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# An overview of low disease activity and remission in psoriatic arthritis

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## ABSTRACT

Psoriatic arthritis (PsA) is a complex, multisystem and potentially disabling disease with musculoskeletal and skin manifestations. In PsA, as well as in the other chronic rheumatic conditions, a state of low disease activity or remission should be the target of treatment but to reach this objective, in the assessment of PsA patients, is still an unmet need due to the heterogeneity of disease manifestations. With the introduction of anti-TNF treatment, low disease activity or remission become an achievable and suitable state that could be reached by 50%–60% of PsA patients. The aim of this paper is to briefly summarise the concept of low disease activity and remission in PsA, with particular focus on anti-TNF therapy.

## Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis, with an estimated prevalence between 0.02 and 0.42% in the general population (1, 2). Several studies have reported an occurrence of erosions ranging from 46 to 62% of patients affected by the disease (3), leading to a current concept of that progressive peripheral joint involvement may occur in a majority of patients. Patients with PsA experience functional impairment, reduced quality of life, and have a significant increase in mortality rates compared to the general population (5). Therefore, an unmet need in PsA is the concept of remission (6). Drug-induced remission may be defined as no clinically detectable disease activity, while continuing drug treatment. Remission also implies reversibility of functional impairment to the greatest extent possible, minimal or no progression to joint destruction and a theoretical possible effect in healing a damaged joint (7). In PsA patients, as well as in rheumatoid arthritis (RA), a state of remission or

low disease activity should be the target of therapy, in patients in whom this goal appears possible.

The introduction of tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) blockers revolutionised the treatment of PsA. This approach proved to be effective in clinical trials and in routine care, with a reduction in disease activity and slowing of radiographic progression (8, 9). A growing body of data addresses the impact of anti-TNF- $\alpha$  therapy in controlling the different clinical features of PsA, such as dactylitis, enthesitis and axial involvement and to induce a state of remission in these domains. In this report we briefly summarise the concept of remission in PsA, with particular focus on anti-TNF therapy.

## The concept of remission in PsA

PsA is a complex disease with various manifestations including involvement of peripheral and axial joints, skin and nails, enthesitis and dactylitis, as well as extra-articular manifestations, such as uveitis and inflammatory bowel disease. All these clinical features should be considered when assessing disease activity, especially because disease activity in different domains of PsA may be unrelated. Remission criteria and composite activity indexes [Boolean criteria, Disease activity score (DAS) 28 joints] borrowed from RA have been used in PsA, but do not include some unique manifestations of PsA (10, 11). Composite measures combine several dimensions of disease status, by combining these different domains into a single score. Such composite indices are needed, since no “gold standard” unidimensional measure is available. At the OMERACT (Outcome Measures in Rheumatology) meeting, it was emphasised that the use of any composite measure should permit the effect of an intervention on each domain to be assessed independently (12).

**Table I.** Definitions of MDA and remission according to various composite outcome indices (19, 31).

DAS28-CRP	$0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.36 \times \ln(\text{CRP}+1) + 0.014 \times \text{PGA} + 0.96$	Low disease activity $\leq 3.2$ ; remission $< 2.6$
DAS28-ESR	$0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{PGA}$	Low disease activity $\leq 3.2$ ; remission $< 2.6$
MDA	TJC $\leq 1$ ; SJC $\leq 1$ ; PASI $\leq 1$ or BSA $\leq 3$ ; VAS pain score of $\leq 15$ ; PGA $\leq 20$ ; HAQ score $\leq 0.5$ ; and tender enthesal points $\leq 1$ .	5/7 of the criteria
CPDAI	68TJC, 66 SJC, PASI, enthesitis scored from 0 to 4, based on palpation of Achilles tendon and bilateral plantar fasciae insertion), dactylitis (a simple count of each digit involved), and spinal manifestations [BASDAI and ASQoL (Ankylosing Spondylitis Quality of Life)].	Low disease activity $< 4$
DAPSA	68 TJC+66 SJC+ PGA+ VAS pain + CRP (mg/dl)	Remission $\leq 3.3$
ACR/EULAR (Boolean remission criteria)	TJC, SJC, CRP (mg/dl), and PGA (on a 0–10 scale)	TJC $\leq 1$ , SJC $\leq 1$ , CRP $\leq 1$ mg/dl, and PGA $\leq 1$ (on a 0–10 scale)
PASDAS	$((0.18 \times \sqrt{\text{Physician Global VAS}}) + (0.159 \times \sqrt{\text{Patient Global VAS}}) - (0.253 \times \sqrt{\text{SF-36PCS}}) + (0.101 \times \text{LN}(\text{swollen joint count} + 1)) + (0.048 \times \text{LN}(\text{tender joints} + 19))) + (0.23 \times \text{LN}(\text{Leeds Entehsitis Count} + 1)) + (0.37 \times \text{LN}(\text{tender dactylitis count} + 1)) + (0.102 \times \text{LN}(\text{CRP} + 1) + 2) \times 1.5$	$< 3.2$ inactive $> 3.2 - < 4.2$ moderate $> 4.2 - 6.0$ active $> 6.0$ very active

