Minimal Disease Activity and Remission in Psoriatic Arthritis Patients Treated with Anti-TNF-α Drugs

Fabio Massimo Perrotta, Antonio Marchesoni, and Ennio Lubrano

ABSTRACT. Objective. A state of remission is the target of therapy in chronic arthritis. The aim of the present study was to assess the rate of minimal disease activity (MDA) and remission in patients with psoriatic arthritis (PsA) treated with tumor necrosis factor (TNF-α) blockers. Disease characteristics and predictors of MDA were also evaluated.

Methods. Patients fulfilling the ClASsification for Psoriatic ARthritis (CASPAR) criteria and treated with TNF-α blockers adalimumab, etanercept, or golimumab were enrolled and prospectively followed every 4 months for 1 year in a clinical practice setting. Patients were considered in MDA when they met at least 5/7 of the criteria previously defined. Other remission criteria evaluated were 28-joint Disease Activity Score-C-reactive protein (DAS28-CRP) < 2.6 and Disease Activity in Psoriatic Arthritis (DAPSA) score ≤ 3.3. Patients achieving MDA were compared to non-MDA to identify outcome predictor factors.

Results. Of the 75 patients treated with TNF-α blockers, at baseline no patients were in MDA or had a DAPSA score ≤ 3.3, while 25 (21.3%) had a DAS28-CRP score < 2.6. Five patients (6%) discontinued treatment because of side effects or inefficacy during followup. After 12 months, MDA was achieved in 46 patients (61.3%). No difference was found among the 3 anti-TNF-α drugs. Predictors for MDA were found to be male sex, high CRP, high erythrocyte sedimentation rate, and low Health Assessment Questionnaire.

Conclusion. In our prospective observational study, based on a clinical practice setting, MDA was achieved in 61.3% of patients treated with TNF-α blockers, identifying this as an achievable target for patients with PsA. Predictors of remission were also identified. (J Rheumatol First Release December 15 2015; doi:10.3899/jrheum.150805)

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

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis with a prevalence of 0.02–0.42%1 in the general population and 13.8–30% among patients with psoriasis1,2. The peripheral joint involvement of PsA is progressive in the majority of patients, reinforcing the need for optimal management and treatment strategies3. Moreover, patients with PsA have functional impairment, reduced quality of life, and a significant increase in early mortality compared to the general population4. In the context of this multifaceted disease, the concept of remission is still considered an unmet need5. Treatment with tumor necrosis factor-α (TNF–α) blockers showed to be effective in clinical trials and in real life, with a reduction in disease activity variables and radiographic progression5,6,7. But the real effect of anti-TNF–α therapy in controlling all the different clinical features of PsA such as dactylitis, enthesitis, and axial involvement is still unclear.

In patients with PsA, as well as in rheumatoid arthritis (RA), a state of remission or low disease activity is the target of therapy. In this context, the definition of clinical response or remission has to consider all disease domains. In 2010, Coates, et al developed a composite outcome measure as a target of treatment for patients with PsA that encompasses most of the disease domains8. Patients are considered in minimal disease activity (MDA) when they meet 5/7 of the following criteria: tender joint count ≤ 1; swollen joint count (SJC) ≤ 1; Psoriasis Activity and Severity Index (PASI) ≤ 1 or body surface area ≤ 3; patient pain visual analog scale (VAS) score of ≤ 15; Health Assessment Questionnaire (HAQ) score ≤ 0.5; and tender entheseal points ≤ 1. These criteria were validated using interventional trial data9. Achieving sustained...
MDA (defined as MDA for over 12 months at consecutive clinic visits) was found to reduce radiographic joint damage progression over a 3-year period, with an increase in damaged joint count of 0.9 in patients persistently in MDA compared to an increase of 2.4 in those not achieving sustained MDA. In a recent study involving 306 patients of a retrospective cohort, Haddad, et al. found that MDA was achieved in 64% of patients, and predictors of MDA were normal erythrocyte sedimentation rate (ESR) and male sex.

