Defining remission in psoriatic arthritis

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ABSTRACT

Driven in part by the introduction of highly effective agents, there has been growing interest in the overall therapeutic approach to patients with psoriatic arthritis (PsA). As with any form of arthritis, the goal of treatment for PsA would be to improve the outcome to the greatest extent possible. In other conditions, such as rheumatoid arthritis, recent discussions have centered on how best to define "remission." For patients with PsA, the heterogeneity among disease manifestations as well as the need to validate outcome measures make definition of remission challenging. In this paper we present a number of key principles and considerations critical to laying the groundwork for defining remission in PsA.

Introduction

Psoriatic arthritis (PsA) is a chronic, autoimmune, systemic inflammatory disorder that affects approximately 0.3% of the population. It is characterized by inflammation of the joints and surrounding structures, in association with cutaneous psoriasis. This seemingly straightforward description belies a complexity and heterogeneity that are quite germane to any attempt at defining remission in PsA.

In addition to the core areas of involvement, namely the skin and peripheral joints, other areas commonly involved in PsA, such as the entheses and the axial spine, can be of considerable significance to affected patients (Fig. 1) (1). Treatment typically involves consideration of these disparate areas of involvement in the individual patient. Although the intensity of therapy tends to be driven primarily by the manifestation that is most severe in the estimation of both the patient and the treating physician, treatment often requires consideration of, and therapy for, all of the various areas of involvement.

Over the past decade, the availability of newer therapies has engendered considerable interest in PsA, in both basic and clinical research, as well as in clinical care of patients. As was the case in rheumatoid arthritis, the notable efficacy of inhibitors of the pro-inflammatory cytokine tumor necrosis factor (TNF) has "raised the bar" regarding goals and expectations for treating PsA. With the introduction of highly effective therapies and treatment paradigms for autoimmune diseases, there has been a growing consensus that disease remission should be considered the ultimate goal when treating patients. Until recently, the idea of remission for inflammatory rheumatic diseases was as unattainable as it was sublime. Therefore, criteria for defining remission were never developed for many of these conditions, including PsA.

In this chapter, we propose a series of positions to develop the framework for defining remission in this complex condition. Further assessment, modification, and validation of these positions should allow creation of criteria for remission in PsA.

Position 1. Clinical remission in PsA can be conceptualized as a complete absence of disease activity, with no signs or symptoms of active disease

The concept underlying such a definition of remission is that patients in a prolonged state of remission would not experience pathologic consequences of disease over longer term periods of follow-up. In recent years, there has been a growing appreciation of the potential severity of PsA, particularly when polyarticular peripheral arthritis is present. Whereas PsA was previously considered to be a relatively mild form of arthritis, it is now clear that it can be progressive, destructive, and deforming (2-6). Erosive and deforming arthritis occurs in 40% to 60% of hospital-based psoriatic arthritis patients and is

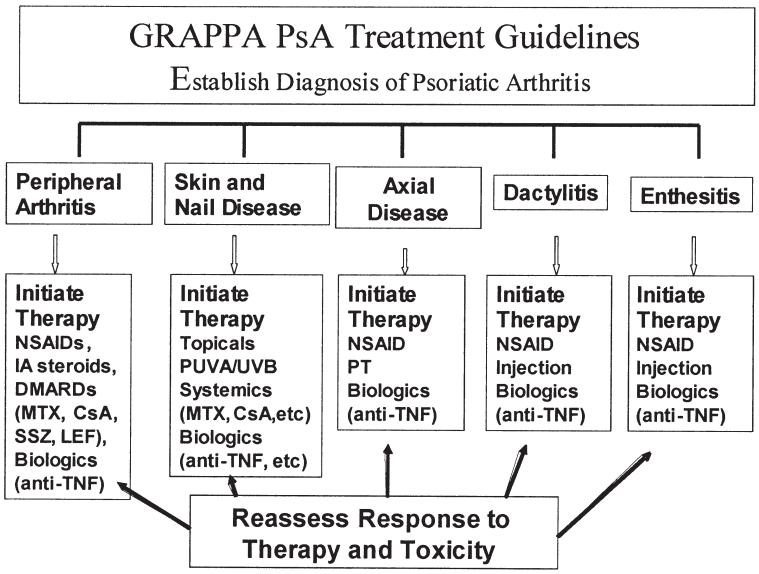

Fig. 1. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment guidelines.
(From Kavanaugh *et al*.: GRAPPA Guidelines for the treatment of psoriatic arthritis. *J Rheumatol* 2006; 33: 1417-21).

progressive from within the first year of diagnosis.

