

Challenges and Advances in Targeting Remission in Axial Spondyloarthritis

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Biologic therapies have vastly improved clinical outcomes for patients with axial spondyloarthritis (axSpA). Consequently, targeting clinical remission/inactive disease is now a major treatment goal as outlined in current treat-to-target recommendations^{1,2}. In March 2016, the current status of treating to target and aiming for remission in axSpA was reviewed by 7 expert rheumatologists and 1 patient representative at an industry-sponsored roundtable discussion. This editorial summarizes the key findings from the meeting and recommendations for future research.

At present, there is no clear, universally accepted definition of remission in axSpA for both clinical trials and routine practice. Clinical remission/inactive disease is defined by the absence of clinical and laboratory evidence of significant inflammatory disease activity in current treat-to-target recommendations^{1,2}; however, it remains unclear how to precisely assess this in practice. Various criteria to measure low disease activity (LDA) and clinical remission have been proposed that while potentially serving as realistic treatment goals in a treat-to-target strategy, require further validation in the clinical setting^{3,4}. In 2001, the Assessment of Spondyloarthritis international Society (ASAS) developed a preliminary definition of clinical remission—ASAS partial remission (ASAS PR), which includes assessment of 4 domains: patient global, spinal pain, physical function, and “inflammation” (a proxy for true inflammation, based on morning stiffness)⁵. In clinical trials, 12–15%^{5,6} of patients with ankylosing spondylitis (AS) receiving nonsteroidal anti-inflammatory drugs (NSAID) achieve partial remission; a ceiling of ~15–40% at 6 months also exists with biologic therapies, including tumor necrosis factor (TNF) inhibitors and secukinumab^{7,8} (Table 1^{9–20}). Treating patients with short symptom duration may increase the proportion of patients reaching clinical remission to ~50%^{9,21,22}.

Several other composite indices evaluating disease activity exist. The Bath AS Disease Activity Index (BASDAI) has been used extensively in clinical trials and practice, and more recently, the AS Disease Activity Score (ASDAS) has been developed. Although a validated definition of clinical remission or LDA for BASDAI is currently unavailable²³, certain cutoffs have been used in clinical trials and observational studies (BASDAI < 4²⁴; < 3 or ≤ 3)^{25,26,27}. For example, in the INFAST study, 76% of patients with early axSpA receiving infliximab plus naproxen achieved a BASDAI < 3 at Week 28⁹. ASDAS offers a more objective assessment of disease activity because it includes

C-reactive protein (CRP), which is a marker of inflammation, and may predict structural progression²⁸. ASDAS disease activity “states” (inactive disease: ASDAS < 1.3; moderate disease activity: ASDAS < 2.1) have been validated in a routine care population and a clinical trial population¹⁸, although further validation in relation to structural damage progression and quality of life is still required. The current lack of consensus on the optimal index of disease activity and cutoffs for disease activity states represents a major hurdle in the development of a treat-to-target approach in axSpA.

Whether current indices of disease activity are sufficient to provide an accurate measure of remission in a complex multifaceted disease such as axSpA is open to debate; the need for a measure that is simple enough to be applicable to clinical practice, while not being so stringent that it offers a target that is impossible to reach, must also be considered. Both ASDAS and ASAS PR fail to consider peripheral extraarticular manifestations of the disease, such as enthesitis and uveitis. ASAS PR also excludes objective signs of inflammation, such as CRP levels. Conversely, ASDAS does not include assessment of function, which might result in patients with extensive structural damage, who would never reach ASAS PR, achieving “inactive disease”¹⁸.

None of the composite disease measures developed to date consider the presence of inflammation on imaging. Magnetic resonance imaging (MRI) is important in the assessment of early axSpA, because inflammation and postinflammatory lesions are associated with new bone formation²⁹. Discrepancies between “clinical” and “imaging” remission have been observed previously, with only a minority of patients achieving both concurrently²². Indeed, a suitable MRI scoring system and corresponding definition of remission is currently unavailable. Thus, is clinical remission alone a sufficiently rigorous measure of disease activity, and does it measure disease activity at all? Future studies are required to investigate this issue further, as well as the role of any residual inflammation in flares. Various definitions of flare have been proposed, yet none have been universally accepted and validated³⁰. Further, both patients and physicians may have difficulty distinguishing mechanical overload from an inflammatory flare, so providing education on the key differences may be essential to ensure consistency in disease activity measurement.

