tests were performed. To analyze categorical data, the chi-square test was performed. When the minimum expected value was $<$ 5, Fisher’s exact test was used. To make predictions, a logistic regression model (stepwise method) was adopted, with MDA as the dependent variable and baseline ESR, CRP, TJC, SJC, PASI, HAQ, BASDAI, BASFI, VAS for pain, clinical subset, presence of MetS, concomitant treatment with traditional disease-modifying antirheumatic drugs (DMARD), and the presence of dactylitis as the independent variables. Because tender and swollen joint and tender enthesal counts are included in the definition of MDA, the multivariate logistic regressions were repeated excluding tender and/or swollen joint count as a covariate. Multicollinearity effect in multivariable regression models was excluded by a stepwise approach with variables included for $p <$ 0.05 and excluded for $p >$ 0.1. Moreover, a tolerance test was employed to exclude models in which the sum of the values exceeded the sum of the variances for all variables. The Hosmer-Lemeshow goodness-of-fit test was performed. All the results are presented as 2-tailed values with statistical significance if p values are $<$ 0.05.

RESULTS

At T0, 146 patients with PsA were enrolled and started the treatment with a TNF- α blocker. Ten patients discontinued before the 3-month followup because of adverse events (3 infusion reactions, 4 systemic atopic reactions, 3 injection site reactions). Because of the very short duration of treatment of these 10 subjects, it was not possible to analyze the whole sample considering them as non-MDA subjects, and they were excluded.

Twenty-two patients (16.2%) had achieved MDA at the 3-month followup; patients’ baseline demographic, clinical, and laboratory characteristics are shown in Table 1. As many as 22 (16.2%) patients were diagnosed with oligoarticular disease, 46 (33.8%) with axial disease, and 68 (50.0%) with polyarticular disease; they were treated with mono- or combination therapy as follows: 48 (35.3%) with etanercept, 28 (20.6%) adalimumab, 4 (2.9%) infliximab, 2 (1.5%) sulfasalazine plus adalimumab, 26 (19.1%) etanercept plus methotrexate (MTX), 12 (8.8%) adalimumab plus MTX, 12 (8.9%) infliximab plus MTX, 2 (1.5%) adalimumab plus leflunomide, and 2 (1.5%) adalimumab plus cyclosporin A. As shown in Figure 1, all clinical outcome measures and the ESR changed significantly from T0 to T3. In contrast, CRP, serum cholesterol, and triglycerides did not change significantly (all $p >$ 0.05; not shown in Figure 1). In accord with our previous findings³⁰, the prevalence of MetS and of some of its features showed no significant difference between those that achieved MDA criteria and those that did not [6 (27.3%) vs 44 (38.6%), respectively; $p =$ 0.347]. The prevalence of liver steatosis was higher in subjects who did not achieve MDA compared to

Table 1. Clinical and demographic characteristics of the study population.

Characteristic	Whole Sample, n = 136	Minimal Disease Activity, n = 22	No Minimal Disease Activity, n = 114	p
Age, yrs	45.62 ± 11.82	37.82 ± 12.21	47.12 ± 11.18	0.001
Male, n (%)	58 (42.6)	12 (54.5)	46 (40.4)	0.245
Clinical pattern, n (%)				
Polyarticular	68 (50.0)	6 (27.3)	62 (54.4)	0.051
Oligoarticular	22 (16.2)	6 (27.3)	16 (14.0)	0.201
Spondylitis	46 (33.8)	10 (45.5)	36 (31.6)	0.226
Disease duration, yrs	5.19 ± 3.04	4.82 ± 3.40	5.26 ± 2.97	0.532
ESR, mm/h	21.93 ± 16.200	28.27 ± 18.73	20.70 ± 15.45	0.044
CRP, mg/l	6.02 ± 8.886	11.40 ± 19.39	5.42 ± 6.79	0.043
SJC	3.13 ± 4.412	1.82 ± 2.03	3.39 ± 4.69	0.013
TJC	13.54 ± 9.791	7.45 ± 5.58	14.72 ± 9.99	0.001
PASI	0.78 ± 0.875	0.82 ± 1.05	0.77 ± 0.84	0.821
HAQ	1.20 ± 1.12	1.25 ± 1.03	1.68 ± 1.33	0.225
VAS	73.4 ± 19.9	72.7 ± 23.9	73.6 ± 19.2	0.857
Ritchie index*	14.6 ± 9.51	10.36 ± 6.98	15.45 ± 9.74	0.006
Tender enthesal count	8.02 ± 2.11	9.33 ± 3.62	8.93 ± 4.12	0.233
BASFI	5.58 ± 2.17	5.11 ± 3.09	5.67 ± 1.94	0.268
BASDAI**	6.39 ± 1.95	5.35 ± 2.24	6.60 ± 1.84	0.021
Dactylitis, n (%)	20 (14.70)	4 (18.2)	16 (14.0)	0.742
MetS, n (%)	50 (36.76)	6 (27.3)	44 (38.6)	0.347
Bright liver, n (%)	51 (38.1)	4 (18.2)	47 (42.0)	0.053

