
Remission in ankylosing spondylitis

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ABSTRACT

Remission is a major goal of medical therapy in chronic disease. Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that affects the axial skeleton and other body structures, causing pain, stiffness, functional loss, and disability. Until recently only symptomatic therapies were available, and control was poor in patients with severe disease. However, the TNF antagonists have now changed this substantially. The concept of disease remission in AS has not received much attention in the current literature. There exists one set of partial remission criteria formally developed by the ASAssessments in Ankylosing Spondylitis (ASAS) working group on the basis of clinical trials with nonsteroidal anti-inflammatory drugs for use in clinical trials. Furthermore, a state of low disease activity has been defined empirically in studies of anti-tumour necrosis factor (anti-TNF) therapy to describe clinically relevant treatment efficacy. As more effective therapies become available for AS, disease remission is increasingly regarded as an appropriate therapeutic goal that may then be translated into modification of progressive structural damage. There is a need to further define and evaluate current proposals concerning remission in AS.

The concept of disease remission in ankylosing spondylitis (AS) has not been widely explored. AS is an inflammatory rheumatologic disease characterised by progressive structural damage of the spine and sacroiliac joints with syndesmophyte formation and joint ankylosis, leading to concomitant loss of mobility, physical function, and quality of life (1-3). In the absence of effective disease-modifying therapies, the natural history of the disease involves a varying rate of radiologic progression (4). A well-recognised, long diagnostic delay results in many patients already having structural damage

at initial presentation (5). Nevertheless, major advances in the modification of signs and symptoms of AS by drug therapy have been seen over the past decade. Use of the TNF antagonists in AS has, for the first time in the medical history of this disease, led to partial remission rates exceeding 30% (6).

The term "disease remission" has recently been defined as a state of persistent absence of clinical and radiologic signs of disease activity without treatment for a specific time period (7). It was recommended that the term remission be reserved for this definition, and the distinction was made between this and less stringent interpretations, including low disease activity without therapy for a set period of time, or even low disease activity whilst on therapy. Applying this definition to AS is problematic; demonstrating the presence or absence of disease activity in AS by radiography is not possible (though it would be possible using magnetic resonance imaging).

However, very much in line with the intent of this proposal, we believe that a definition of remission should address the degree of structural damage that is considered to be consistent with remission. Can one realistically describe a patient with AS who has lost his horizontal vision due to hyperkyphosis but has no more active disease as being in remission? Should we define a cut-off for structural damage that is still consistent with remission, or is the issue of structural damage one of disease regression, entirely separate from disease activity and remission? The problem of controlled clinical disease activity but ongoing radiographic progression, which appears to be the situation for therapy with etanercept (8), illustrates the complexity of separating disease activity and structural damage when considering remission.

Furthermore, the time period that indicates persistence must be defined. Little information is available on "persis-

tent absence of disease activity” in AS. In a recent study, the time to disease flare was measured after discontinuation of anti-TNF therapy in patients who had responded to therapy (9). Flare was defined as Bath AS Disease Activity Index (BASDAI) >4. The mean time to flare was 18 weeks in that trial. We suggest therefore that “persistent absence” must be somewhat longer than the 18 weeks it takes for disease activity to return after cessation of anti-TNF therapy; at least 6 months and perhaps even 12 months may be an appropriate time frame.

The natural history of AS is one of ongoing disease activity and radiologic progression over decades in the majority of patients (4), with some studies suggesting that progression is most rapid in the first 10 years of disease (10, 11). It may be that true disease remission (as defined by complete absence of disease in all aspects of disease activity, function, and damage) can occur in patients with a mild disease course. However to make a diagnosis of AS, the modified New York diagnostic criteria require a patient to have existing structural damage of the sacroiliac joints (12); these criteria ensure that the disease is already well established, suggesting that it may not readily be reversed.

The presence of radiologic damage at the spine at presentation has also been shown to be related to radiologic progression and poorer prognosis (13). It may be that earlier forms of spondyloarthritis (SpA) such as undifferentiated SpA (uSpA), including early axial SpA, may be better candidates for potential remission, when there is no definite structural damage at baseline. Population studies of uSpA patients over 11 years have shown that approximately 60% of patients with uSpA will progress to AS, with most of the remainder remaining as uSpA (14-16). The incidence of disease remission has not been reported in these studies.

There has been only one set of formally derived remission criteria in AS, the ASAS partial remission criteria (17). Other groups have introduced the concept of low disease activity (18), however this has been defined intuitively

rather than statistically or based on the results of clinical trials.

Partial remission criteria (ASAS)

The ASAssessments in Ankylosing Spondylitis (ASAS) group is an international collaboration of clinicians, researchers, and industry representatives who share the common goal of promoting the well-being and good outcome of patients with SpA. Among other objectives, ASAS is committed to the development and validation of disease assessment tools and the evaluation of treatment modalities in AS. The ASAS partial remission criteria for AS were developed alongside the preliminary definition for symptomatic improvement in AS (17), using patient data from five short-term nonsteroidal anti-inflammatory drug (NSAID) trials (19-23). Partial remission was defined *a priori* as a state of low level disease activity at the end of a clinical trial, so use of the term “remission” could already be challenged.

