Therapy strategies in psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is a heterogeneous condition with a myriad of different clinical presentations. It commonly affects the skin and musculoskeletal system causing psoriasis, peripheral arthritis, axial arthritis, enthesitis and dactylitis. Many patients also have related conditions, such as those within the metabolic syndrome and associated spondyloarthritis (SpA) conditions including inflammatory bowel disease and uveitis. Any therapeutic strategy must be tailored to the individual patient, taking into account her/his complete clinical presentation and comorbidities. New treatment recommendations from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) provide evidence based recommendations on effective therapies for the management of each different manifestation of PsA, and how treatment may be affected by comorbidities (1). *However, the limited evidence comparing different treatment strategies in PsA is recognised as a limitation in these recommendations and further information is detailed below.*

Treatment plans: step up *versus* step down?

Research into therapeutic strategies in PsA is limited. When using disease-modifying anti-rheumatic drugs (DMARDs), one of the common questions, more widely studied in RA, involves step up *versus* step down therapy. In step up, one therapy is prescribed initially, before moving onto combined therapies if there is an incomplete response (or none) according to defined criteria. By contrast, step down therapy directs that treatment is initiated aggressively with combination therapies, and these are gradually reduced if patients achieve a predefined goal. To date, no research in PsA has compared these approaches. The potential benefits of early combination or aggressive treatment strategies should be examined in an RCT and the associated potential risks of these should be elucidated.

Currently, most clinical practice is to use a step up approach to minimise potential toxicity, as chosen by the expert committee drafting the European League Against Rheumatism (EULAR) recommendations for PsA. The committee recommends initial use of single DMARDs, followed by a second DMARD either in series or in combination, or an escalation to biologic therapy, depending on the presence or absence of poor prognostic markers (2). The markers included are based on prognosis studies investigating predictors of subsequent joint damage and functional impairment and include raised inflammatory markers, polyarticular involvement, previous joint damage and functional impairment.

Early intervention

Observational data have indicated that a longer delay in diagnosis is associated with poorer outcomes in PsA. A shorter duration of symptoms prior to diagnosis was associated with improved disease activity outcomes at 5-year follow-up (3) in patients in a Swedish early PsA registry. Tillett *et al*. identified that a >12 months delay in diagnosis was a significant predictor of functional impairment at 10 years (4). Haroon *et al*. found in 283 patients with PsA that patients with more than 6 months of symptoms prior to a diagnosis are more likely to have erosive peripheral joint disease, arthritis mutilans, joint deformity, functional impairment and sacroiliitis, and were significantly less likely to achieve a drug free remission (5).

The above evidence supports a likely benefit for early intervention in PsA, but prospective clinical trial evidence is limited. The only trial assessing immediate *versus* delayed DMARD prescription did not show a significant difference at 6 months but it was markedly underpowered with only 35 patients in the entire study. This trial also was an

open label study and patients were trated with relatively low doses of methotrexate (10 mg/week) which may not be effective. There has been one large randomised controlled trial (RCT) of a tumour necrosis factor inhibitor (TNFi) in early PsA which showed higher than expected responses in both the methotrexate (control) group and the TNFi group (6), potentially suggesting a better outcome when therapies are used earlier in the course of the disease. However, this study was also open label in comparison to the majority of TNFi trials in established disease which report double-blind outcomes. There are obvious cautions in comparing outcomes between two separate trials, so again this evidence is inconclusive.

Treatment to target

The concept of "tight control" or "treat-to-target" was developed in rheumatoid arthritis (RA) following clinical and imaging studies suggesting that active inflammation predicted future joint damage (7, 8). A pivotal study was the Tight Control of RA (TICORA) study which showed a significant benefit after 18 months of therapy despite only using conventional DMARDs and corticosteroids. Patients in the tight control arm who continued to have a DAS>2.4 at their monthly visits had their DMARD therapy escalated and were given additional systemic or intra-articular steroids up to 120 mg per visit. At the end of the study, 82% of tight control patients met the EULAR good response compared to 44% of controls ($p<0.0001$) (9). Further studies confirmed the benefit of treating to an objective target including using computer designed algorithms (10, 11) and this approach is now recommended in the UK as standard of care in the clinic with newly diagnosed RA patients (12).

Following the success in RA, the concept of treat to target developed in the spondyloarthritides (SpA). In PsA, data support a link between inflammation and subsequent radiographic damage, such as evidence from the Toronto cohort that active inflamed joints predict future radiographic joint damage (14). A large literature review was performed in 2011 by EULAR to identify research relevant to treat to target in SpA (15). They were principally looking for "strategic studies that compared a therapy steered towards a prespecified treatment target *versus* a conventional non-steered approach". At the time, they identified that there were no studies in any of the SpA, including PsA that fulfilled this description. They did find a small number of studies where treatment was changed based on a prespecified target, but not with a comparison group. The majority of these were large RCTs of TNF inhibitors in PsA which had "early escape" arms if a minimal improvement in joint counts was not seen at 12 or 16 weeks (15).