DAS: Disease Activity Score; TJC: tender joint count; SJC: swollen joint count; PGA: patient global assessment, CRP: C-reactive protein; ESR: erythrodeposition rate; MDA: minimal disease activity; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Activity And Severity Index; BSA: body surface area; CPDAI: Composite Psoriatic Disease Activity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DAPSA: Disease Activity Index for Psoriatic Arthritis; PASDAS: Psoriatic Arthritis Disease Activity Score.

Criteria for remission in PsA should address all different dimensions of disease (10). The complexity of disease has led to the development of a number of disease activity measures and definitions of remission beyond those available for RA, such as the Disease activity Index for Psoriatic arthritis (DAPSA), the Composite Psoriatic Disease Activity Index (CPDAI), the Psoriatic Arthritis Disease Activity Score (PASDAS) (13-15). These indices have been used in clinical trials and in routine clinical care. In 2010, Coates *et al.* developed a composite outcome measure as a target of treatment for patients with PsA that encompasses most disease domains (16). Patients are considered in minimal disease activity (MDA) when they meet 5/7 of the following criteria: tender joint count (TJC)  $\leq 1$ ; swollen joint count (SJC)  $\leq 1$ ; psoriasis activity and severity index  $\leq 1$  or body surface area  $\leq 3$ ; patient pain visual analogue scale (VAS) score of  $\leq 15$ ; patient global disease activity VAS score of  $\leq 20$ ; Health Assessment

Questionnaire (HAQ) score  $\leq 0.5$ ; and tender enthesal points  $\leq 1$ . These criteria were validated using interventional trial data (17).

Achievement of sustained MDA (defined as MDA for over 12 months at consecutive clinic visits) was found to reduce progression of radiographic joint damage over a 3-year period, with an increase in damaged joint count of 0.9 points in patients persistently in MDA compared to an increase of 2.4 points in those not achieving sustained MDA (18). However, It has been suggested that MDA may not define a state of remission or near remission (16): in this context, the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and other groups are actively working to validate all the composite disease activity scores mentioned above, and definitions of remission to address all clinical domains of PsA (14). Moreover, recent effort aimed to describe the cut points values of these indices and their performance to define remission in PsA, but these

outcome measures were not widely used in clinical trials and require further validation (19) (Table I).

### Remission in observational and RCTs studies

In the era prior to biologic agents, limited data were reported regarding the possibility to achieve remission in patients with PsA treated with synthetic DMARDs. A recent review stated that a condition of remission may be achievable in 25% of PsA patients on DMARDs (20). Gladman *et al.* reported remission, defined as no actively inflamed joints on at least 3 consecutive visits, in 17.6% of a cohort of 391 patients with PsA treated with conventional DMARDs (21).

The introduction of anti-TNF treatment dramatically changed the possible outcomes of PsA patients. Data coming from over ten years of experience with RCTs and observational studies indicated the efficacy of anti-TNF in all PsA domains (peripheral arthritis, axial involvement, enthesitis, dacty-

