Remission in Psoriatic Arthritis

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ABSTRACT. Psoriatic arthritis (PsA) is a multifaceted disease that challenges outcome methodologists. A number of measures have been used to define remission in PsA but they have been mostly articular. Composite measures of disease activity and low disease states are now emerging, but further work is required to assess the implications of achieving these goals and to develop cost-effective treatment strategies to achieve them. (J Rheumatol 2012;39 Suppl 89:19–21; doi:10.3899/jrheum.120235)

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Psoriatic arthritis (PsA) is a heterogeneous disorder affecting peripheral and axial joints and having other features such as dactylitis, enthesitis, and skin and nail disease. Although not all these clinical features may occur together at any one time, it is important to be able to measure them all to assess their effect on the patient and the response to treatment (which may not be consistent across features).

There is little evidence for most traditional disease-modifying antirheumatic drug (DMARD) treatments[1], but there is evidence that tumor necrosis factor (TNF) therapy is superior when compared with methotrexate monotherapy[2]. Those who do not respond to any or a combination of traditional DMARD should be considered for treatment with TNF inhibitors[3], which have proven efficacy. TNF therapy has the added benefit of treating all aspects of disease, including extraarticular features. However, longterm safety data for these treatments are lacking and economic considerations not unimportant. Further, data on rates of improvement and achievement of low disease states are only just emerging: Until recently, there have been few validated outcome measures in PsA, particularly to define disease states such as remission. By analogy to rheumatoid arthritis (RA), the goal of achieving clinical remission is to prevent joint damage and disability. However, in PsA and the other spondyloarthropathies, bone destruction is seen alongside new bone formation, so that the RA paradigm may not hold for these diseases. Further work is needed to obtain longer-term data on bone destruction and formation in PsA treated with TNF inhibitors.

DEFINITIONS OF REMISSION IN PsA

Gladman, *et al* proposed remission to be an absence of actively inflamed joints[4]. However, this definition excludes the significant burden of extraarticular disease and other articular features common to PsA. These other musculoskeletal features were included in remission criteria by an Italian group that used RA remission criteria as a starting point (Table 1)[5]. These criteria allowed virtually no active disease. Skin was presumably included among the extraarticular features, but this was not stated in the text. In a longitudinal cohort, 236 patients with PsA were followed for several years[5]. Interestingly, 60% of that cohort who were treated with TNF inhibitors, and 19% of those given traditional DMARD, achieved remission by these criteria.

The disease activity score for 28 joints (DAS28), originally developed for RA[6], has been found useful for assessing the articular response in PsA[7]. In a study from Dublin, remission in PsA, defined as a DAS score of ≤ 2.6, was achieved in 58% of 152 patients at 12 months[8]. In this study, the Health Assessment Questionnaire score at baseline was the best predictor of achieving remission. Using an observational cohort of people starting DMARD, Lie, *et al* also used the DAS28 remission criteria to assess treatment response[9]. In that study, 24% of 430 patients with PsA had a score of ≤

Table 1. The remission criteria of Cantini, *et al*[5]. All items had to be fulfilled for the patient to be regarded as in remission.

Feature	Cutoff
Fatigue by VAS (0–100)	< 10
Pain by VAS (0–100)	< 10
Morning stiffness, min	≤ 15
Tender joint count	0
Swollen joint count	0
ESR, mm/h	Women ≤ 30; men ≤ 20
CRP, mg/dl	≤ 0.5
Dactylitis	Absent
Enthesitis	Absent
Inflammatory back pain	Absent
Extraarticular features	Absent

VAS: visual analog scale; ESR: erythrocyte sedimentaiton rate; CRP: C-reactive protein.

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2.6 at 6 months. Interestingly, 7% also had a "remission" score at inception, suggesting the treating physicians were basing the need for therapy on other features of the psoriatic disease. The DAS28, although useful in RA, involves a limited joint count. In PsA, the number of joints assessed optimally is 68 tender and 66 swollen, including the distal interphalangeal joints. Although the DAS28 has been shown to distinguish patients with PsA who were treated with anti-TNF agents from those receiving placebo, it was noted that 25% of the patients would not have been included because the primary joints involved were below the knees, joints that are not assessed as part of the DAS28[7].