The project (17) began with the five core outcome domains specified in the ASAS Core Set for symptom-modifying antirheumatic drugs (SMARDs) and physiotherapy in AS: physical function, pain, spinal mobility, patient global assessment, and inflammation (24). These domains have been identified previously on the basis of expert consensus, research evidence, and statistical approaches (24). The most appropriate measures for each core set domain have been recommended based on literature evidence of validity and consensus opinion (25, 26). To define improvement criteria, all outcome measures used in the five NSAID trials for each domain (not solely those defined in the SMARD/physiotherapy core set) were examined for validity, reliability, and the capacity to differentiate between treatment and placebo therapies. This resulted in the exclusion of spinal mobility (poor responsiveness to therapy) from the final set of domains recommended to measure symptom improvement or partial disease remission.

A number of different conceptual definitions for symptomatic improvement were tested, including single outcomes and different combinations of multiple

domains, and then validated using patient data from the aforementioned clinical trials. The final multiple domain response criteria, named the ASAS20 response criteria (Table I) had the best discrimination between treatment and placebo groups among the different combinations tested. These criteria have now been validated in prospective clinical trials. Modifications to the original ASAS20 have been developed and validated for use in trials of anti-TNF treatment designed to detect the larger treatment responses expected with these therapies (Table I) (27).

The authors defined “partial remission” as a value of less than 20/100 in each of the four response criteria domains at the end of the trial (Table II) (17). As might be expected, more than 95% of patients from the five NSAID randomised controlled trials studied who were identified as achieving partial remission at the end of the trial were also seen to have improved using the ASAS20 response criteria. The improvement and partial remission criteria have been validated against expert opinion and in clinical trials (28, 29).

Use of a composite measure such as partial response can simplify interpretation of study results, by using the dichotomous result of “responder” or “non-responder” to calculate the percentage of patients who respond to therapy. This can be more meaningful to the clinician than the concept of a 20% symptomatic improvement, which can have a different meaning in different clinical situations. It also allows future pooling of the results of clinical trials (when valid) and calculation of the “number needed to treat” (NNT) to achieve a clinical response.

Partial remission using these criteria is now being introduced as an outcome measure in clinical trials of NSAIDs and TNF blockers in AS. Etoricoxib therapy has been shown to result in an ASAS20 response of 65%, naproxen therapy 53%, and placebo 20% in a 6-week randomised controlled trial; corresponding partial remission rates were 15%, 9%, and 3% respectively (30), much lower than the response rates. Importantly, all NSAID trials use the flare design, while all anti-TNF trials

Table I. Assessments in Ankylosing Spondylitis (ASAS) response criteria.

Instrument	Abbrev.	Description
ASAS improvement criteria (17)	ASAS-IC	4 domains, based on the discrimination between NSAID treatment and placebo <ul style="list-style-type: none"> - Physical function, measured by the BASFI - Spinal pain, measured on a 0-100 mm VAS - Patient global assessment in the last week, on a 0-100mm VAS - Inflammation, measured as the mean of the last 2 BASDAI questions (intensity and duration of morning stiffness)
ASAS 20% response criteria (17)	ASAS20	Treatment response is defined as: <ul style="list-style-type: none"> - $\geq 20\%$ and ≥ 10mm VAS on a 0-100 scale in at least 3 of the 4 ASAS-IC domains, and - No worsening of $\geq 20\%$ and ≥ 10 mm VAS on a 0-100 scale in the remaining 4th domain
ASAS 40% response criteria (27)	ASAS40	Treatment response is defined as: <ul style="list-style-type: none"> - $\geq 40\%$ and ≥ 20 mm VAS on a 0-100 scale in at least 3 of the 4 ASAS-IC domains, and - No worsening of $\geq 40\%$ and ≥ 20 mm VAS on a 0-100 scale in the remaining 4th domain
ASAS 5 out of 6 response criteria (27)	ASAS 5/6	Developed for use in trials of anti-TNF therapy, 6 domains were included: <ul style="list-style-type: none"> - Pain - Patient global assessment - Function - Inflammation - Spinal mobility - C-reactive protein (acute phase reactant) Treatment response is defined as improvement in 5 of 6 domains without deterioration in the 6th domain, using predefined % improvements.

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NSAID: nonsteroidal anti-inflammatory drug; VAS: visual analogue scale; TNF: tumour necrosis factor.

have been performed on the basis of an insufficient response to NSAIDs, so response criteria developed in NSAID trials may not be valid in trials of biologic therapies.

Anti-TNF therapy shows a similar pattern regardless of which biologic agent is used, with ASAS20 response rates around 60% for active therapy and 20% to 25% for placebo groups, compared

to partial remission rates of usually around 20% to 40% for active therapy and less than 5% in placebo groups (Table III) (6, 31-36). The only study to evaluate partial remission rates after discontinuation of anti-TNF therapy has shown that after 3 years of infliximab therapy, 15 of 42 patients (36%) fulfilled the partial remission criteria; however, only one patient remained in

partial remission after 1 year without therapy (9), indicating that anti-TNF therapy does suppress symptoms but may not definitely influence the disease process.