litis and extra-articular manifestations) (22). In addition, remission has become an achievable target, particularly when a treat-to-target strategy is employed (22). Most published data concerning the efficacy on anti-TNF therapy in PsA did not identify remission or MDA as a primary or secondary endpoint; however, reports are available concerning post-hoc analysis and observational studies after anti-TNF treatment. In a sub-analysis of the ADEPT trial, 39% of 67 PsA patients treated with adalimumab, achieved a state of MDA, compared with 7% of patients randomised to control group ( $p < 0.001$ ) after 24 weeks (23). In the IMPACT1 trial, 48% of 31 patients treated with infliximab achieved MDA compared to 3% of 32 patients in the control group after 16 weeks of treatment (17). In IMPACT2, 52% of 77 patients treated with infliximab achieved MDA, compared to 21% of 80 control patients not treated with infliximab after 24 weeks (17). Recently, in post-hoc analysis of the GO-REVEAL study, treatment with golimumab was associated with significantly larger proportions of patients who achieved MDA compared to control patients, during the placebo controlled period at week 24 (28.1% vs. 7.7%). Long-term follow-up at five years demonstrated that MDA was achieved at least once by approximately 50% of golimumab treated patients (24). Furthermore, achievement of persistent MDA was associated with significantly less radiographic progression and significantly more improvement in components of the MDA criteria that allow specific assessment of physical function (HAQ), and overall disease activity (PtGA), when compared with patients who never achieved MDA (24). This long-term study demonstrated that a condition of remission or near remission status (MDA) is an achievable and suitable target in many PsA patients. In a recent study involving 306 patients of a retrospective cohort, Haddad *et al.* found that MDA was achieved in 64% of patients after an average duration of 1.30 years (25). In a large study including early PsA patients from a Swedish registry, the authors demonstrated a substantial rate of MDA (40.1%) after 5

years of follow-up (26). Van den Bosch *et al.* showed data on remission in patients with PsA treated with adalimumab in a 12-week open-label study. At Week 12, of the 268 patients with active baseline disease, 64.9% achieved remission of joint and/or skin symptoms; 27.2% achieved joint remission defined as TJC  $\leq 1$  + SJC  $\leq 1$ , irrespective of skin remission fulfillment; and skin remission (physician's global assessment = clear/almost clear) regardless of joint remission status was observed in 53.7% patients. One limitation of these studies is that several domains of PsA, such as enthesitis and dactylitis, were not assessed, and a new, not (yet) validated definition of remission was used (27). Similar results were obtained from a retrospective study conducted in 74 PsA patients treated with biologic agents who were evaluated in a dermatological setting. In this study, more than 40% of patients achieved clinical remission, defined as documented absence of clinical signs related to arthritis (no tender or swollen joints), enthesitis or dactylitis after one year of treatment (28).

Data from the literature suggest that in PsA patients, MDA or remission might be achieved during anti-TNF- $\alpha$  therapy by about 50–60% of patients. The remaining 40–50% of patients that did not achieve MDA after therapy might either experience an early loss of efficacy or have a disease driven by cytokines other than TNF- $\alpha$ . In the latter case other treatments targeted to different inflammatory pathways might prove to be useful. Inhibition of IL-12/23 axis with ustekinumab proved efficacious in reducing sign and symptoms in active PsA (29).

As discussed, clinical remission or a MDA leads to better outcomes for PsA patients. However, using highly sensitive imaging techniques (ultrasound, MRI) it is possible to detect the presence of subclinical activity (inflammation) in patients with no clinical evidence of disease activity; therefore achieving a “real” or complete condition of remission may be different than achieving clinical remission (30). Only a few studies assessed remission from the perspective of imaging. Recently, Husic *et al.* investigated the association

between PsA specific clinical composite scores and definitions of remission with ultrasound-verified pathology. Ultrasound remission and minimal ultrasound disease activity were defined as power Doppler-score = 0 and  $\leq 1$ , respectively, at joints, peritendinous tissue, tendons and entheses. Interestingly, the results showed a discrepancy between clinical and ultrasound remission, with an increased tendency to achieve a clinical remission compared to the ultrasound remission. Moreover, only a DAPSA score  $\leq 3.3$  and Boolean definition of remission of the different used score were able to predict ultrasound remission (31). In this scenario, imaging should be a useful tool in PsA, but further studies are needed to integrate information coming from imaging techniques and clinical evaluation to assess remission in PsA patients.

## Conclusions

Despite the relatively small number of studies and the difficulty to define remission objectively in a complex disease such as PsA, a high rate of patients treated with anti-TNF- $\alpha$  drugs may achieve a condition of MDA or remission. Further studies, primarily from registries and the clinic, will provide more data about remission or MDA, and hopefully more insights from predictive factors and biomarkers that will help in defining better the treatment approaches most likely to achieve remission for patients with various manifestations of PsA.

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