One issue raised by the EULAR literature review and subsequent recommendations on treatment to target in SpA (16) was the difficulty in identifying an appropriate target. The EULAR taskforce recommended remission as the main target for all SpA with low disease activity as an alternative target (16). At that time, there are were remission criteria validated in PsA; The best validated criteria defining low disease activity and remission combined are the minimal disease activity (MDA) criteria for PsA (17). These criteria do not provide a disease activity score, only a definition of a low disease state. They have been validated in observational cohorts and in RCT data showing responsiveness to change, agreement with treatment decisions (18), differentiation between drug and placebo and correlation with other outcome measures.

These analyses also confirmed prognostic value with patients in consistent MDA having less progression in clinical joint damage (18) and radiographic outcome (19). Proposed definitions of low disease activity have also now been developed for the new composite measures in PsA: the PASDAS, the GRACE index and the CPDAI (20) but these have not yet been validated. The other key consideration for routine clinical use is feasibility. The MDA criteria can be applied in around 5–10 minutes in the clinic, but the PASDAS, CPDAI and GRACE indices require more time to perform.

The TICOPA study

Since the EULAR review and recommendations have been published, one study has been reported which does fit the primary search: "strategic studies that compared a therapy steered towards a prespecified treatment target *versus* a conventional non-steered approach". The Tight Control of Psoriatic Arthritis (TICOPA) study recruited 206 patients with recent onset PsA. They were randomised 1:1 to tight control or standard care. Patients in the tight control arm were reviewed every 4 weeks by the research rheumatologists, and treatment was escalated if they did not meet MDA criteria. The study used a treatment algorithm of methotrexate, combination DMARDs and biologic agents in a step-up design. Patients in the standard care arm were reviewed every 12 weeks and were treated by their usual rheumatologist. There were no limitations on their care, except compliance with UK NICE criteria for the use of TNF inhibitors in PsA which was standard across both trial arms (21).

The odds of achieving ACR20, the primary outcome, at 48 weeks were significantly higher in the tight control arm (OR 1.91, $p=0.0392$) using intention to treat analysis. The odds of achieving ACR50, ACR70 and PASI75 also were significantly higher for the tight control group. Greater improvements were also seen with tight control in patient-reported outcomes including physical function (HAQ), quality of life (PsQOL) and also BASDAI and BASFI for those with axial disease. No difference was seen in radiographic progression between the two arms; however, the mean change in modified van der Heijde-Sharp score was zero in both groups. The tight control arm was associated with increased rates of adverse events and serious adverse events, which may have been due to the more rapid escalation of DMARD therapy (22).

Reduction or withdrawal of therapy

Given the excellent responses with newer biological drugs and their relatively high cost, research has been initiated to address whether treatments could be reduced or withdrawn (23). Cantini *et al*. reported over 50% of PsA patients achieving remission by strict, though unvalidated, criteria modified from the ACR RA criteria. Medication was suspended after patients had

been in remission for ≥4 months, and the mean duration of remission was 12 months after this treatment suspension (24). This report encouraged further treatment withdrawal studies; however, two recent studies have shown a high rate of relapse. In one study, 20 of 26 patients had disease recurrence after a mean of just 74 days (25). In a small pilot study in the UK, 17 patients were randomised 2:1 to treatment withdrawal with 6 of the 11 flaring within 3 months and additional patients flaring beyond the follow up time of the trial (26). In both studies, most patients were able to recapture their disease control after restarting therapies (25, 26).

Other studies have looked at dose reductions with greater success. In Barcelona, 153 patients who were taking biologic agents were reviewed, including 20 with PsA. Half of the PsA patients had reduced the dose of their therapy with no adverse effects (27). In a later study, 102 PsA patients on treatment were assessed using clinical outcome measures and musculoskeletal ultrasound. One quarter were receiving tapered doses of biologic agents following a period of time in remission or MDA. No significant differences were seen in any of the outcomes for those taking full dose, or those who had reached satisfactory disease control and had their treatment doses reduced (28).

Summary

The key to managing PsA effectively is to tailor treatment to the individual patient depending on the manifestation of their disease. Recent international treatment recommendations provide evidence based and expert opinion based therapy options, but considerable research is required to establish optimal treatment algorithms for patients with PsA. There is evidence that treating to target using the MDA criteria can improve outcomes across multiple measures in patients with recent onset PsA. In those responding well to therapy, treatment withdrawal often has been associated with recurrence of disease, but there is an increasing observational body of evidence for safe dose reduction after remission or low disease activity has been reached.

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