Low disease activity

Partial remission criteria are defined so as to be a measure of low or minimal disease activity rather than of true disease remission. The concept of low disease activity is a valid end point for therapy of AS, particularly as true remission remains elusive. Recent studies have used an empiric definition of low disease activity to be a BASDAI ≤ 3 (9, 18), in contrast to the common definition of active AS being a BASDAI > 4 (used in the inclusion criteria for most anti-TNF clinical trials). A state of low disease activity as defined by this cut-off was achieved by 12 of 21 patients (57%) after 2 years in a more complete analysis of open-label extension therapy with etanercept (15); similarly, 9 patients (43%) met the ASAS criteria for partial remission at this time-point. Intention-to-treat analysis indicated a corresponding ASAS40 response of 54%.

Interestingly, a BASDAI cut point of 3.9 cm (3.6 cm in males and 4.4 cm in females) has recently been shown to best discriminate between well-controlled and poorly controlled SpA patients (37), and the minimal clinically important difference for the BASDAI has been calculated to be 1.0 cm on a 0-10 scale (or 22.5%) (38). However, a BASDAI cut point > 3 has been used in recent clinical trials of sulfasalazine (39) and infliximab (40) for including patients for active therapy. Taken together, the use of a BASDAI ≤ 3 as defining low disease activity must be validated in further prospective randomised controlled trials.

Disease remission in AS

Is it sensible to define a more stringent "disease remission" for AS? The aforementioned criteria are conceptually both measures of low or minimal disease activity or partial remission with complete remission, or do we need to define "absence of disease activity" as

Table II. Assessments in Ankylosing Spondylitis (ASAS) partial remission criteria.

Value of < 20 mm (on a visual analogue scale of 0-100 mm) in *each* of the following 4 domains:

- Patient global assessment (in the last week)
- Pain (spinal pain)
- Function (measured by the BASFI)
- Inflammation (mean of intensity and duration of morning stiffness, from the BASDAI)

Adapted from Anderson *et al.* (17).

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index.

Table III. Assessments in Ankylosing Spondylitis (ASAS) response and partial remission rates in randomised placebo-controlled trials and open extension trials of tumour necrosis factor blockers.

TNF-blocker	Study	Duration, weeks	N	ASAS20 response, %		Partial remission, %	
				Active	Placebo	Active	Placebo
Infliximab	Braun <i>et al.</i> (31)	12	70	68	25	18	0
	Braun <i>et al.</i> (32)	54	69	62	-	18	-
	van der Heijde <i>et al.</i> (33)	24	279	61	19	22	1
Etanercept	Davis <i>et al.</i> (34)	12	227	59	28	17	4
	Brandt <i>et al.</i> (35)	6	30	79	25	0	0
	Brandt <i>et al.</i> (6)	54	26	73	-	31	-
Adalimumab	van der Heijde <i>et al.</i> (36)	12	315	58	21	22	6

ASAS20: Assessments in Ankylosing Spondylitis 20% response criteria; TNF: tumour necrosis factor.

an additional outcome measure in AS? Clinical experience has taught us that patients in partial remission may have no symptoms indicating disease activity or significant damage, consistent with a BASDAI of 0 to 1, a Bath AS Functional Index (BASFI) of 0 to 1, and an ASAS remission state of 0 to 1. This state of disease has not been formally defined yet, but we assume that this description comes very close to a possible definition of complete remission.

Although no intervention has yet proven to modify the natural history of AS, measuring disease remission has some priority because this should be the goal of optimal medical therapy. However, the assessment of low disease activity—or patient acceptable symptom states—as end points in clinical trials are important because clinical experience also tells that we usually cannot achieve remission in all patients. Thus, we propose to develop a valid and reliable instrument to measure remission. As it stands now we can only hypothesise what remission rates may be.

The current partial remission criteria are responsive to treatment with anti-TNF therapies, but lack face validity for use to define complete disease remission. Physical function (measured by the BASFI) can be impaired significantly due to structural damage in AS and not solely due to disease activity/inflammation. Similarly, spinal pain can be of mechanical origin due to syndesmophyte formation and ankylosis. Therefore, criteria for complete disease

remission should include primarily domains consistent with disease activity; inclusion of domains measuring aspects of structural damage could provide a background that sets a threshold of damage that may not be consistent with remission. This would imply that after a certain level of damage, remission can no longer be achieved because the health problem is too severe to seek remission.

How long a patient should remain in such a state to be defined as in remission is not clear. Is 6 months long enough to assume disease activity is under control, or is a year more appropriate? And how do we classify the asymptomatic patient with fused sacroiliac joints, or the patient with minimal or no measurable disease activity but nevertheless progressive spinal structural damage, in which progression contradicts a clinical impression of remission based on disease activity? Further studies are required to answer these questions. If we are to establish the true rate of disease remission in population studies of AS, or to identify therapeutic strategies that may induce remission in patients with active AS, a valid definition and a valid measurement instrument for disease remission is required.

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