Although retardation of structural progression is considered a key therapeutic goal, it is absent from current

Table 1. Achievement of ASAS partial remission and ASDAS inactive disease with pharmacologic treatment in clinical trials.

Indication	Drug	Study	Timepoint	No. Patients	ASAS Partial Remission (%)	ASDAS Inactive Disease (%)	Reference
Axial SpA	Naproxen	INFAST	Week 28	51	35.3	19.6	Sieper, <i>et al.</i> Ann Rheum Dis 2014 ⁹
Nr-axSpA	Golimumab	—	Week 16	97	33	33	Sieper, <i>et al.</i> Arthritis Rheumatol 2015 ¹⁰
	Adalimumab	ABILITY-1	Week 12	91	16	24	Sieper, <i>et al.</i> Ann Rheum Dis 2013 ¹¹
AS	Certolizumab pegol	RAPID-axSpA	Week 12	200 mg: 46 400 mg: 51	200 mg: 28.3 400 mg: 29.4	200 mg: 30.4 400 mg: 25.5	Landewé, <i>et al.</i> Ann Rheum Dis 2014 ¹²
	Adalimumab	ATLAS	Week 12	208	20.7	36.5	van der Heijde, <i>et al.</i> Arthritis Rheum 2010 ¹³
	Etanercept	—	Week 24	138	17	—	Davis, <i>et al.</i> Arthritis Rheum 2003 ¹⁴
	Golimumab	GO-RAISE	Week 14	50 mg: 138	50 mg: ~22*	50 mg: 20.3	Inman, <i>et al.</i> Arthritis Rheum 2008 ¹⁵
				100 mg: 140	100 mg: ~20*	100 mg: 23.7	van der Heijde, <i>et al.</i> J Rheumatol 2015 ¹⁶
	Infliximab	ASSERT	Week 24	201	22.4	—	van der Heijde, <i>et al.</i> Arthritis Rheum 2005 ¹⁷
				163	23.3	31.9	Machado, <i>et al.</i> Ann Rheum Dis 2011 ¹⁸
	Certolizumab pegol	RAPID-axSpA	Week 12	200 mg: 65 400 mg: 56	200 mg: 20 400 mg: 19.6	200 mg: 21.5 400 mg: 16.1	Landewé R, <i>et al.</i> Ann Rheum Dis 2014 ¹² (mixed anti-TNF-naive and anti-TNF-IR population)
				Secukinumab	MEASURE 1	Week 16	75 mg: 124
	150 mg: 125	150 mg: 15					
TNF-naive 75 mg: 90	TNF-naive 75 mg: 20						
150 mg: 92	150 mg: 16.3						
MEASURE 2	Week 16	75 mg: 34	75 mg: 5.9				
		150 mg: 33	150 mg: 12.1				
		TNF-IR 75 mg: 73	TNF-IR 75 mg: 15				
		150 mg: 72	150 mg: 14				
			TNF-naive 75 mg: 45	TNF-naive 75 mg: 20			
			150 mg: 44	150 mg: 18.2			
			TNF-IR 75 mg: 28	TNF-IR 75 mg: 7.1			
			150 mg: 28	150 mg: 7.1			

*Value estimated from graph in manuscript; data not cited in text. ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; TNF-IR: tumor necrosis factor inhibitor inadequate responder; TNF-naive: TNF inhibitor naive; SpA: spondyloarthritis; nr-axSpA: nonradiographic axial SpA.

