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# Psoriatic arthritis: treat-to-target

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## ABSTRACT

Recently, the concept of “treat-to-target” has emerged as a topic of great interest in rheumatology, particularly as regards the therapeutic approach to patients with rheumatoid arthritis (RA). From observational data as well data from controlled clinical trials, there is a body of evidence supporting this idea. Thus, closely monitoring RA patients and adjusting therapies with the goal of achieving the lowest disease activity possible can result in optimal outcomes for patients. Based on the success in RA, interest in adopting a treat-to-target approach in other rheumatic conditions, including psoriatic arthritis (PsA) has arisen. It would appear logical that some data from “treat-to-target” approaches in RA may readily be extrapolated to PsA, particularly as it relates to PsA patients with polyarticular peripheral arthritis. However, PsA is a heterogeneous disorder, with involvement in areas quite distinct from RA, including the skin and nails, the axial spine, and the entheses. Therefore, developing a treat-to-target strategy in PsA will require additional disease specific considerations to optimise its implementation.

## Introduction

The introduction of highly effective biologic agents, particularly inhibitors of tumour necrosis factor (TNF), has changed the therapeutic approach to patients with psoriatic arthritis (PsA). In other forms of arthritis, for example rheumatoid arthritis (RA), novel therapies and therapeutic strategies have resulted in newer definitions of remission and newer concepts including “treat-to-target” (1). In PsA as well, there has been increasing interest in concepts such as minimal disease activity and remission (2-4). A natural follow-on to this is the idea that PsA patients should also be treated to a target. Different than RA, however, the heterogeneity in disease manifestations in patients with

PsA makes this potentially more challenging.

Psoriatic arthritis (PsA), a chronic systemic inflammatory disorder characterised by inflammation of the joints and surrounding structures, in association with cutaneous psoriasis, can be more heterogeneous and more complex than other inflammatory arthritides such as RA. Skin and nail involvement, arthritis of the peripheral and axial joints, and inflammation of entheses, sometimes presenting as dactylitis, are all clinically relevant and can impact PsA patients' quality of life (5, 6). Involvement in these areas is variable among patients. In most cases therapy is driven largely by the manifestations most active and severe for the individual patient, although optimal treatment requires consideration of all areas of active involvement.

In recent years, the availability of newer highly effective therapies has allowed greater levels of disease control for affected patients. With greater clinical success, there has been a growing consensus that the goal of treatment for all PsA patients should be achieving the lowest level of disease activity possible for all domains of the disease. In past years, although there were PsA patients who had spontaneous remission, older therapies and treatment paradigms rarely induced remission. Probably related to this, specific criteria for defining remission were never developed for PsA. More recently, as has been seen in RA, there is increasing interest in defining levels of disease activity including remission and low disease activity, and in forming treatment approaches that help achieve these states.

## For the concept of “treat-to-target” in PsA, what can and what cannot be derived from RA?

In areas such as the introduction of novel immune modulating therapies and creation of outcome measures, developments in PsA have often fol-

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lowed initial developments in RA. For a concept such as treat-to-target then, it could be reasoned that there could be extrapolation of the concepts developed in the RA experience into PsA. Indeed, an international group has begun meetings to develop treat-to-target into PsA (Prof. Josef Smolen, personal communication). Broad concepts, such as the “overarching principles” developed by Smolen and colleagues for RA would seem to be very appropriate for PsA as well (1). Thus, the concept that appropriate management of disease requires patient involvement is certainly applicable to PsA. Also, the ultimate goal of therapy is maximise health related quality of life and preventing untoward sequelae of the disease. As in RA, control of the local and systemic inflammation would be an important way of achieving that goal.

One important difference between the disease states however is that there is an abundance of data from clinical trials as well as clinical registries and experience that support treating RA to a target; many studies clearly demonstrate significantly improved outcomes among RA patients treated according to treat-to-target paradigms, compared to those RA patients receiving customary therapy (1). By contrast, there is a dearth of data addressing this in PsA. Of note, a controlled study specifically addressing this, called TICOPA (Tight Control Of Psoriatic Arthritis) achieved full enrollment in 2012 (Prof. Phillip Helliwell, personal communication); results of this trial are eagerly awaited. Another factor that will impact the implementation of Treat-to-Target guidelines in PsA is that as compared to RA, there is still much work that needs to be done as regards definitions of disease states that could be considered suitable targets. Thus, to date, there are no validated definitions of remission specific for PsA. Researches with interest in PsA, such as those in the GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) group, are actively working on development and validation of PsA specific measures. To date, several assessments have borrowed definitions for particular domains of disease, such as DAS,

