Trial design in psoriatic arthritis: what could be changed?

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ABSTRACT

A greater understanding of the underlying disease process, combined with the development of novel therapeutic agents, has led to innovative strategies in the treatment of psoriatic arthritis (PsA). This report addresses unmet needs in clinical trial design in PsA, and proposes some amendments that may yield data that can potentially improve patient outcomes in the management of PsA.

Introduction

Recent years have witnessed tremendous progress in our treatment approach to psoriatic arthritis (PsA). Driven in large part by the introduction of highly effective biologic therapies, particularly tumour necrosis factor inhibitors (TNFi), research efforts have furthered our understanding of the immunopathogenesis of this disease. This, in turn, has lead to the development of innovative treatment strategies and novel therapeutic agents. Greater clinical success has highlighted the unmet need to more accurately assess and characterise disease activity, so that patient outcomes might be further improved.

Most of the key advances in PsA can be traced to data derived from clinical trials. Of note, through the late 1990s, there were relatively few clinical studies in PsA, particularly in comparison to the number of trials conducted in rheumatoid arthritis (RA). Many PsA studies have been modeled closely on RA studies, focusing on peripheral arthritis and using outcome measures created for and validated in RA, such as the American College of Rheumatology response criteria (ACR20/50/70) and the disease activity score (DAS). This approach risks neglecting disease activity in some of the other clinical domains manifested in a disease as heterogeneous as PsA.

Just as more effective therapy and improved patient outcomes have elevated treatment goals in PsA, these advances have also highlighted a number of considerations that could improve the conduct of clinical trials in PsA. Further refinement of clinical trial methods in PsA could optimise the utility of data obtained, and thereby improve patient outcomes even further. Herein we consider several questions concerning areas where trial design in PsA might be enhanced (Box I).

Optimising clinical trials in PsA

What domains of disease should be assessed?

PsA is a heterogeneous disease, with potential involvement in peripheral joints, axial joints, skin, nails, entheses, dactylitis and other areas (1). For practical considerations, one of these domains, for example peripheral arthritis, is often the primary criterion for enrollment in individual clinical trials. This ensures that there is some homogeneity in at least one domain such that analysis of efficacy can be robust. However, enrolled patients will have varying involvement across diverse domains of disease. It is crucial that these domains also be assessed such that the impact of therapy can be determined.

What outcome measures should be used to evaluate these domains?

There is brisk and active research investigating the optimal measures that should be used to assess the various domains of PsA, both in clinical trials and also in clinical practice. Measures for some domains have been 'borrowed' from other diseases, such as the psoriasis severity-and-index (PASI) score for skin psoriasis and the ACR 20/50/70 and DAS28 for peripheral arthritis. However, these extrapolated measures have not been fully validated specifically in PsA. Measures for the other domains of disease are also being developed and need to be validated (2). In addition, given the importance of accounting for several domains of disease activity, composite outcome

1. What domains of disease should be assessed?
2. What outcome measures should be used to evaluate these domains?
3. What is the role of highly sensitive imaging (*e.g.*, MRI, MSKUS)?
4. How can PsA patients with early disease be best studied?
5. What is the role of MTX as an anchor therapy in PsA studies?
6. How can studies of switching TNFi be best conducted?
7. How should newer agents be best studied?
8. What is the most appropriate way to study T2T in PsA?
9. What is the most appropriate way to study tapering of therapy?
10. How should biomarkers be studied in PsA?

Box I. Unmet needs in psoriatic arthritis trial design. MRI: magnetic resonance imaging; MSKUS: musculoskeletal ultrasound; PsA: psoriatic arthritis; MTX: methotrexate; TNFi: tumour necrosis factor inhibitor; T2T: treat to target.

measures that provide a more complete clinical picture have gained considerable support (3).

What is the role of highly sensitive imaging?

