

Aiming for remission in psoriatic arthritis

Psoriatic arthritis is a complex and heterogeneous disease that can manifest in several different ways, and is known to have variable outcomes. Although several definitions of remission have been proposed, none are validated, and few encompass all aspects of the disease. On the other hand low, or minimal, disease activity is an achievable target in psoriatic arthritis and using this treatment strategy results in improved clinical outcomes. Whatever target is chosen, it is clear that it is not sufficient to measure only the articular involvement in this disease, but to define remission and low disease activity in terms of the major manifestations of this disorder.

Keywords: disease activity • psoriatic arthritis • remission • treatment

Although inflammatory arthritis associated with psoriasis has been recognized for many years, initially, there was controversy about whether it represented a separate disease entity, or simply the coexistence of rheumatoid arthritis and psoriasis [1,2]. Psoriatic arthritis (PsA) was recognized as a separate disease by the American Rheumatism Association (now the ACR) in 1964, and is now classified as a member of the spondyloarthropathy spectrum [3]. PsA was initially defined by Moll and Wright as “an inflammatory arthritis in the presence of psoriasis with a usual absence of rheumatoid factor” [4]; however, more robust classification criteria have now been developed [5]. Although thought initially to be a relatively benign disorder more recent work has demonstrated the destructive and progressive nature of the disease with increased mortality and, particularly, significant cardiovascular comorbidity [6]. At the same time, advances in treatment, in particular with biological drugs, have provided effective tools with which to control the disease and, more recently, treating to predefined targets has shown improved outcomes in this disease [7,8].

Natural history of PsA

PsA is a heterogeneous disease. Clinical manifestations vary from a mild, slightly

troublesome oligoarthritis to a severe, mutilating polyarticular form. At any one time, the severity of skin and joint manifestations may be quite different. Generally, when and whether the skin clears, long-term skin sequelae (scarring) does not occur. The same cannot be said about the joints as it is likely that repeated episodes of inflammation will cause damage that cannot be repaired. Ideally, in that case, treating early and aggressively to achieve early remission should prevent this long-term damage. It is also pertinent to note that there is evidence of increased cardiovascular morbidity and mortality in both psoriasis and PsA – and in the case of psoriasis, this risk increases with increasing severity of skin disease [9]. It is not yet clear that achieving disease remission in PsA will reduce this risk.

Most early work in PsA suggested that, on the whole, this was a less severe form of arthritis when compared with rheumatoid arthritis [10,11]. It was acknowledged, however, that in some people the disease followed a particularly aggressive and deforming course. The initial cohort of patients collected by Wright in Leeds [4] was later reviewed by Roberts and the largely benign nature of the condition restated: 78% of a group of 178 patients were classified as ‘mild’ with only 11% of this

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group deteriorating over a follow-up period of more than 10 years [12].

Further clinical studies have challenged the notion that PsA is a benign disease compared with rheumatoid arthritis [13]. Methodological differences may have accounted for some of these inconsistencies. For example, in comparative studies, cases should be appropriately matched with comparator conditions, something that was not always apparent in earlier studies. Another example, in longitudinal studies, would be the importance of maximizing follow-up – milder cases may be more likely to default, thus skewing the results towards a more severe outcome.

One explanation for these discrepancies may be that PsA is a heterogeneous disease both clinically and prognostically. Clinical experience would suggest, and some publications would support, the contention that up to a third of patients with PsA either have a mild, minimally progressive disease that requires only symptomatic treatment, or an oligoarticular disease limited to a few affected joints. The former group include those with arthralgia and low-grade inflammation – sometimes only a ‘cold’ swollen knee is observed over many years with little progression to joint damage. Later studies, particularly those from Toronto, have also hinted at a milder nonprogressive, oligoarticular group. For example, the first complete series published by Gladman included a large nonerosive group [14]. Subsequent series have looked at progression of damage and identified a group of 33–36% of patients who had no evidence of damaged joints at either presentation or follow-up [15,16]. A similar proportion of patients – 28% – remained without disability over a 10-year period [17]. An earlier study, looking at remission in PsA, using rather exacting criteria of no inflamed joints over three consecutive visits, found 18% of 391 patients fulfilled these criteria in an 18-year period. It is important to note, however, just over half of these subsequently relapsed [18].