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-life experiences. The aim of our study was to identify MDA at 12 months in patients with PsA taking TNF-α blocker therapy and to describe the disease characteristics of patients who achieve MDA. Secondary targets were to compare MDA status with the indices of disease activity and to identify predictors for MDA.

**MATERIALS AND METHODS**

Patients were enrolled at the Rheumatology Unit, Department of Medicine and Health Science, University of Molise. All patients fulfilled the CASSification for Psoriatic Arthritis (CASPAR) criteria. TNF-α blockers were prescribed according to the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations. Each subject’s written consent was obtained according to the Declaration of Helsinki, and the study was approved by the local ethics committee.

**Patient selection.** All the patients with PsA who were taking adalimumab (ADA; 40 mg every other week), etanercept (ETA; 25 mg twice/weekly or 50 mg/weekly), or golimumab (GOL; 50 mg/monthly) from October 2012 to September 2014 were considered potentially eligible for the study. Exclusion criteria were (1) age < 18 years; (2) treatment with anti-TNF-α blockers. Methotrexate, sulfasalazine, leflunomide, and cyclosporine were used, respectively, in 67 (89.3%), 36 (48%), 10 (13.3%), and 19 (25.3%) patients. No patients were in MDA or had a DAPSA score ≥ 3.3 at baseline, while 25 (21.3%) had a DAS28-CRP score < 2.6. Table 1 shows the demographic and clinical characteristics of the study population. No differences were found between males and females. Five patients (6%) discontinued treatment because of side effects or inefficacy during followup. After 12 months, MDA was achieved in 46 (61.3%) of the 75 patients with PsA. Figure 1 shows MDA, DAS28-CRP remission, and DAPSA remission at baseline, 4 (T4), 8 (T8), and 12 (T12) months. At T12, DAPSA and DAS28 remission was achieved, respectively, in 36% and 69.3% of patients. The percentage of patients achieving MDA, DAPSA remission and DAS28 remission increased significantly from baseline to T12. Moreover, the percentage of patients achieving DAPSA remission was significantly lower than the percentage of patients achieving DAS28-CRP remission criteria (p < 0.001) or MDA (p < 0.01). No statistical differences were found among the 3 anti-TNF-α in relation to the index used to define remission, but the study was underpowered to detect differences. MDA rates for the 3 drugs at the various timepoints are depicted in Figure 2.