* Performed only in subjects with peripheral disease. ** Performed only in subjects with axial disease. SJC: swollen joint count; TJC: tender joint count; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; VAS: visual analog scale for pain; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MetS: metabolic syndrome.

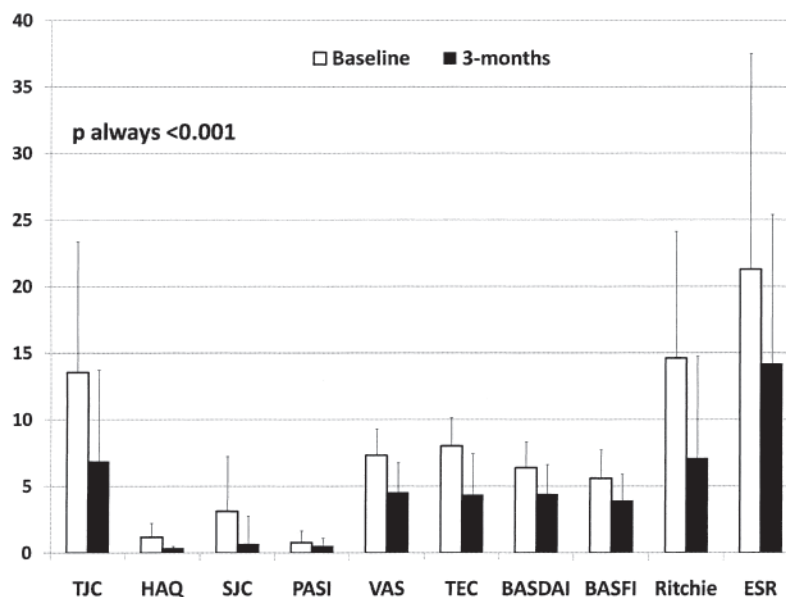


Figure 1. Clinical and laboratory variables at baseline (T0) and after 3 months. TJC: tender joint count; HAQ: Health Assessment Questionnaire; SJC: swollen joint count; PASI: Psoriasis Area and Severity Index; VAS: visual analog scale (for pain); TEC: tender enthesal count; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; RITCHIE: Ritchie articular index; ESR: erythrocyte sedimentation rate.

those who did (42.0% vs 18.2%, respectively). These differences were not significant ($p = 0.053$), although demonstrating a strong trend. Analyzing by disease activity, patients achieving MDA after a 3-month treatment were found to be younger than those not achieving MDA (37.82 ± 12.21 yrs vs 47.12 ± 11.18 yrs, respectively; $p = 0.001$). Baseline ESR and CRP were found to be higher in those achieving MDA at 3 months than those not ($ESR 28.27 \pm 18.73$ mm/h vs 20.70 ± 15.45 mm/h; $p = 0.044$; $CRP 11.10 \pm 19.39$ mg/l vs 5.42 ± 6.79 mg/l; $p = 0.043$). Lower baseline TJC (7.45 ± 5.68 vs 14.72 ± 9.9 ; $p = 0.001$), SJC (1.82 ± 2.03 vs 3.39 ± 4.69 ; $p = 0.013$), BASDAI (5.35 ± 2.24 vs 6.60 ± 1.84 ; $p = 0.021$), and Ritchie articular index (10.36 ± 6.98 vs 15.45 ± 9.74 ; $p = 0.006$) were noted in subjects who achieved MDA as compared with those who did not. By contrast, BASFI did not show any significant difference ($p = 0.268$). Among the 22 subjects with MDA at 3 months, 20 (90.9%) maintained the MDA at 6 months and only 2 (9.1%) showed a relapse of disease activity ($p < 0.001$). A regression analysis showed that some baseline clinical variables were able to predict the 3-month status of MDA. In particular, whereas age (OR 0.896, 95% CI 0.826–0.971, $p = 0.003$) and BASFI (OR 0.479, 95% CI 0.280–0.821, $p = 0.007$) inversely predicted achievement of MDA, CRP (OR 1.078, 95% CI 1.004–1.157, $p = 0.018$) directly predicted achievement of MDA after 3 months of anti-TNF therapy. In contrast, sex ($p = 0.783$), clinical pattern ($p = 0.969$), ESR ($p = 0.843$), SJC ($p = 0.336$), TJC ($p = 0.964$), PASI ($p = 0.387$), HAQ ($p = 0.948$), VAS for pain ($p = 0.206$), Ritchie index ($p = 0.607$), BASDAI ($p = 0.690$), presence of dactylitis ($p = 0.877$), MetS ($p = 0.391$), and concomitant treatment with traditional DMARD ($p = 0.289$) were found not to predict achievement of MDA at 3 months. The Hosmer-Lemeshow goodness-of-fit test showed no evidence of lack of fit ($p = 0.638$).