Disability and quality of life are adversely affected in patients with PsA to an equivalent degree as in rheumatoid arthritis (6). By extrapolation to RA, definitions of remission in PsA should include absence of peripheral arthritis. For other articular and periarticular involvement, 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. However, in the absence of data to the contrary, it is presumed that ongoing inflammation in these areas will result in tissue damage and untoward outcomes.

Similarly, for dermatologic involvement, the baseline presumption is that uncontrolled inflammation will lead to deleterious consequences. Therefore, complete absence of disease is required for remission. Interestingly, patients with psoriatic skin lesions may suffer fewer adverse effects of particular types, such as superinfection, compared to patients with other inflammatory skin diseases such as atopic dermatitis. This difference is independent of the extent of disease and presumably reflects differences in immunopathogenesis. Nevertheless, psoriasis is clearly an indicator of alteration in normal immunologic function, with resultant systemic inflammation.

Position 2. Clinical remission in PsA requires absence of disease activity in all facets of disease. This definition allows for continued treatment, if necessary to maintain response

Given the multifaceted nature of PsA, there is great heterogeneity among patients. One patient may have severe aggressive peripheral arthritis, and a few small lesions of skin psoriasis at the hairline. Another patient may have severe active skin psoriasis, inflammatory back pain, and several joints with dactylitis.

In the clinic, treatment decisions are often based on the preponderance of activity, taking into account all of the disparate features. However, for a patient to be in remission, all facets of disease should be considered (Fig. 1), and all should be devoid of activity. Thus, a PsA patient in remission would have no peripheral arthritis, no skin or nail disease, no spondylitis, no enthesitis, and no dactylitis. In addition, because PsA is a systemic inflammatory condition, measures of the acute phase response (e.g., C-reactive protein, erythrocyte sedimentation rate) should be normal.

It is certainly possible that a patient considered to have no activity in each of these facets of disease may have some subclinical disease activity. Indeed, in the absence of the induction of immunologic tolerance, it can be reasoned that the disease state remains immunologically active. This has been shown to be the case in PsA, RA, and ankylosing spondylitis with currently available therapies. Thus, almost all responding patients, even those with excellent clinical responses or apparent clinical remission, experience reactivation of disease upon discontinuation of therapy.

The concept of remission implies disease control to such an extent that sequelae of disease are avoided. Thus, continued treatment would not obviate a state of remission, if such treatment was necessary to maintain this state. This may be a matter of semantics, with some considering remission to require the lack of need for continued treatment, while others consider treatment-free remission to be a "cure," as is the case in oncology. In any event, cure is indeed the ultimate, definitive goal in the treatment of autoimmune diseases. Part of the rationale for earlier intervention with highly effective therapies is that there may be a "window of opportunity" during which responses of greater extent, including treatment-free durable remissions, might be achieved more readily than when using similar treatments later in the disease course.

Position 3. "Near remission" or "low disease activity" are different from "remission", but might be an appropriate goal for individual patients

An old axiom among dermatologists was that "if you treat a patient with psoriasis and they have no skin lesions whatsoever remaining, then you are treating too aggressively." This concept is based upon an overall assessment of the risks of therapy balanced against the benefits of minimizing disease activity. While such suggestions were more common before the availability of newer, more effective agents, they raise the possibility that lower levels of disease activity may be acceptable.

Assessing dermatologic involvement and its implications for treatment can be a difficult issue, particularly at lower levels of activity. Most rheumatologists have cared for PsA patients whose interactions in the rheumatologists' office focus largely on arthritis. Patients, particularly if their arthritis is severe but their psoriasis is mild and involves a limited amount of nonexposed skin, may be less concerned about their skin psoriasis. Also, although skin psoriasis can have profound affects on patients' quality of life, the long-term sequelae of psoriasis in terms of the end organ damage and dysfunction may seem less direct than they are for arthritis of the hand joints, for example.

For other patients, the inverse may be the case. A patient with severe active psoriasis involving a substantial amount of skin, including that of the face and hands, who also happens to have mild inflammation at a few entheses, may be concerned almost entirely with the dermatologic involvement. In these cases, the clinician and the patient may choose therapeutic strategies that focus less on certain manifestations of disease, and may be satisfied with a treatment that allows residual minor disease activity. Such choices are not uncommon in the clinic, and depend on issues such as fear of adverse effects, cost issues, and other factors. Although these states of "near remission" or "low disease activity" may become the agreed upon goal of treatment for an individual patient, the definition of "remission" should preclude even mild activity in any facet of PsA.

Position 4. The measurement of the various facets of PsA disease activity should utilise outcome measures and instruments validated in PsA; until validated instruments are not available, surrogate measures developed for other diseases can be used

PsA is inherently multifaceted. Patients may have a peripheral arthritis nearly indistinguishable from rheumatoid arthritis; others have spinal involvement very similar to that in ankylosing spondylitis. Skin psoriasis precedes joint disease in 70% of PsA patients and occurs concomitantly in 15%.