Kavanaugh and Fransen suggested that remission in PsA be characterized by "a complete absence of disease activity, with no signs or symptoms of active disease"[10]. However, these authors also recognized that remission was not only difficult to achieve and maintain but that, in some patients, mild disease activity in 1 domain may be acceptable. Given this, they concluded that "near remission" or "low disease activity" could be an appropriate goal for an individual patient's treatment[10]. Given this context, minimal disease activity has been defined as "that state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations"[11]. Most recently, criteria for minimal disease activity (MDA) in PsA have been developed and validated. These criteria use 7 measurements including entheseal and skin assessments (Table 2)[12]. Further work has demonstrated that these criteria have some predictive validity — achieving MDA by these criteria results in less radiographic damage in the long term[13].

CAN REMISSION BE MAINTAINED AFTER TREATMENT WITHDRAWAL?

Interestingly, the work of Cantini, *et al* has shown that remission may be sustained despite treatment interruption[5], with a mean duration of remission without drugs of 12 months. If we borrow from work in early RA, it should be possible to identify those patients who can successfully stop treatment entirely without adverse outcome[14]. In RA, sustained remission following treatment withdrawal was predicted by a relatively short duration of symptoms before starting treatment; certain T cell characteristics were also predictive, including abnormal differentiation subsets and T regulatory cells[14].

Table 2. The minimal disease activity (MDA) criteria of Coates, *et al*[12]. Patients are deemed to be in MDA when they meet 5 of 7 of the criteria.

Feature	Cutoff
Pain by VAS, 0–100	< 15
Global disease by VAS, 0–100	< 20
HAQ, 0–3	≤ 0.5
Tender joint count	≤ 1
Swollen joint count	≤ 1
PASI, 0–72	≤ 1
OR body surface area involved, 0–100%	≤ 3
Entehsitis	≤ 1

VAS: visual analog scale; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area and Severity Index.

NEW APPROACHES TO DEFINING LOW DISEASE ACTIVITY AND REMISSION

A composite measure is one way of assessing all relevant clinical outcomes in 1 single instrument. By definition, it incorporates several dimensions of disease status, often by combining these different domains into a single score. Such instruments are well established in RA, and these have been adopted for use in clinical trials involving patients with PsA. Measures adopted from RA include the American College of Rheumatology (ACR) responder index[15] and, as mentioned, the DAS28. The ACR responder index measures improvement in tender and swollen joint counts plus improvement in at least 3 of the following 5 measures: acute-phase reactant, patient global assessment of disease activity by visual analog scale (VAS), physician global assessment of disease activity by VAS, pain by VAS, and physical function using the Health Assessment Questionnaire. The ACR20, 50, and 70 scores refer to ≥ 20/50/70% improvements in these measures, but obviously these scores do not necessarily relate to disease states such as remission.

A number of additional composite measures for assessing disease activity in PsA have been proposed. First, an adaptation of the Disease Activity index for Reactive Arthritis has been renamed the Disease Activity index for PSoriatic Arthritis (DAPSA), developed from a clinical cohort and validated using clinical trial data[16,17]. Secondly, a domain-based approach has been proposed with the development of a composite measure known as the Composite Psoriatic Disease Activity Index (CPDAI)[18]. In the CPDAI, disease involvement is assessed in up to 5 domains: peripheral joints, skin, entheses, dactylitis, and spinal manifestations. For each domain, instruments are used to assess both the extent of disease activity as well as the effect of involvement in that domain on patient function and health-related quality of life (HRQOL). Domains are scored 0–3, with empirical cutoffs for disease severity/activity proposed in each, largely based on the literature. Individual domain scores are summed to give an overall, composite score (range 0–15). Both these composite scores could be developed further to provide cutoffs for high, moderate, and low disease activity, and a cutoff for remission.