One of the important goals of treatment of inflammatory arthritis is the prevention of structural damage. Traditionally, this has been assessed by conventional radiography. However, there are issues that impact the ability to utilise this modality going forward. Changes on plain radiographs are often driven by a subset of the PsA population that will undergo progression during the study. However, ethical considerations preclude withholding effective therapy from patients with active disease. This makes demonstration of differences in radiographic changes more challenging, and highlights the need for more sensitive imaging techniques, including musculoskeletal ultrasound (MSKUS) and magnetic resonance imaging (MRI). In addition to damage, these highly sensitive imaging techniques can detect evidence of inflammation (4). With standardisation and validation, these techniques might become routinely used in clinical trials.

How can PsA patients with early disease be best studied?

The importance of early intervention and initiation of therapy in PsA has become increasingly recognised. This is largely due to the growing recognition that PsA is a more severe disease than previously thought. Indeed, 40-60% of patients experience a severe and deforming arthritis with early radiographic changes (5-7). A prospective study of 129 patients with early PsA treated with traditional disease-modifying anti-rheumatic drug (DMARD) therapy detected erosive disease in 47% of patients at 2 years, despite clinical improvement (8). Another study found a delay as short as 6 months from symptom onset to first rheumatologic assessment was associated with the development of peripheral joint erosions and worse functional outcome in PsA (9).

The introduction of medications capable of altering the disease course in PsA has made the idea of early treatment more appealing. In PsA, the onset of skin disease precedes the onset of arthritis in more than 80% of patients, often by more than a decade (10). As a result, there is a unique opportunity in PsA to identify and treat patients with musculoskeletal manifestations early in the disease course (11).

What is the role of methotrexate as an anchor therapy in PsA studies?

Most studies of new therapies in PsA have allowed, but not required, the concomitant use of methotrexate (MTX). This is in keeping with clinical practice, where the use of DMARD therapy is not universal, but depends on domains of active disease, patient preference, and other factors. However, these study designs have precluded the ability to ascertain whether there may be synergy between MTX and other therapies, such as TNF inhibitors. This differs from RA, where MTX is the anchor drug in the clinic and in most clinical trials, and where the combination of MTX and anti-TNF therapy has demonstrated synergistic efficacy in clinical trials (12). Data from PsA patients in the NOR-DMARD registry showed that while clinical outcomes were similar among patients on TNFi monotherapy compared with those receiving concomitant MTX, drug survival was increased with combination therapy (13). Whether this is true in PsA remains an important question for clinical practice, so it will be important to formally establish the utility of methotrexate co-therapy in rigorous clinical trials.

How can studies of switching TNFi be best conducted?

TNFi are effective in PsA, with many patients achieving a prompt and sustained response. Nevertheless, some patients have clinical manifestations that either do not respond to TNFi or achieve less of a clinical response than desired, initially or later in the course. With the availability of five different TNFi worldwide, studies of the efficacy of TNFi switching are important. Theoretically, 'TNF failures' can be classified as either 'primary failures' (*i.e.* lack of any initial response) or 'secondary failures' (*i.e.* loss of effect after initial response). In practice, while the former situation is relatively straightforward, it is also quite uncommon, as few patients do not have any clinical benefit. The latter situation is much more common, but also more complex.

Reasons patients stop treatment include the extent of initial clinical benefit, safety and tolerability issues, convenience and other patient preference factors, and cost considerations in some jurisdictions. For individual patients who discontinue TNFi, it would be very difficult to sort out the relative contributions of these different factors. Therefore, it may be more realistic to focus simply on TNFi exposed patients. There is some evidence supporting the concept of switching from one TNFi to another in PsA. Data from the RAPID-PsA study showed comparable outcomes for certolizumab in PsA patients who had been previously exposed to TNFi and those who were TNFi-naïve (14). Also, registry data, especially from the Norwegian DMARD (NOR-DMARD) registry and the Danish

nationwide registry of biologic therapies (DANBIO), have revealed that switching TNFi can result in clinical improvement, albeit to a somewhat lesser extent than TNFi naïve patients (15, 16).

How should newer agents be best studied?

