Is reduction or discontinuation of therapy an acceptable possibility in psoriatic arthritis?

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ABSTRACT

Remission in psoriatic arthritis (PsA), albeit variably defined, is a desirable and achievable state, especially in the era of biologic therapy. Historically, studies have used remission criteria derived from rheumatoid arthritis (RA), which indicate that remission is seen in a greater percentage of patients than in RA, including the possibility of drug-free remission in some patients. The Minimal Disease Activity (MDA) measure developed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is a currently acceptable goal of therapy, taking into account PsA-specific elements such as skin disease and enthesitis. Newer PsA composite measures which include thresholds for remission are under development and are now included in prospective clinical trials. Once remission is achieved and sustained on therapy, a natural question is whether treatment can be reduced or discontinued to avoid treatment toxicities and costs. Exploratory data are being analysed from observational cohorts regarding the capacity to reduce treatment dose, dose frequency, or discontinue use of a medication whilst maintaining remission. A controlled dose-reduction and discontinuation study design is outlined, which may provide controlled evidence for such a paradigm of treatment.

A goal of targeted therapy in psoriatic arthritis (PsA) is remission, in order to relieve symptoms, inhibit progressive joint damage, restore normal (or near normal) function and quality of life, and reduce the impact of co-morbidities such as premature cardiovascular morbidity and mortality (1). Until the era of biologic therapy of PsA, "remission" was considered attainable in only a few (if any) patients. With the use of more effective therapies, remission is increasingly attainable, but remains a concept in evolution (2). Are we striving to achieve "clinical" remission, *i.e.* absence of the clinical manifestations of PsA including arthritis, enthesitis, dactylitis, spondylitis, and skin and nail disease, as well as normalisation of laboratory-assessed inflammatory markers? Or are we trying for more absolute remission, including absence of structural damage as judged by evaluation of erosions and joint space narrowing, or signs of inflammation assessed by advanced imaging techniques such as ultrasound or MRI, since "smoldering" damage and inflammation identified by these imaging techniques may be present despite quiescent clinical manifestations? A further issue is that PsA may be characterised not only by erosive damage but also osteoproliferation in the form of syndesmophytes if spondylitis is present, as well as peripheral osteitis, osteophytes, and ankylosis, unlike rheumatoid arthritis (RA). Indeed, Finzel has recently noted that metacarpophalangeal joint osteophytes can progress in PsA despite good clinical control and absence of erosion progression in PsA patients on methotrexate and anti-TNF therapy (3).

Kavanaugh and Fransen suggested that remission in PsA should be defined as "a complete absence of disease activity," nonetheless recognising that absolute remission may be difficult to achieve and maintain, and minimal disease activity in at least one domain may be acceptable (4). In patients with more advanced disease, with irreversible joint damage and impaired function, is remission even possible? In a patient who is highly infection-prone, is the degree of immunomodulation necessary to achieve remission desirable? A recent task force convened to address "treatment to target" in PsA concluded that, in these types of situations, low disease activity state rather than true remission may be acceptable (1).

Various methods for ascertaining remission or low disease activity state in PsA have been either "borrowed" from RA or developed specifically for PsA, as reviewed below. If remission can be achieved and sustained for a long period, the patient, physician and/or payer may wonder if dose reduction or discontinuation of therapy can be attempted, in order to reduce medication usage, diminish risk of medication side effects, and reduce costs (5). The question then arises, can drug-free remission be maintained in some patients, and, if not, what will be the parameters for return to original dosing or re-institution of therapy? Evidence for dose reduction or discontinuation of therapy, and strategies to investigate this approach, are explored here.