Wright reported a group of patients who developed a severely deforming arthritis, termed arthritis mutilans, with osteolysis of the digits, polyarticular involvement and frequent spinal involvement [19]. Subsequent reports have also described this most severe form of PsA, which results in marked disability [20,21]. Affected individuals often have flail digits in both hands and feet resulting in the ‘*main en lorgnette*’ deformity described by Wright. Fortunately, this distinctive subgroup only represents a small proportion of affected people, rarely more than 5% of the total. Between the mild, nonprogressive forms, and the severe arthritis mutilans, there is a predominantly polyarticular group in which progressive deformity and damage is slow but persistent. These people slowly accrue damage to joints and become

progressively more disabled, as demonstrated by several cross-sectional and longitudinal surveys, particularly from the Toronto group [13,22]. In Dublin, follow-up of a cohort of patients presenting to the early arthritis clinic with recent-onset disease showed that 40% developed erosions by the 2-year assessment, a figure often used to emphasize the progressive nature of the disease [23]. In addition, a cohort from Bath demonstrated progression from oligoarthritis to polyarthritis and increasing disability during follow-up [24].

Given the disease is often less benign than first thought, a treatment approach to quell any signs of inflammation should now be recommended, as in rheumatoid arthritis, although things may not be as straightforward in PsA. A study from the Toronto group demonstrated radiological progression of spinal disease in the absence of clinical progression (as indicated by symptoms and spinal movements) over a mean follow-up period of 57 months. Therefore, in this cohort, symptomatic and disease-modifying treatment did not prevent progression of the disease [25]. We can conclude that spinal ‘damage’ can progress in the absence of symptoms and it has also been shown recently that peripheral bone anabolic changes can progress despite abrogation of peripheral inflammation with a TNF inhibitor [26].

Outcome measures & definitions of remission

It is beyond the scope of this article to go into detail on outcome assessments in PsA; there are a number of review articles already available [27–30]. Unlike in rheumatoid arthritis, the acute phase response is not a reliable indicator of disease activity, nor is it a predictor of radiographic damage and further developments in soluble and genetic biomarkers are eagerly awaited [31,32]. Disease-specific composite measures have more recently been developed: these are more comprehensive in their coverage of the diverse manifestations of the disease and permit a single ‘snapshot’ of disease activity as a whole [30,33]. Furthermore, these measures may function both as disease activity and responder measures, and it is possible to develop cut-offs for low, moderate and high disease activity. In addition, a specific minimal disease activity (MDA) state measure has been developed (Table 1) allowing treat to target strategies to be implemented [34].

Definitions of remission

A systematic literature review for articles pertaining to remission and low disease activity in PsA was conducted using the EMBASE and Cochrane libraries (Box 1). A hand search identified a further additional three relevant references.

Table 1. Criteria for minimal disease activity.

Literature search	Remission (n)	Low/minimal disease activity (n)
Hits	477	315
Duplicates	53	40
Not psoriatic arthritis	141	138
Paper not available for review	6	1
Not relevant to remission or review paper only	277	132
Remaining papers for review	6	4

A review of the rather limited literature shows that there has been little in the way of validated outcome measures to define disease remission in PsA (Table 2). Gladman *et al.* originally proposed remission to be an absence of actively inflamed joints [18]; however, this excludes the significant burden of extra-articular disease. Cantini *et al.*'s criteria for remission were wider, but without evaluating the skin [35]. A more realistic target may be MDA. Recently criteria for MDA have been developed and validated, as noted above. In a secondary analysis of an interventional trial database, those patients found to be in MDA at follow-up had less progression of radiological damage [36].

Definitions of (absence of) disease activity are wide and include some to all domains of psoriatic disease (Table 2). Given these definitions, it would appear that between 0 and 36% of patients can achieve remission and between 34 and 52% can achieve MDA; however, these figures are clearly dependent on outcome measure, the demographics of the cohort and treatment used.

Since the systematic review, at least one other paper on remission has been published [43]. In this study from Rome (Italy), 47 patients treated with etanercept were found to be in remission for a period of at least 36 weeks. Remission included a Disease Activity Score for 28 joints (erythrocyte sedimentation rate) score of less than 2.6, no swollen and tender joints, low patient and physician visual analog scale scores, and no enthesitis or dactylitis. In addition, and in contrast to Cantini *et al.*, the patients were also required to have had a greater than 75% reduction in Psoriasis Area and Severity Index score since the baseline assessments. After etanercept withdrawal all patients relapsed with a mean period before relapse of 18 weeks. All patients achieved disease control after restarting etanercept.