DISCUSSION

This is the first study to our knowledge aimed at identifying predictors of early achievement (3 months) of minimal disease activity in a group of PsA patients treated with TNF blockers. At variance from other authors¹⁹ who investigated the frequency, duration, the potential features associated with achievement of MDA, and the prognostic ability of these criteria in an independent observational PsA cohort, we prospectively evaluated predictors of early MDA. Coates, *et al*¹⁹ investigated how many PsA patients achieved MDA over 12 months at consecutive clinic visits and whether this was associated with a reduction in the progression of joint damage, and showed that low ESR and oligoarthritis were predictors of achieving sustained MDA. In addition, patients achieving sustained MDA had a significant reduction in progression of joint damage¹⁹. Given the short followup, a measurement of joint damage progression was not performed in our study. Moreover, whereas Coates, *et al*¹⁹ in their observational study

included PsA subjects regardless of their current treatment, we prospectively evaluated only patients beginning anti-TNF- α treatment. This might be useful to identify predictors of clinical response to this specific therapy. Although the 2 studies aimed at evaluating the clinical predictors of MDA, comparisons of similarities and differences could be biased by the radically different study designs.

Whereas all outcome measures that we evaluated significantly improved after 3-month treatment with TNF- α antagonists, only BASFI, age, and CRP were found to be predictors of clinical remission. According to other studies²³, although significant clinical improvement was found between 3 and 12 months of treatment, most indicators showed the greatest response within the first 3 months. Recent data²³ reported that the baseline HAQ was a predictor of remission (that is, 28-joint Disease Activity Score < 2.6) after 12 months of treatment. In line with these results, in spite of the different criteria for defining remission, our study also found that a measure of physical function, the BASFI, was a predictor of MDA. Moreover, even if our study showed that the HAQ was not a predictor of achievement of MDA, we did find a direct correlation between BASFI and the HAQ (Pearson's exact test: $r = 0.419$, $p < 0.001$). These findings are in agreement with other groups who showed that severe disability predicted poor response to anti-TNF therapy³¹.

In current clinical practice, disease activity and function in patients with spondyloarthritis such as PsA are frequently assessed using the BASDAI and the BASFI^{32,33}, because they broadly evaluate some main symptoms of PsA: fatigue, neck pain, upper and lower back pain, stiffness, joint pain, and joint pain with pressure. Higher BASDAI and BASFI values indicate different levels of disease activity and joint dysfunction.

Although the Ritchie articular index, derived for RA, performs less well in PsA than other outcome measures, it represents a useful method for joint assessment, in particular for peripheral disease³⁴. High Ritchie index values reveal severe peripheral involvement. Thus the finding that older age is an inverse predictor of a good clinical response may be related to better physical function in younger subjects.

As for the measures of acute-phase reactants, as ESR and CRP levels are often normal in PsA, these features were excluded from the MDA criteria measures. Despite this, in view of our purpose, we took measurements of inflammatory indicators at baseline and at 3 months, which demonstrated that higher baseline CRP levels are predictive of good response. This is in line with the literature³¹, but, differently from other studies, we highlighted the role of CRP in the prediction of early clinical response.