A variety of measures have been employed in various studies of remission in PsA, including DAS28 ≤2.6 and the 1981 American College of Rheumatology (ACR) remission criteria (6), which have been developed for RA. Cantini *et al*. modified the 1981 ACR remission criteria for PsA, including absence of dactylitis, enthesitis, evidence of inflammatory back pain and extra-articular features, as well as normalisation of C-reactive protein (CRP), as additional elements (Table I) (7). It should be noted that whereas the DAS28 performs well in PsA when analysed in standard PsA clinical trial cohorts (8), it has been recognised that assessing only 28 joints underestimates joint involvement in PsA because, in some patients, primary joint involvement may occur below the knee (9); therefore, some have recommended performance of a 68 tender/66 swollen joint count in PsA (10). Also, the DAS28 and the ACR remission criteria do not take into account the potential for disease activity in PsA-specific clinical domains such as enthesitis, dactylitis, spondylitis, and skin and nail disease.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has developed criteria for minimal disease activity (MDA) (Table II), which have been validated in a PsA clinical disease registry and an anti-TNF phase 3 PsA study (11-13). These criteria do take into account the PsA-specific domains of enthesitis and skin disease. In the clinical trial data set, it was shown that these criteria have predictive ability, *i.e*. those achieving MDA ultimately had less radiographic damage (12). Newer composite measures of disease activity in PsA have been developed by GRAPPA, which will allow better quantification of various thresholds of disease activity, including remission, low, moderate and high disease activity. They take into account the complex array of clinical domains of PsA, including arthritis, enthesitis, dactylitis, skin disease and potentially spondylitis if present. These new measures include the Psoriatic Arthritis Disease Activity Score (PASDAS), the Composite Psoriatic Arthritis Disease Activity Index (CPDAI), and the Arithmetic Mean of Desirability Functions (AMDF) (10, 14). These are currently being tested in prospective clinical trials. The new ACR-EULAR remission criteria for RA (15) have not been used to date in PsA studies.

Table I. 1981 ACR RA remission criteria modified for PsA by Cantini *et al*. (7).

Feature	Cut-off
*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
Extra-articular features	Absent

*Elements of the 1981 ACR remission criteria for RA (6).

Table II. The minimal disease activity (MDA) criteria of Coates *et al*. (11). Patients are deemed to be in MDA when they meet 5 of 7 of the criteria.

Feature	Cut-off
Patient pain VAS, 0–100	≤15
Patient global disease activity 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
Enthesitis	≤1

In 2001, Gladman *et al*. reported remission rates from the University of Toronto PsA registry, defining remission as a period of at least 3 consecutive visits with 0 tender and swollen joints, with patient visits occurring at 6 to 12 month intervals (16). Of 391 patients, 69 (17.6%) achieved drug-induced remission with a mean duration of 2.6 years. Of these, 20 (29%) were drug-free. Univariate analysis showed that male sex, fewer actively inflamed and damaged joints, and better functional class at presentation predicted remission. Fifty-two percent of subjects went on to experience flare after a mean of 1.8 years. Utilising the 1981 ACR RA remission criteria (6) (Table I), Kane *et al*. reported a PsA cohort of 129 patients treated with traditional DMARDs that demonstrated 26% remission rate at one year, including 12% who were drug-free (17). At two years in this cohort, 20% were in remission, including 11% drug-free.

As noted above, Cantini *et al*. modified the 1981 ACR RA remission criteria for PsA in a strict manner (Table I) (7). Of 236 patients, 24% achieved remission, more so in those treated with anti-TNF agents than with traditional DMARDs. Upon discontinuation of treatment, remission endured an average of 12 months. Multivariate analysis did not identify predictors of remission. These results were more robust compared to a "control" group of RA patients, amongst whom 7.5% achieved remission, enduring an average of 4 months post cessation of drug therapy. Saber *et al*., defining remission as DAS28-CRP ≤2.6, noted that 58% of 152 PsA patients treated with anti-TNF therapy achieved remission. Higher functional status at baseline was the best predictor for remission (18). In a Norwegian registry, Lie *et al*. noted that 24% of 430 subjects achieved DAS28 remission criteria at 6 months of observation (19). Several of these studies have noted that drug-free remission can be achieved and sustained for at least a year in a small percentage of patients. Predictors

of remission, including higher functional status at baseline, have been noted. However, predictors of sustained drug-free remission have not been identified as of yet. In order to better understand whether remission can be sustained while reducing the dose or discontinuing a medication, controlled withdrawal trials are needed, although even these results may not allow definitive information in all individual patients.