The most facile method to assess disease activity in PsA has been to use outcome measures developed for these other conditions that have close semblance to the various features of PsA (7-9). However, this extrapolation may be inexact, as PsA is distinct from these other disorders. For example, as compared to rheumatoid arthritis, the peripheral arthritis in PsA has a greater tendency towards asymmetry and oligoarticular involvement. Also, certain joints such as the distal interphalangeal (DIP) joints are more frequently involved, and associated features such as enthesitis and dactylitis are more common. Similarly, compared to ankylosing spondylitis, spinal involvement in PsA has a greater tendency towards asymmetry and discontinuous involvement. Regarding the skin, the overall level of severity may be lesser among PsA patients as compared to those with psoriasis without arthritis.

These considerations suggest that while outcome measures that have been validated in other diseases can be useful in patients with PSA, these measures should be validated in PsA. In some cases, this has been accomplished. Regarding peripheral arthritis in PsA, the disease activity score (DAS) and the American College of Rheumatology (ACR) response criteria, both developed for rheumatoid arthritis, have been shown to be effective at assessing response in PsA (10). However, response measures may not be well suited to assess remission, which is a state of being. Because of the complexities of the DAS formula, not all patients having very low DAS values have absence of disease activity. A number of outcome measures are available for assessing various facets of disease activity in PsA (Table I) (7). Only a few have been validated specifically in PsA; this would be valuable to their use in defining remission in PsA sAy.

Research agenda for the definition of remission in PsA

On the basis of the positions described above, it is clear that considerable research is needed in order to adequately define remission in patients with PsA. For example, outcome measures to define absence of activity in the various facets of disease must be validated. As part of that validation, the criteria defining "absence" can be established, bearing in mind the variability inherent in the measures themselves.

Several areas in which further research is needed to define how best to modify the definition of remission to incorporate these concepts are discussed below:

1. Subclinical disease

Among patients with no disease activity, it remains possible that there may be subclinical disease activity using appropriate clinical metrics for all of the various facets of PsA. For example, inflammation might be detected in a target organ using highly sensitive imaging techniques in a patient with no clinical evidence of disease activity. Or a biomarker might indicate ongoing immunologic and inflammatory activity, in the absence of clinical activity. Whether or not such cryptogenic activity obviates the definition of remission would depend upon whether such patients experienced sequelae of disease. As a starting point, it might be considered that until it is shown that persistent nonclinical activity is associated with a relevant outcome, such activity would not preclude the patient being defined as "in remission."

2. Consequences of disease

As noted above, a state of remission is ideally associated with no disease-related progression of damage to target organs. For joints, such damage and its progression must be measured accurately, and remission would imply no progression of joint damage. For disability, there would be no disease-related increase in disability, although one might allow for age-related decreases in functional status and hence increases in disability.

3. Functional status, quality of life, fatigue, participation

Functional status and quality of life (QOL) are crucial aspects of disease,

Table I. Outcome measures used to assess psoriatic arthritis

Domain	Area of involvement	Instruments	Composite indices
	Articular		
Disease activity	Peripheral arthritis	Tender joint count (78, 68, 28, other)	ACR20/50/70
		Swollen joint count (76, 66, 28, other)	DAS/EULAR
		Patient assessment of joint pain (VAS)	PsARC
		Morning stiffness	
		Physician global assessment of arthritis (VAS)	
		Patient global assessment of arthritis (VAS)	
		ESR	
		CRP	
	Axial arthritis	Pain (VAS)	BASDAI
			ASAS
	Enthesitis	Mander	
		MASES	
	Dactylitis	Dactylitis Severity Score (Leeds; Helliwell)	
	Dermatologic		
	Skin psoriasis	Erythema	PASI
		Induration/thickness	NPF-Ps
		Scale	
		extent (BSA)	
	Nail psoriasis		NAPSI
			mNAPSI
Function	Peripheral arthritis	Damaged joints	
	Axial arthritis		BASMI
	PsA		HAQ
			AIMS
	Fatigue		FACIT
Quality of life			PsAQOL
			SF36
			DLQI
Damage	Peripheral arthritis	Radiographs	Steinbrocker score (modified)
			Sharp score (modified)
			Rau/Wassenberg score
	Peripheral and axial arthritis	Other imaging modalities (e.g., MRI, US)	To be developed

ACR: American College of Rheumatology; ASAS; assessment in ankylosing spondylitis; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BSA: body surface area; CRP: C reactive protein; DAS: Disease Activity Score; DLQI: dermatology life quality index; ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; mNAPSI: modified NAPSI; MRI: magnetic resonance imaging; NAPSI: Nail assessment in psoriasis; NPF-Ps: National psoriasis foundation psoriasis score; PASI: psoriasis area severity index; PsARC: Psoriatic Arthritis Response Criteria; QOL: quality of life; SF-36: short form 36; US: ultrasonography; VAS: visual analog scale.