Treat to target in PsA

The concept of treat to target in rheumatoid arthritis, with improved clinical and radiographic outcomes, may also be applicable to other inflammatory rheumatic

diseases, such as PsA. However, the absence of a suitable target has hampered efforts to demonstrate this in psoriatic disease. This is, in part, owing to the diverse clinical manifestations both in the sense of including all of them in a composite measure, and in the assumption that they all share the same underlying pathophysiological process as well, and would, therefore, share equally in the response to treatment.

Although the treat-to-target principal has been incorporated into guidelines and is intuitively good clinical practice, no formal studies on the concept had been reported until recently [44,45]. A formal tight control treat-to-target study has now been published, albeit in abstract form at the present time [8]. In this study, 206 patients with early (less than 2 years of symptoms) PsA were randomized to an intensive treat-to-target arm or a standard care arm. Those in the intensive arm were treated according to an algorithm that was driven by clinical state at each monthly visit – if patients were not in MDA, their treatment was changed to achieve that state. The algorithm dictated a rapid introduction of methotrexate to a target dose of 25 mg, followed by the addition of sulfasalazine to a dose of 40 mg/kg/day, according to response. Further drug escalation depended on the number of tender and swollen joints – if sufficient disease was present TNF inhibitors were introduced; if not then leflunomide or ciclosporin either alone or in combination were substituted. Patients in the standard care arm received usual clinical care, with no

Box 1. Results of search strategy for articles on remission in psoriatic arthritis.

Five of seven criteria must be fulfilled:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- Psoriasis Area and Severity Index ≤ 1 or body surface area $\leq 3\%$
- Patient pain visual analog scale ≤ 15 mm
- Patient global activity visual analog scale ≤ 20 mm
- Health assessment questionnaire ≤ 0.5
- Tender enthesal points ≤ 1

Table 2. Relevant articles from literature search.

Study (year)	Definition	Achieving target (%)	Factors predicting target achievement	Ref.
Cantini <i>et al.</i> (2008)	Absence of joint disease, enthesal disease, dactylitis	24 at 12 months	More frequent in those on anti-TNF	[35]
Lindqvist <i>et al.</i> (2008)	Absence of joint activity, normal inflammatory markers	17 at 6 months	Oligoarticular disease, physician VAS, nail disease	[37]
Gladman <i>et al.</i> (2001)	Absence of joint activity on three consecutive visits	17.6 lasted 2.6 years	Males, fewer joints, lower HAQ	[38]
Saad <i>et al.</i> (2010)	DAS28 rheumatoid arthritis remission criteria	36.1 at 12 months after TNF	Younger age, male, lower inflammatory markers, lower HAQ	[39]
Atteno <i>et al.</i> (2010)	Remission: absence of joint activity MDA: no SJC, <2 TJC, HAQ <0.5	0 42 at 12 months	NA NA	[40]
Coates <i>et al.</i> (2010)	Development of MDA – composite measure of joints, skin, entheses, PROMs	NA	NA	[34]
Coates and Helliwell (2010)	MDA	34	Oligoarticular disease, low inflammatory markers	[41]
Coates and Helliwell (2010)	MDA	48–52	NA	[36]
Lie <i>et al.</i> (2010)	DAS28 rheumatoid arthritis remission DAS28 rheumatoid arthritis low disease activity	24 at 6 months 42 at 6 months	NA NA	[42]

DAS28: Disease Activity Score for 28 joints; HAQ: Health assessment questionnaire; MDA: Minimal disease activity; NA: Not applicable; SJC: Swollen joint count; TJC: Tender joint count; VAS: Visual analog scale.

restrictions on prescribing from a rheumatologist on a 3 monthly basis. Blinded assessments were performed at 12 weekly intervals and the primary outcome measure was the proportion of patients achieving an ACR20 response at 48 weeks. The results demonstrated that tight control, treating to target, was able to achieve better clinical outcomes than standard rheumatologist care (at 48 weeks: ACR20: tight control 62%; standard care 45%; odds ratio: 1.91; 95% CI: 1.03–3.55; $p = 0.04$).

Ultrasound data

Although clinical remission is a laudable goal, experience in rheumatoid arthritis has indicated that even though clinical low disease activity may have been achieved, subclinical synovitis, demonstrated by ultrasound, may persist and may explain subsequent structural progression [46]. Therefore, it is clear, at least for rheumatoid arthritis, that even in states of clinical

low disease persistent synovitis may occur. That this also occurs in PsA is suggested by a study of subclinical disease in early cases, where 87% of patients had at least one joint that demonstrated subclinical synovitis on ultrasound examination [47]. The same group were, however, not able to show significant levels of subclinical enthesitis in an early cohort of patients [48]. In fact, in this study, clinical enthesitis was found more often than evidence of enthesitis on ultrasound.