Cantini *et al*. studied the effect of reducing adalimumab dose in 76 PsA and 55 RA patients seen consecutively in a single centre (20) who had active disease for which adalimumab, 40 mg every other week, had been administered until remission, as previously defined (7), had been present for at least 6 months. By chance, the patients were relatively well matched in terms of disease duration, disease activity as measured by DAS scores, active joint count, acute phase reactants, fatigue and pain, and differed statistically only in enthesitis and dactylitis. Background methotrexate was taken by 84% of PsA patients and 85% of RA patients. Using the previously defined 1981 ACR RA remission criteria modified for PsA (Table I) (7), if patients achieved this state for 6 consecutive months, adalimumab dose was halved to 40 mg every 4 wks. Total study duration was 3 years.

Of the 76 PsA patients, 53 (69.7%) achieved clinical remission on standard dose adalimumab and 17 out of 55 (30.9%) RA patients did so on at least 2 visits. After adalimumab reduction to 40 mg monthly, 47 of the 53 (88.6%) PsA patients and 3 of 17 (17.6%) RA patients maintained remission (p=0.016). Relapse, defined as return of any active disease, occurred in 6 of 47 PsA patients who were in remission while taking the reduced adalimumab dose with a mean time to recur of 8.3 months. These patients returned to standard dose adalimumab (40 mg every other week) and achieved remission again in a mean interval of 5.1 months. Adalimumab antibodies were observed in approximately 10% of both PsA and RA patients. Thus it appeared that remission could be achieved more readily in PsA as compared to RA patients, and be maintained more readily at half the standard dose of adalimumab in PsA than in RA.

In practice, a decision concerning which drug to reduce dose or discontinue first is not always clear. NSAID? Traditional oral DMARD? Methotrexate? Biologic agent? Prednisone? The decision is often nuanced, depending on relative risk, tolerability, and cost factors. Typically the focus of a randomised withdrawal study would be either the biologic agent or background oral DMARD, depending on the interests of the investigative group. If cost consciousness or biologic safety are the major concerns, then reducing the dose or stopping the biologic agent would be tested. If poor tolerability of the oral DMARD is of concern, then one would like to assess the capacity of the biologic agent to sustain remission when used as monotherapy. For the purpose of hypothetical study design discussion, which follows, it is assumed that the biologic agent has the dose reduced or is discontinued.

A hypothetical study design could involve PsA subjects who are treated with an open-label biologic agent for one year. Those who had been treated with a prior traditional oral DMARD therapy are allowed to continue this treatment in a stable dose, although it is not required. Those achieving "remission" – defined either as MDA (the currently accepted target for PsA) or as the remission threshold of one of the new PsA composite measures, such as the PASDAS or CPDAI – are then randomised to one of three arms. Arm 1 continues standard dose and dose frequency of biologic agent. Arm 2 utilises either half-dose or decreased administration frequency of the biologic agent. Arm 3 subjects discontinue the biologic agent. Subjects will be monitored monthly, and if their disease worsens and they lose their "remission" (MDA) state for two consecutive months, they will return to the standard dose of the biologic. Subjects in Arm 1 who flare may have further adjustment of their overall treatment regimen or may drop out if the decision is made to switch to another biologic agent. All of these subjects will be considered to have lost response.

Key endpoints to be analysed would include:

- Time to loss of remission state due to inefficacy;
- Time to loss of remission state for any reason;
- Mean difference in remission at 6 months post baseline (start of randomised withdrawal period of study) between the two arms.

For those losing remission status over the 6-month period, last observation carried forward (LOCF) analysis will be conducted.

Conclusion

Remission in PsA, albeit variably defined, is a desirable and achievable state, especially in the era of biologic therapy. Historically, studies have used remission criteria derived from RA. The MDA measure developed by GRAPPA is a currently acceptable goal of therapy, taking into account PsA-specific elements such as skin disease and enthesitis. Newer PsA composite measures which include thresholds for remission are under development and are now included in prospective clinical trials. Once remission is achieved and sustained while taking a specific therapy, a natural question is whether treatment can be reduced or discontinued to avoid treatment toxicities and costs. Exploratory data are being analysed from observational cohorts regarding the capacity to reduce treatment dose, dose frequency, or discontinue use of a medication whilst maintaining remission. A controlled dose-reduction and discontinuation study design, as outlined above, may provide controlled evidence for such a paradigm of treatment.

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