There are, however, disadvantages with developing a composite score: a single score may underestimate improvements in some domains and deterioration in others that may be of importance in randomized controlled trials (RCT) of therapies that improve disease domains in different ways. Examples include agents that may improve skin manifestations more than articular ones, or those that benefit periph-

eral joints but not spinal manifestations or enthesitis. On the other hand, if such scores are adopted by regulatory agents, a single score may have the advantage of "qualifying" a patient for further treatment when that patient may not qualify based on disease activity in a single domain. Ideally, a composite measure in an individual patient should also indicate which domains are affected.

NEW DEVELOPMENTS IN COMPOSITE SCORES AND DEFINITIONS OF LOW DISEASE ACTIVITY AND REMISSION

The Group for the Research and Assessment of Psoriasis and Psoriatic Arthritis has recently completed a prospective longitudinal study to develop new composite measures for assessment of PsA[19]. This study, involving more than 500 patients recruited worldwide, used a decision to change treatment as the measure of active disease. Two new measures have emerged: (1) PsA disease activity score (range 0–10), a weighted composite score assessing VAS scores, joint counts, dactylitis, enthesitis, HRQOL, and C-reactive protein; and (2) arithmetic mean desirability function (score range 0–1), a composite score including the core domains of joint counts, VAS scores, HRQOL, physical function, and skin assessment.

The new measures have been compared to existing composite measures, including the DAPSA, CPDAI, and DAS28[20]. These preliminary data demonstrated good discriminatory capacity of both the new and the existing measures. The GRACE (GRAppa Composite Exercise) study will also permit calculation of cutoffs for low, moderate, and high disease activity and remission, based on patient-reported items. Further work on validating these measures by assessing their performance in RCT is ongoing. Ultimately, it should be possible to develop targets for treatment using composite measures, thus providing the possibility of early and "tight" control of this potentially destructive disease.

CONCLUSION

The search continues for an ideal composite measure for PsA. Incorporating clinical assessment into a single composite measure presents several challenges, including feasibility and validity in this multifaceted disease. The goal of treatment remains remission in all aspects of the disease. Further work is required: how is this state defined in PsA and what treatment strategies best achieve remission?

REFERENCES

1. Kavanaugh A, Ritchlin CT, and the GRAPPA treatment group. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. J Rheumatology 2006;33:1417-21.
2. Heiberg M, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 2008;59:234-40.
3. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis 2012;71:4-12.
4. Gladman DD, Hing EN, Schentag CT, Cook RJ. Remission in psoriatic arthritis. J Rheumatol 2001;28:1045-8.
5. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology 2008;47:872-6.
6. Prevoo ML, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a proposed study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35:1101-5.
7. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. Ann Rheum Dis 2006;65:1373-8.
8. Saber T, Ng C, Renard G, Lynch B, Pontifex E, Walsh C, et al. Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis Res Ther 2010;12:R94-R100.
9. Lie E, van der Heijde D, Uhlig T, Heiberg MS, Koldingsnes W, Rødevand E, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:671-6.
10. Kavanaugh A, Fransen J. Defining remission in psoriatic arthritis. Clin Exp Rheumatol 2006;24 Suppl 43:S83-7.
11. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016-24.
12. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48-53.
13. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res 2010;62:965-9.
14. Saleem B, Keen H, Goeb V, Parmar R, Nizam S, Hensor EM, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? Ann Rheum Dis 2010;69:1636-42.
15. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
16. Nell-Duxneuner VP, Stamm TA, Machold KP, Pflugbeil S, Aletaha D, Smolen JS. Evaluation of the appropriateness of composite disease activity measures for assessment of psoriatic arthritis. Ann Rheum Dis 2010;69:546-9.
17. Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis 2010;69:1441-7.
18. Mumtaz A, Gallagher P, Kirby B, Waxman R, Coates L, Veale DJ, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis 2011;70:272-7.
19. Helliwell PS, Fitzgerald O, Strand V, Mease PJ. Composite Measures in Psoriatic Arthritis: a report from the GRAPPA 2009 annual meeting. J Rheumatol 2011;38:540-5.
20. Helliwell PS, Fitzgerald O, Mease PJ. Development of Composite Measures for Psoriatic Arthritis: A Report from the GRAPPA 2010 Annual Meeting. J Rheumatol 2012;39:398-403.