DAS28, CDAI, SDAI, and RAPID3 definitions of remission and low disease activity. Such measures would probably be appropriate considering PsA patients with polyarticular peripheral inflammatory arthritis; however, they do not account for the other domains of disease involvement. Of note, a definition of minimal disease activity (MDA) has been developed specifically for PsA (2). According to these criteria, a PsA patient may be classified as having MDA if they meet 5 of these 7 criteria: 1) tender joint count  $\leq 1$ ; 2) swollen joint count  $\leq 1$ ; 3) Psoriasis Area and Severity Index (PASI)  $\leq 1$  or body surface area (BSA) of psoriasis involvement  $\leq 3\%$ ; 4) patient pain visual analogue scale (VAS)  $\leq 15/100$ ; 5) patient global assessment of PsA disease activity VAS  $\leq 20$ ; 6) Health Assessment Questionnaire (HAQ) score  $\leq 0.5/3$ ; and 7) tender enthesal points  $\leq 1$ . These criteria were developed using “paper patients” and achieving consensus among dermatologists and rheumatologists with expertise in psoriasis and PsA. Subsequently, they have been further validated looking at data from therapeutic trials in PsA (3). In two studies of infliximab in PsA, absence of any progression of radiographic damage was observed in 96% and 78% of PsA patients in MDA compared with 67% and 57% of patients not in MDA, respectively (3). Perhaps the biggest challenge in developing Treat-to-Target guidelines in PsA, as compared to RA, is the heterogeneity of disease. For peripheral arthritis, similar to RA, there is substantial data showing that PsA can be progressive, destructive and deforming (7-10). Disability and quality of life are adversely affected in patients with PsA to an equivalent degree as in rheumatoid arthritis (7-16). Therefore, by extrapolation to RA, the appropriate ultimate target for treatment for PsA patients with peripheral arthritis would be absence of peripheral arthritis. However, for other articular and periarticular disease, including axial arthritis, dactylitis, and enthesitis, there is a paucity of data clearly establishing that absence of disease activity is required to prevent damage or other sequelae. While it is reasonable to assume

that ongoing inflammation could beget tissue damage that would lead to functional impairment and reduced quality of life this has not been fully established. Similarly, for dermatologic involvement, the baseline presumption is that uncontrolled dermatologic inflammation will lead to deleterious consequences. However, relevant to defining goals of treat-to-target, the specific consequences of persistent yet low levels of disease activity in these areas have not been defined. However, this may be viewed from an alternative standpoint. There is a large body of data establishing the importance of comorbidities in patients with psoriasis and psoriatic arthritis (11). Important comorbidities, many of which are associated with the severity and activity of disease, include obesity, insulin resistance/diabetes mellitus, hypertension, non-alcoholic fatty liver disease, and accelerated atherosclerotic cardiovascular disease, with an increased risk of myocardial infarction. To the extent that these correlate with uncontrolled disease, a case could be made that the appropriate treatment target for PsA is remission or low disease activity in all domains of disease.

#### **Might treat-to-target in PsA lead to overtreatment?**

Years ago, an axiom among dermatologists was that if a patient with psoriasis was treated to the extent that they were totally clear, then they may be overtreated. While this was based on the perceived risk/benefit ratio of therapies available at that time, and before the introduction of novel agents, it does raise the question as to whether lower levels of disease activity in some domains of PsA may be acceptable. Interestingly, this is an avid and ongoing discussion in other areas of medicine, including some considered the bedrock of treat-to-target ideology. In the treatment of diabetes and hypertension, diseases that served as a template for the concept of tight control in rheumatologic conditions, there has been discussion as to whether a greater level of disease control is always better (12, 13). This is of great importance in PsA, as the benefits of tighter disease control must be weighed against the potential risks of therapy.

### Research Agenda for treat-to-target in PsA

In RA, there has been considerable discussion about defining disease activity with highly sensitive imaging techniques, such as magnetic resonance imaging (MRI) and ultrasound (US). Many studies have shown that there appears to be active inflammatory disease, for example as defined by observable power Doppler signal in the synovium, even in RA patients considered to be in remission by standard clinical evaluation (14). This discussion is relevant to PsA as well, as highly sensitive imaging can detect evidence of inflammation in articular and periarticular tissues in the absence of clinical signs and symptoms. In the future, it is possible that a biomarker might indicate ongoing immunologic and inflammatory activity, in the absence of clinical activity. This has critical implications for the concept of treat-to-target. Should such patients be treated? Should the “target” include not only clinical measures, but imaging and biomarkers?

In treat-to-target discussions in the clinic, it is often reluctance on the part of the patient that is a key factor affecting when additional therapies and therapeutic strategies are actually introduced (15). It is therefore critically important that all means possible to involve the patient in such discussions are utilised. Ultimately, it is their choice as to what therapies and which treatment paradigms will actually be used.

Achievement of targets such as remission and low disease activity would be desirable goals, as they should indicate that the disease process has been

arrested to such an extent that disease related damage and attendant outcomes could be avoided. However, given the realities of health economics as well as the relatively high acquisition costs of newer therapies, the overall “value” of treat-to-target strategies will also need to be established (16). To what extent do PsA patients in remission or low disease activity retain employment and incur fewer healthcare costs than those with lesser levels of disease control?

### Conclusion

Treat-to-target has been established as an important concept in RA. Certainly, the idea has considerable appeal for patients with PsA as well. However, differences in the disease states require specific validation of the utility of this concept in PsA, and there are several key issues that need to be addressed in that regard. It is hoped that with additional data, the concept of tighter disease control for PsA patients can be validated, implemented, and that it will help improve outcomes for affected patients.

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