If patients are in remission, can treatment be withdrawn?

There are a number of open-label studies describing treatment withdrawal in patients with PsA, most of who were on biologic drugs. Definitions of remission varied as indicated above. Cantini *et al.* withdrew patients who had achieved remission by their strict criteria for at least 4 months [35] and, overall, just

over half of the 73 PsA 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%; $p < 0.001$) and the overall mean duration of remission after therapy interruption was 12 ± 2.4 months. However, (more recent) preliminary data from a small open-label study have shown almost universal relapse over a period of 3 months following withdrawal of therapy, although, fortunately, with recapture of disease control on restarting the drugs in most patients [49]. More recently, Chimenti *et al.* have withdrawn therapy in 47 patients in remission finding universal relapse, with a mean interval from

discontinuation to relapse of 18 weeks [43]. It seems, therefore, that treatment withdrawal for those patients who do achieve low disease activity, usually on biologics, will eventually lead to disease relapse. Perhaps a better way forward would be to reduce the dose of target drug used to obtain remission rather than to withdraw it completely. This would still result in significant savings and a reduction in potential adverse events.

Conclusion

Low disease activity is an achievable target in PsA; however, validated definitions of remission remain works in progress. What is clear is that it is not sufficient to measure only the articular involvement in this complex

Executive summary

Introduction to psoriatic arthritis & disease assessment

- Psoriatic arthritis is not a benign disease, but demonstrates progressive functional loss and increased morbidity and mortality.
- Achieving remission may improve these outcomes.

Natural history of psoriatic arthritis

- There are inconsistencies in the literature about the natural history of the condition, which may reflect true differences, but which may also be methodological.
- The majority of patients have progressive radiological changes and loss of function.
- A subset of patients have an aggressive form of the disease known as arthritis mutilans, which results in accelerated joint destruction and deformity.

Outcome measures & definitions of remission

- Outcome measures in psoriatic arthritis are still in development.
- Composite measures consider all aspects of the disease including skin, joints, entheses and dactylitis.
- Composite measures may take the form of responder indices, disease activity measures or both, and provide numerical definitions of remission.
- Definitions of remission vary from pure articular definitions to multidimensional, incorporating several aspects of the disease.

Treat to target in psoriatic arthritis: what is the evidence?

- The concept of treat to target in psoriatic arthritis is only just emerging, as both the target and the treatment have only recently been defined.
- Recent evidence from a randomized controlled trial of a treat to target strategy has shown improved outcomes.

Ultrasound data: are clinical definitions of remission supported by imaging data?

- As in rheumatoid arthritis, clinical definitions of remission are not supported by imaging.
- In particular, synovial inflammation may be present in the absence of clinical evidence.

Remission & treatment withdrawal: can patients in remission have their treatment successfully withdrawn?

- Early studies suggested that treatment withdrawal for patients in remission was more successful than for patients with rheumatoid arthritis.
- More recent evidence indicates that the majority of patients in low disease activity who have their treatment stopped will relapse.
- If treatment is restarted then disease control is once more achievable.

Conclusion

- Low disease activity is an achievable target in psoriatic arthritis.
- It is not sufficient to measure only the articular involvement in this complex heterogeneous disease, but to define remission, and low disease activity in terms of all the major manifestations of this disorder.

Future perspective

- Future developments in treatment strategies and treatment targets will refine treatment algorithms in this disease.
- Studies in development will help determine biomarkers for the development and control of this complex disorder.

heterogeneous disease, but to define remission, and low disease activity in terms of the major manifestations of this disorder.

Future perspective

As time moves on, there will be two key developments in this field. First, validated and widely used composite measures of disease activity will be available. Such measures will include definitions of remission, low and high disease activity, and response. These will provide a target for treatment and for monitoring flares of disease activity. Second, different treatment strategies will be developed including treat to target (low disease activity), as well as withdrawal strategies for patients in stable low disease activity. It is also likely that better disease phenotyping will include prediction algorithms

that permit the treating physician to anticipate treatment responses and the likelihood of achieving remission. In conjunction with this the development of soluble biomarkers will support these prediction rules and improve their efficiency.

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