The association of MDA with the main variables was studied. For this purpose, the values categorized were age (≤ or > 40 yrs), disease duration (≤ or > 2 yrs), CRP (low ≤ 0.5, high > 0.5 mg/dl), ESR (low ≤ 15, high > 15 mm/h), and HAQ (low ≤ 0.5, high > 0.5). Table 2 shows the OR (95% CI) of achieving MDA at Month 12 according to the baseline values of the studied variables, by univariate and/or multivariate analysis. Independent predictors of MDA were male sex (2.67/1.21–5.90; p = 0.01), high CRP (3/1.07–8.38; p = 0.04), high ESR (3.3/1.61–5.98; p = 0.03), absence of axial involvement (4.26/1.42–12.7; p = 0.01), and low HAQ score (9.56/2.11–43.24; p < 0.01). Table 3 shows the concordance between the 3 indices in defining remission. Overall, the
Table 1. The main demographic and clinical features of the study population (75 patients with PsA treated with TNF-α blockers). Results are expressed as median/25th–75th percentile unless otherwise indicated.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Male/female</th>
<th>Age, yrs</th>
<th>Disease duration, yrs</th>
<th>Articular manifestations (%)</th>
<th>Extraarticular manifestations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>35/40</td>
<td>52/46.75–62</td>
<td>6.5/3–12</td>
<td>Axial</td>
<td>Uveitis</td>
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<td>Articular manifestations (%)</td>
<td>Axial</td>
<td>50.6</td>
<td></td>
<td>Peripheral arthritis</td>
<td>2/0–7</td>
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<tr>
<td>Disease duration, yrs</td>
<td>Peripheral arthritis</td>
<td>91.9</td>
<td></td>
<td>Enthesitis</td>
<td>5.6</td>
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<td>Articular manifestations (%)</td>
<td>Enthesitis</td>
<td>41.4</td>
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<td>Dactylitis</td>
<td>IBD</td>
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<tr>
<td>Extraarticular manifestations (%)</td>
<td>Dactylitis</td>
<td>22.6</td>
<td></td>
<td>ESR, mm/h</td>
<td>DAS28-CRP* 3.71/2.7–5.06</td>
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<tr>
<td>Variables of PsA treated with TNF-α blockers</td>
<td>ESR</td>
<td>23/12.75–29</td>
<td>0.8/0.39–1.2</td>
<td>VAS pain</td>
<td>52/45–60</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>VAS physician</td>
<td>45/35–50</td>
<td>0.75/0.62–1.25</td>
<td>HAQ</td>
<td>1.3/0–2.05</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>HAQ</td>
<td>20.6/13.6–29.6</td>
<td>1.3–0.39–1.2</td>
<td>PASI</td>
<td>1.3/0–2.05</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>PASI</td>
<td>52/46.75–62</td>
<td>0.8/0.39–1.2</td>
<td>MASES</td>
<td>1/0–2</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>MASES</td>
<td>52/46.75–62</td>
<td>0.8/0.39–1.2</td>
<td>DMARD</td>
<td>40 (39.5)</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>DMARD</td>
<td>39 (31.5)</td>
<td></td>
<td>Prednisone intake</td>
<td>40 (31.5)</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
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<td>99 (79.8)</td>
<td></td>
<td>NSAID intake</td>
<td>99 (79.8)</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
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<td>39 (31.4)</td>
<td></td>
<td>Anti–TNF-α therapy (%)</td>
<td>ADA</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>ADA</td>
<td>62 (50)</td>
<td></td>
<td>ADA</td>
<td>39 (31.4)</td>
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<td>Variables of PsA treated with TNF-α blockers</td>
<td>ETA</td>
<td>23 (18.5)</td>
<td></td>
<td>ETA</td>
<td>62 (50)</td>
</tr>
<tr>
<td>Variables of PsA treated with TNF-α blockers</td>
<td>GOL</td>
<td></td>
<td></td>
<td>GOL</td>
<td>23 (18.5)</td>
</tr>
</tbody>
</table>

PsA: psoriatic arthritis; TNF: tumor necrosis factor; IBD: inflammatory bowel disease; DAS28: 28-joint Disease Activity Score; DAPSA: Disease Activity Index for Psoriatic Arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PtGA: patient’s global assessment; VAS: visual analog scale; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area and Severity Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; ADA: adalimumab; ETA: etanercept; GOL: golimumab.

Concordance was poor at all timepoints, with the exception of the concordance between DAPSA score and MDA at 4 and 12 months, which was moderate.

**DISCUSSION**

Remission or low disease activity status is the goal of therapy in chronic inflammatory arthritis. In RA, using DAS28 or American College of Rheumatology criteria, remission was achieved in about one-third of patients, especially in early disease. In axial spondyloarthritis (axSpA) treated with anti-TNF-α, remission was achieved in 53.2% of the patients with the nonradiographic form and in 50.9% of the patients with ankylosing spondylitis (AS), in a clinical practice setting.

In our study, 61.3% of the patients with PsA treated with ETA, ADA, or GOL were in MDA after 12 months of treatment. In the ADEPT trial, it was demonstrated that MDA could be reached in 33.8% of patients after 24 weeks of ADA treatment, while in the IMPACT1 and IMPACT2 trials, MDA was reached in 48% and 52% of patients after 16 and 24 weeks of treatment, respectively, with infliximab. Our real-life data showed a similar response rate, but with an increase in the number of patients who reached MDA at 12 months. In a recent report, Haddad, et al demonstrated a very similar rate of MDA (64%) in a cohort of patients with PsA treated with anti-TNF-α. Other studies in a setting of clinical practice reported very similar response rates. An interesting result of our work was the almost doubling in efficacy of anti-TNF in achieving remission from T4 to T8. This could be related to some components such as PtGA, VAS pain, and SJC. These were the main clinical components improved by the biologic treatment in that period of observation, as demonstrated by the increasing percentage of patients who reach VAS pain ≤ 15, PtGA ≤ 20, and SJC ≤ 1 (respectively, 117%, 64.2%, and 53.3%) at T8 increases compared to T4. The consistency of the data yielded by observational studies seems to suggest that in patients with PsA, the expected MDA rate after 12 months of anti-TNF-α therapy should be about 60–65%. The remaining 35–40% of patients not in MDA after 1 year of this therapy might either experience an early loss of efficacy or have a disease driven by cytokines other than TNF-α. In the latter case, other treatments targeted to different inflammatory pathways might prove useful.