and are correlated strongly with important outcomes for patients. A number of measures have been developed to assess function and QOL, either generally, or focusing on individual features of PsA (11-15). Some measures have been developed for and validated in PsA patients (14), and others have been validated in other autoimmune diseases. Fatigue can be an important symptom and of great concern to patients. However, inclusion of functional status, QOL, and fatigue into clinical remission criteria for PsA is not straightforward, as these aspects of clinical status are not influenced by disease activity alone. For example, functional status and QOL are influenced by factors such as age, damage already caused by the disease, comorbid conditions, and other variables. It is therefore possible that functional status and QOL will vary significantly among patients with no active clinical disease. Although incorporation of these key aspects of disease would be an important addition to definitions of remission, further delineation of their measurement in populations is needed.

4. Implications of remission

In and of itself, achievement of clinical remission would be a laudable and desirable goal, as it would imply that the disease process has been arrested to such an extent that disease-related damage and other outcomes can be avoided. However, in the current health economic environment, and given the relatively high acquisition costs of newer therapies, it will be important to determine the implications of achieving disease remission in PsA. Do patients in remission have improved survival, compared to those with active disease but low disease activity? More germane to pharmacoeconomic analyses, do PsA patients in remission retain employment and incur fewer healthcare costs than those with lesser levels of disease control? Such data are vital in proving the value of the therapies that may be necessary in order for PsA patients to achieve clinical remission.

Conclusions

Currently, a state of near-remission or low disease activity is a laudable and achievable goal. The ultimate aim of achieving lower levels of disease

activity is to minimize the likelihood of disease progression and thereby avoid the attendant sequelae of disease-related damage, while optimising functional status and QOL. Therefore, there is a need to define states of remission and near-remission and for validating instruments to measure disease activity and outcomes in PsA, especially in the lower spectrum of disease activity. The capacity to define remission accurately will be valuable to the extent that the prognostic, personal, and healthcare implications of being in remission are delineated.

References

1. KAVANAUGH A, RITCHLIN C: GRAPPA Guidelines for the treatment of psoriatic arthritis. *J Rheumatol* 2006. 2006; 33: 1417-21.
2. 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.
3. HANLY G, RUSSELL ML, GLADMAN DD: Psoriatic spondyloarthropathy: a long term prospective study. *Ann Rheum Dis* 1988; 47: 386-93.
4. TORRE AJ, RODRIGUEZ PA, ARRIBAS CJ, BALLINA GJ, RIESTRA NJ, LOPEZ LC: Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. *Br J Rheumatol* 1991; 30: 245-50.
5. MCHUGH NJ, BALAKRISHNAN C, JONES SM: Progression of peripheral joint disease in psoriatic arthritis. *Rheumatology (Oxford)* 2003; 42: 778-83.
6. SOKOLL KB, HELLIWELL PS: Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol* 2001; 28: 1842-6.
7. KAVANAUGH A, CASSELL S: Outcome measures in psoriatic arthritis. *Current Rheumatology Reports* 2005; 7: 195-200.
8. GLADMAN DD, HELLIWELL P, MEASE PJ, NASH P, RITCHLIN C, TAYLOR W: Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum* 2004; 50: 24-35.
9. TAYLOR WJ: Assessment of outcome in psoriatic arthritis. *Curr Opin Rheumato*l 2004; 16: 350-6.
10. FRANSEN J, ANTONI C, MEASE P, KAVANAUGH A, VAN RIEL P: Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: Analysis of data from randomized controlled trials of two TNF inhibitors. *Ann Rheum Di*s. In press.
11. MEASE PJ, ANTONI CE, GLADMAN DD, TAYLOR WJ: Psoriatic arthritis assessment tools in clinical trials. *Ann Rheum Dis* 2005; 64 (Suppl. 2) ii49-ii54.
12. HUSTED JA, GLADMAN DD, FAREWELL VT, LONG JA, COOK RJ: Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. *J Rheumatol* 1997; 24: 511-7.
13. HUSTED JA, GLADMAN DD, FAREWELL VT, COOK J: Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 2001; 45: 151-8.
14. MCKENNA SP, DOWARD LC, WHALLEY D, TENNANT A, EMERY P, VEALE DJ: Development of the PsAQoL: a quality of life instrument specific to psoriatic arthritis. A*nn Rheum Dis* 2004; 63: 162-9.
15. DE KORTE J, MOMBERS FM, SPRANGERS MA, BOS JD: The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Arch Dermatol* 2002; 138: 1221-7.