There is tremendous excitement about the potential utility of drugs with novel mechanisms of action in PsA. At the same time, newer therapies have not yet had a chance to demonstrate an extensive safety profile. This raises an important question: with the available therapeutic options, what is the most appropriate PsA patient population in which to assess novel therapies? Given the largest unmet need in the clinic may well be for patients who have had insignificant response to available treatments, studies among such patients – particularly those with prior TNFi exposure – would be important. However, such patients may be somewhat refractory to treatment. It would, therefore, also be reasonable to study less refractory patients, including treatment-naïve patients, to determine if the new agent might exhibit some advantage in such populations.

What is the most appropriate way to study T2T in PsA?

The concept of treat to target (T2T), widely accepted in RA, requires an accepted therapeutic goal. Until recently, one of the major challenges for implementing T2T approach in PsA was the lack of a clearly defined, pre-specified target on which to base treatment decisions, as no remission criteria have yet been validated for PsA. Of note, criteria for minimal disease activity (MDA) have been developed that include measures of disease activity across relevant clinical domains (17). The MDA criteria have been validated in clinical trials as well as observational cohorts, and are now considered an acceptable therapeutic target (18, 19).

To date, there has been a paucity of data addressing T2T in PsA. Results of the TICOPA (TIght COntrol of Psoriatic Arthritis) trial suggest improved outcomes with intensive treatment in newly diagnosed PsA: patients treated using a tight control strategy achieved significantly better clinical outcomes in ACR20/50/70 responses (61.8/51.2/38.4% *vs*. 44.6/25.0/17.4%, respectively) and PASI75 (58.7% *vs*. 33.4%) at week 48 compared with those in the standard care group (20, 21). However, patients in the tight control group also experienced more adverse events. Hence, there is a need for further T2T studies, using various treatment algorithms and outcomes, to fully assess the utility of T2T in PsA.

What is the most appropriate way to study tapering of therapy?

In contrast with patients who have active disease, PsA patients achieving low disease activity or remission may not require ongoing maintenance therapy at the same levels required to induce remission. This is an emerging concept of intense interest in rheumatology that is being studied extensively in RA with some notable success, particularly patients achieving very low levels early in their disease course (22). Potential benefits of dose reduction include a reduced risk of adverse events, alignment with patient preferences, and cost savings.

Two strategies of dose reduction include tapering and discontinuation of therapy. Tapering or withdrawing therapy can be performed either through reducing the dose of the agent given, or alternatively increasing the interval of administration. There is some evidence to support tapering biologic therapy in PsA. In a prospective study of PsA patients who had previously had a 'complete response' to adalimumab therapy, 86.6% of patients remained in remission when the interval of administration was increased from every 2 to 4 four weeks (23).

Although a number of studies have examined clinical outcome after discontinuation of biologic therapy in RA, important differences in study design and patient characteristics make pooling data across studies difficult. Nevertheless, published data from several RA studies suggests that discontinuation of TNFi may be associated with sustained clinical benefit (24). Clinical outcome after tapering or discontinuation of therapy in PsA patients who have achieved low disease activity or remission remains to be delineated. This is a large unmet need in PsA that should be addressed with rigorous clinical trials.

How should biomarkers be studied in PsA?

Biomarkers could potentially assist in the management of PsA in multiple ways. For example, detection of early or subclinical disease, quantification of disease activity, and identification of the most appropriate therapy for an individual patient through analysis of biomarkers would greatly optimise patient care. There has been a great deal of research into identifying biomarkers in PsA with some promising data, including a study of PsA patients treated with golimumab showing an association of several biomarkers with improvement in clinical response (25). However, no biomarkers have yet proven sufficiently robust to be of value in clinical practice. This area of research also remains an unmet need in PsA, which should be addressed both in registry studies as well as therapeutic trials.

Conclusions

There has been tremendous progress in recent years in the approach to treatment of PsA. Much of this progress relates to data generated from clinical trials. Advances in treatment have led to improved clinical outcomes in PsA, and consequently the goals of therapy have been elevated. Future studies, addressing some of the unmet needs discussed in this article, will provide additional data with the potential to further optimise outcomes for PsA patients.

References

1. GLADMAN D, ANTONI C, MEASE P, CLEGG DO, NASH P: Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; 64 (Suppl. 2): ii14-17.
2. MEASE PJ: Measures of psoriatic arthritis. Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada

(SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res* (Hoboken) 2011; 63 (Suppl. 11): S64-85.