In our study, predictors of response to treatment with TNF-α blockers were male sex, preserved functional status, high ESR, and CRP. The finding that patients with high inflammatory burden were more likely to achieve MDA when treated with anti-TNF-α is in keeping with findings in studies on patients with AS or axSpA. However, Haddad, et al showed normal ESR as a predictor factor for MDA. This difference could be explained by the different characteristics of the 2 cohorts of patients and by the different design of the study: in our prospective work, 64% of patients had abnormal ESR values (defined as ESR > 20 mm/h) as opposed to 25% of patients in the study by Haddad, et al. In a large study including patients with early PsA from a Swedish register, a high rate of MDA (40.1%) was found after 5 years of followup. Also in that study, male sex was a predictor of MDA. Although no statistical difference was found in the item of pain or PtGA between men and women, a sex-related propensity for higher pain levels cannot be excluded and may explain these results. Another association was with lower HAQ. Although HAQ might be related to damage, it is also associated with disease activity. Our results could be in contradiction, because the chance of achieving MDA is associated with higher disease activity (i.e., high CRP and ESR), but also with lower HAQ. In our study, however, HAQ
correlated well with the number of damaged joints, while a poor correlation was found between ESR and CRP. Indeed, this could be in keeping with a possible role of HAQ as a measure of severity in this group of patients.

In our work, the absence of axial involvement is associated with higher probability to reach a state of MDA. In particular, our results showed that the absence of axial involvement was associated with higher probability to reach a state of MDA. MDA, per se, is more influenced by peripheral joint involvement; or alternatively, the presence of axial involvement might be associated with a more severe disease. It has been suggested that MDA may not define a state of remission or near-remission. A definition of remission in PsA has not been uniformly accepted; DAPSA score ≤ 3.3 and DAS28-CRP < 2.6 could be useful surrogates of remission, especially in patients with PsA who have predominant peripheral joint involvement. In our study, the percentage of patients achieving DAS28-CRP remission criteria (69.3%) and MDA did not statistically differ, while the percentage of patients with PsA who reached DAPSA score (36%) was significantly lower (p < 0.01). It is clear that composite measures used in RA such as the DAS28 rely mainly on disease activity in 28 joints, and therefore do not fully represent the peripheral joint involvement of PsA. In fact, DAS28 is a measure tailored mainly for small joint involvement of the hands, while PsA is a real heterogeneous
achieved by patients with PsA treated with anti-TNF.

The present study confirmed that a high rate of MDA may be suitable to assess disease activity in PsA. However, because they are not used in our clinical practice on a regular basis, we could not include them in our study.

Table 3. Concordance (Cohen’s 𝜃) between the different response criteria. T numbers refer to months.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>T0</th>
<th>T4</th>
<th>T8</th>
<th>T12</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA and DAS28-CRP remission</td>
<td></td>
<td></td>
<td>0.18</td>
<td>0.11</td>
</tr>
<tr>
<td>DAPSA remission and DAS28-CRP remission</td>
<td>0.30</td>
<td>0.13</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>MDA and DAPSA remission</td>
<td>0.53</td>
<td>0.36</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

MDA: minimal disease activity; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis.

It also showed that MDA, DAS28, and DAPSA are not easily interchangeable measures of disease activity in PsA.

REFERENCES