Our data show that the presence of MetS does not impair the antiinflammatory effect of TNF- α blockers, and does not affect the achievement of MDA. Our group has recently shown that the influence of MetS on the measurement of carotid intima-media thickness (IMT) was significant in patients treated with DMARD, but not in those treated with

TNF blockers³⁰. Considering that IMT encompasses the effects of both vascular risk factors and inflammation on atherogenesis, our previous data may confirm and extend our present findings.

On the other hand, the difference in the prevalence of “bright liver” among MDA and non-MDA subjects was just below statistical significance ($p = 0.053$), suggesting a strong trend. Further studies could be useful to address this issue.

According to other reports²⁴ the concomitant treatment with traditional DMARD was not found to predict achievement of MDA at 3 months in patients with PsA. This is supported by the evidence that concomitant use of MTX and TNF- α blockers was not more effective in achieving response in subanalyses of results from randomized clinical trials^{14,35}.

Of note, other studies used different criteria to define good clinical response. Lacking an agreed “gold standard,” and considering that some of these criteria (28-joint Disease Activity Score) do not include assessment of the distal interphalangeal joints and are not recommended for assessment of disease activity in PsA by the Outcome Measures in Rheumatology (OMERACT)³⁶, we chose the definition of MDA that we have used for its usefulness in “real-life” practice.

Minimal disease activity is defined by OMERACT as “that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations,” and this encompasses both remission and low disease activity³⁷. Recently, Coates and Helliwell recognized the usefulness of the proposed criteria for assessing MDA in providing an outcome measure for clinical trials²². It is important to note that patients achieving MDA, although showing a marked reduction in the progression of joint damage, reported progression of joint impairment³⁸. This finding supports the hypothesis that these criteria are not for full remission but rather for MDA, with a small residual amount of disease activity remaining³⁸.

Investigating predictors of response to anti-TNF is important because of the potential side effects of biological therapies, such as the increased incidence of infections, the unclear relationship between TNF- α antagonists and malignancies, and the need for caution in patients with a depressed cardiac ejection fraction³⁹. Identification of predictors of response may reduce the use of TNF- α antagonists in patients with low probability of good clinical response, preventing the occurrence of unnecessary side effects.

In addition, although pharmacoeconomic studies have demonstrated that TNF- α blockers are cost-effective treatment options for psoriatic disease, they remain expensive and not widely available to patients, depending on the different national health systems⁴⁰. Thus reliable predictors may also reduce unnecessary costs, and help clinicians to identify the patients most likely to respond to anti-TNF- α treatments. In our opinion early identification of patients with MDA is required for optimal control and prevention of joint damage.

Bond, *et al*⁴¹ demonstrated that the number of actively inflamed joints (by SJC) predicts the progression of radiological joint damage, supporting that control of joint inflammation in PsA is necessary to prevent progression of both clinical and radiological involvement. Thus management of patients with PsA should aim to minimize the number of inflamed joints and the control of evident inflammation should continue even in the presence of damage. Recently, Cresswell, *et al*⁴² demonstrated that tender joints are also important predictors of joint damage, as they are indicative of active joint disease.

As for different clinical patterns, the prediction of MDA according to oligoarticular, axial, and polyarticular presentations would be of major interest. However, because of the relatively small sample size of our study, this analysis could not be carried out. Estimates of the sample size imply that 2–3 times as many patients are needed to allow a reliable analysis. This is supported by the finding that such stratification did not play a significant role in the prediction of MDA (regression analysis) in our report.

The finding that PASI scores were quite low in our sample requires further investigation. TNF- α blockers should be used in individuals with PsA only after the failure of traditional DMARD; all subjects in our study, although they were not in a state of MDA, were under treatment with drugs other than TNF- α blockers at the time of enrollment, and baseline PASI scores may have been affected by such treatment. Nevertheless, PASI scores decreased significantly during treatment with TNF- α blockers.

Our data suggest that young age, high level of inflammatory activity, and a preserved joint function at the time of enrollment for TNF blocker treatment might identify patients most likely to respond to these therapies, and that subjects with lower baseline TJC, SJC, BASDAI, and Ritchie articular index more frequently meet the criteria for achieving MDA. Although MDA was achieved by only 16% of our PsA population at 3 months, considering that most (90.9%) of the subjects achieving MDA at 3 months were found to maintain it at 6 months, the observation of early (3 months) achievement of MDA might be considered as a predictor of treatment efficacy with TNF- α blockers. Further studies with a higher number of subjects are needed to address this issue.

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