Can biologic therapies be withdrawn or tapered in psoriatic arthritis?

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Received on August 16, 2013; accepted in revised form on August 26, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 78): S51-S53.

Key words: psoriatic arthritis, treatment, disease flare, biologic drugs

Competing interests: L.C. Coates has received honoraria/speakers' fees and research funding from AbbVie, Celgene, Janssen, MSD, Pfizer, and UCB; the other co-authors have declared no competing interests.

ABSTRACT

There is a paucity of data on tapering and withdrawing therapy in psoriatic arthritis but advances in treatment and outcome measures suggest it is now time to be looking more closely at this. Several highly effective therapies are available providing the opportunity to achieve low disease activity. However, these therapies are associated with a marked increase in direct costs and patients are exposed to potentially life threatening adverse events. In addition to effective therapies the science of outcome assessment means that there are now suitable validated criteria for low disease activity which will allow both treat-to-target and a suitable measure of continuing low disease. Given these conditions, suitably designed randomised controlled trials of treatment withdrawal are now needed. Such studies will allow us to determine disease characteristics predictive of flare upon treatment withdrawal. In this way identifying which patients can successfully stop therapy will allow a more personalised approach to treatment decisions in PsA and will minimise risks and costs associated with ongoing therapy.

Psoriatic arthritis is defined as an inflammatory arthritis affecting bone, tendon and joint and is associated with psoriasis of the skin or nails (1). The prevalence of psoriasis in the general population has been estimated between 2% and 3% (1), and the prevalence of inflammatory arthritis in patients with psoriasis has been estimated to be up to 30% (2).

Historically there has been little evidence-base to support treatment decisions in PsA, with limited randomised controlled trial (RCT) evidence to support the use of individual or combination DMARDs (3). The evidence base for the use of methotrexate monotherapy has recently been expanded by the publication of the methotrexate in psoriatic arthritis (MIPA) trial (4). The MIPA trial failed to reach the primary outcome of the psoriatic arthritis response criteria (PsARC) but doubts remain about the study design and the modest dose of methotrexate used (target 15 mg/wk).

With the advent of the TNF blockers, a significant treatment effect with therapy has been confirmed in RCTs in PsA when compared with methotrexate (MTX) monotherapy (5). TNF has the added benefit of showing clear evidence of improvement in all aspects of disease, including extra-articular features. However, there remains very little research addressing treatment algorithms in PsA, and whether treatment should use a "step-up" or "step-down" approach.

It has recently been shown that remission may be sustained in PsA despite treatment interruption (6). This raises the possibility of stopping therapy either temporarily or permanently in some patients, anticipating prolonged drug-free remission. Potential benefits of this approach would include prevention of drug side effects for patients, removal of risk from long-term immunosuppressant therapy, and significant financial savings. However, preliminary data from an open label small study have shown almost universal relapse over a period of three months following withdrawal of therapy, although, fortunately, with recapture of disease control on restarting the drugs in most patients (7).

The economic costs of PsA have not been well quantified to date. In the United States (US), the mean annual direct (health and social care) cost per patient with PsA is estimated as $3,638 according to data from Medstat Market Scan in 1999-2000 (8). In Germany, the mean annual direct cost per patient with PsA is estimated as €3,162, with the mean indirect cost (time lost from work and normal activities) per patient

Table IA. Cantini criteria for remission in psoriatic arthritis (6).

Fatigue VAS <10mm	No dactylitis
Pain VAS <10mm	No enthesitis
Swollen joint count = 0	No spinal pain
Tender joint count = 0	No extra-articular involvement
Early morning stiffness <15min	(with the exception of psoriasis)
ESR and CRP normal	
Tender joints = 0	
Fatigue VAS <10mm	

Table IB. Criteria for minimal disease activity (MDA) (26).

Five of seven criteria must be fulfilled:
Tender joint count ≤1
Swollen joint count ≤1
PASI ≤1 or BSA ≤3%
Patient pain VAS ≤15mm
Patient global activity VAS ≤20mm
HAQ ≤0.5
Tender entheseal points ≤1

of €11,075 (9). As in psoriatic arthritis (9), studies in rheumatoid arthritis (RA) (10-12) and psoriasis (13) have shown that costs increase with the severity of both diseases, and productivity losses are significant (14, 15), largely as a consequence of extensive work disability.

Studies of the economic impact of RA in the United Kingdom (UK) before the introduction of biologic therapies found that direct healthcare costs represented about one-quarter of all costs and these were dominated by inpatient and community day care (16), with DMARD drugs representing a minor proportion: 3–4% of total costs and 13–15% of direct costs (17). Evidence from the US after introduction of biologic agents suggests that expenditure on biologics might represent 35% of direct cost (18), but similar data are not yet available for the UK. Increasing expenditure on biologics might be at least partly offset by cost savings related to reduced inpatient care (19), though as yet no evidence for this has been documented. In fact, the improvement in indirect costs related to PsA has not been shown to be greater than the direct cost of the therapy (20). If patients could remain in remission whilst experiencing some degree of treatment interruption, it would significantly reduce the treatment cost for PsA patients in the UK.