3. GLADMAN DD, MEASE PJ, STRAND V *et al*.: Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 2007; 34: 1167-70.
4. KAVANAUGH A: Psoriatic arthritis: treat-to-target. *Clin Exp Rheumatol* 2012; 30 (Suppl. 73): S123-5.
5. MCHUGH NJ, BALACHRISHNAN C, JONES SM: Progression of peripheral joint disease in psoriatic arthritis. *Rheumatology* (Oxford) 2003; 42: 778-83.
6. GLADMAN DD, STAFFORD-BRADY F, CHANG CH, LEWANDOWSKI K, RUSSELL ML: Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 1990; 17: 809-12.
7. SOKOLL KB, HELLIWELL PS: Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 2001; 28: 1842-6.
8. KANE D, STAFFORD L, BRESNIHAN B, FITZGERALD O: A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. *Rheumatology* 2003; 42: 1460-8.
9. HAROON M, GALLAGHER P, FITZGERALD O: Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2015; 74: 1045-50.
10. HUYNH DH, KAVANAUGH A: Psoriatic arthritis: current therapy and future approaches. *Rheumatology* (Oxford) 2015; 54: 20-8.
11. ANANDARAJAH AP, RITCHLIN CT: The diagnosis and treatment of early psoriatic arthritis. *Nat Rev Rheum* 2009; 5: 634-41.
12. KAVANAUGH A, COHEN S, CUSH JJ: The evolving use of TNF inhibitors in rheumatoid arthritis. *J Rheumatol* 2004; 31: 1881-4.
13. FAGERLI KM, LIE E, VAN DER HEIJDE D *et al*.: The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. *Ann Rheum Dis* 2014; 73: 132-7.
14. MEASE PJ, FLEISCHMANN R, DEODHAR AA *et al*.: Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomized placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73: 48-55.
15. FAGERLI K, LIE E, VAN DER HEIJDE D *et al*.: Switching between TNF inhibitors in psoriatic arthritis: data from the NOR-DMARD study. *Ann Rheum Dis* 2013; 72: 1840-4.
16. GLINTBORG B, OSTERGAARD M, KROGH NS *et al*.: Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO registry. *Arthritis Rheum* 2013; 65: 1213-23.
17. COATES LC, FRANSEN J, HELLIWELL PS: Defining minimal disease activity in psoriatic arthritis: a proposed objective for treatment. *Ann Rheum Dis* 2010; 69: 48-53.
18. COATES LC, HELLIWELL PS: Validation of minimal disease activity for psoriatic arthritis using interventional trial data. *Arthritis Care Res* 2010; 62: 965-9.
19. COATES LC, COOK R, LEE KA, CHANDRAN V, GLADMAN DD: Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. *Arthritis Care Res* 2010; 62: 970-6.
20. COATES LC, MOVERLEY A, MCPARLAND L *et al*.: Results of a randomized control trial comparing tight control of psoriatic arthritis (TICOPA) with standard care: tight control improves outcome. ACR meeting, San Diego, 2013. Abstract 814.
21. COATES LC: Treating to target in psoriatic arthritis. *Curr Opin Rheumatol* 2015; 27: 107-10.
22. EMERY P, HAMMOUDEH M, FITZGERALD O *et al*.: Sustained remission with etanercept tapering in early rheumatoid arthritis. *N Engl J Med* 2014; 371: 1781-92.
23. CANTINI F, NICCOLI L, CASSARA E, KALOUDI O, NANNINI C: Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study. *Biologics* 2012; 6: 201-6.
24. KAVANAUGH A, LEE S, CURTIS JR *et al*.: Discontinuation of tumour necrosis factor inhibitors in patients with rheumatoid arthritis in low-disease activity: persistent benefits. Data from the Corrona registry. *Ann Rheum Dis* 2015; 74: 1150-5.
25. WAGNER CL, VISVANATHAN S, ELASHOFF M *et al*.: Markers of inflammation and bone remodeling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. *Ann Rheum Dis* 2013; 72: 83-8.