There has, until recently, been little in the way of validated outcome measures in PsA, particularly to define disease states such as remission (21). This has been a significant limitation in the development of research studies into remission and potential withdrawal of therapy. Gladman originally proposed remission to be an absence of actively inflamed joints (22) but this excludes the significant burden of extra-articular disease. According to previous published research reports, definitions of (absence of) disease activity used are wide and include a variable number of domains of psoriatic disease.

Perhaps the most useful primary research identified to date is an Italian case-controlled study by Cantini *et al*., which discusses treatment 'interruption' in psoriatic arthritis (6). Medication was 'suspended' if patients achieved and maintained clinical remission for at least four months. The definition of remission was based on the ACR RA remission criteria, which were adapted by the authors for use in PsA but have not been validated (see Table IA). Overall, just over half of the 73 psoriatic arthritis patients achieved at least one period of remission. The frequency of remission was significantly higher in those who were treated with anti-TNF than in those treated with methotrexate alone (79.5% *vs*. 20.4%, $p<0.001$). The overall mean duration of remission after therapy interruption was 12±2.4 months, and this was not significantly different in those who interrupted therapy with respect to those who received continuing treatment (14±8.1 months).

The criteria for remission in the Cantini paper do include other domains of PsA in addition to peripheral arthritis, but do not include a skin score (6). A more realistic surrogate for remission would be minimal disease activity (MDA). Criteria for MDA in PsA have recently been developed by consensus of a panel of international experts from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). They have since been validated in longitudinal observational cohorts and randomised clinical trial datasets. These use seven parameters including entheseal and skin assessments (Table IB) (23).

Given the preliminary evidence in PsA and the existing ongoing research interest in rheumatoid arthritis (24), it should be possible to identify those patients who can successfully stop treatment entirely without adverse outcome (25). Development and validation of the MDA criteria for PsA has provided a tool for future research into treatment withdrawal. Recently, a randomised controlled trial of treatment withdrawal has been designed and a small pilot study is underway in three sites in Yorkshire UK to inform sample size calculations for a large national RCT (REmoval of TREATment in psoriatic arthritis: RETREAT). In this study, medications will be tapered and discontinued over a twelve-month period with monthly assessments and recourse to an emergency helpline in case of flare, when previous medications will be re-started. Patients who are in stable minimal disease activity for at least 6 months will be randomised into one of two groups, comparator and intervention. To ensure stable MDA, patients enter via a run-in period of two visits, one month apart. Within the comparator group, patients will continue with their current therapy for twelve months after randomisation. However, their treating clinician will be free to change their treatment if clinically indicated to do so (*e.g*. escalate treatment doses if patient is relapsing or decrease/change treatment if there are side-effects). Patients in this group will be seen as per usual practice, which is every 12 weeks.

Patients in the intervention group will undergo a phased withdrawal of their medications using the treatment philosophy of "last treatment added = first treatment withdrawn." Treatments will be withdrawn in a stepwise fashion, phasing out and stopping each drug

over three months. These patients will be seen more frequently than usual practice, every 4 weeks, in order to monitor their response to their change in treatment. If the patient maintains her/his minimal disease status on withdrawal of the first medication, the second-to-last treatment will be withdrawn, again in a stepwise fashion over a subsequent period of three months. This process will continue until the patient has potentially discontinued all disease-modifying medication.

If there is evidence of disease flare, currently defined as the patient not achieving MDA, the last removed medication will be re-introduced in a step-wise reversal process, with use of intramuscular or intra-articular steroids if required. As skin assessments are part of the MDA, relapses of the skin component may contribute to measurement of disease flare. The primary outcome will be the proportion of patients who flare in each group. Secondary outcomes will include laboratory, clinical and imaging variables in order to identify possible predictors of relapse, and thus those patients in whom drug withdrawal is a feasible prospect.

There are many reasons why it is time now to start thinking about tapering and withdrawing therapy in psoriatic arthritis. We have a number of successful therapies in place providing the opportunity to obtain true minimal disease activity, but these are associated with a marked increase in direct costs and some patients experience adverse effects related to their therapy. There are now suitable validated criteria for low disease activity which will allow both treat-to-target and a suitable measure of continuing low disease. A gap in outcomes is the absence of a validated definition of flare in this disease. If we can maintain low disease activity with treatment interruption within the RETREAT trial, we should be able to assess disease characteristics predictive of flare. Identifying which patients can successfully stop therapy will allow a more personalised approach to treatment decisions in PsA and will minimise risks and costs associated with ongoing therapy.

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