composite measures for axSpA assessment^{1,2}. NSAID have shown some positive effects on spinal radiographic progression, which were more prominent in patients with increased CRP levels^{28,31}. The anti-TNF therapies adalimumab, etanercept, and infliximab did not show inhibitory effects on radiographic progression in AS after 2 years of continuous therapy [change in modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) ~0.8–0.9]^{32,33,34}. The latest data have nevertheless suggested that anti-TNF therapy may be effective in the long term^{27,35,36}, especially when initiated early³⁵. Indeed, recent data with certolizumab showed a change in mSASSS of –0.01 at 2 years in patients

with nonradiographic axSpA, versus 0.67 in patients with AS³⁷. Finally, recent evidence suggested a low rate of structural progression in patients with AS receiving secukinumab at 2 years (~80% no progression; change in mSASSS of 0.3)³⁸. These data are not directly comparable with studies of anti-TNF therapies because of differences in study designs and populations³⁸, and require further investigation in longterm controlled trials. Nevertheless, because high disease activity is associated with accelerated radiographic spinal progression²⁸, control of inflammation and disease activity may offer a sufficient surrogate for structural damage prevention.

Prevention of further structural progression and low/minimal disease activity or ASDAS inactive disease may be an acceptable alternative treatment target in patients with existing irreversible structural progression. The patient's perspective should also be considered when setting treatment goals, although caution is recommended to avoid measures becoming too subjective. Treatment priorities for patients are pain and fatigue, as well as physical and social functioning³⁹. Although pain is a central component of all existing indices of disease activity, sensitivity to pain may decrease over time; thus, the variability within patient-reported outcomes may represent an issue when aiming to measure remission consistently. Discrepancies between a patient's and a physician's view of remission are likely to exist because of differing perceptions of disease activity, disease severity, and treatment priorities. Comparing patient- and physician-reported remission in a real-life setting showed higher thresholds for patients (ASDAS ≤ 2.2) versus physicians (ASDAS ≤ 2)⁴⁰. It will be important to ensure patient understanding of the remission concept and its feasibility as a goal in the treat-to-target approach. A simple and easy-to-understand definition of remission is required, and effective patient-physician communication will be vital. Lessons can be learned from the ASAS Health Index and the Patient Acceptable Symptom State, which may be more easily understood by patients than remission.

Our main knowledge gap in targeting remission in axSpA is evidence from well-designed clinical trials that a treat-to-target approach is beneficial versus standard care. Although the TICOPA trial has shown this previously in psoriatic arthritis⁴¹, data from ongoing similar studies in axSpA are awaited. While challenging to assess in international, multicenter studies, the cost of treating to target is another important consideration in the context of shrinking healthcare

budgets and evidence that tight control of disease activity is more expensive in psoriatic arthritis and may be associated with an increased rate of adverse events⁴¹. Additionally, we do not yet know the minimum duration of remission that is beneficial for longterm outcomes in axSpA. Current guidelines from the European League Against Rheumatism recommend a sustained remission period of at least 6 months before tapering biologic therapy; more data are required to establish whether there is any association between length of time in remission and likelihood of flare².

Strategy trials will be required to establish the best approach for reaching and sustaining remission. Patients should first be treated to remission, undergoing regular monitoring and adjustment of dose as necessary, before being randomized to different management strategies for the maintenance of sustained remission (> 2 yrs). Ideally, such a trial should enroll only a homogeneous group of patients at a similar stage of early disease (disease duration < 3 yrs) and without advanced structural progression, with a longterm followup. Careful planning is essential to ensure that data collected provide answers to key issues relating to the optimum time at which to assess whether a treatment target has been reached, including predictors of response/nonresponse; optimal dosing, sequences/combinations; predictors of flare; and strategies for dose tapering/reduction. Further studies are required to establish the role of physiotherapy in achieving remission, as a parallel or combination treatment to pharmacotherapy; its use in the maintenance of drug-free remission after biologic therapy tapering/withdrawal may be particularly important.

A number of questions need to be answered before a treat-to-remission strategy can be incorporated into clinical practice (Table 2). The next step in targeting remission in

Table 2. Remission in axSpA research agenda.

Topics	Specific Questions
Definitions of remission	Do current definitions of remission include the necessary components? Is low disease activity a suitable alternative target? Do patients with irreversible structural damage require separate definitions of remission/low disease activity from patients without structural damage? Should additional outcomes, such as measures of structural damage or objective signs of inflammation (MRI and CRP), be included in a treat-to-target strategy for axSpA? How can the patient perspective be incorporated into the definitions of remission/low disease activity?
Optimal treatment strategy for remission	Are we allowing enough time for patients to achieve remission once receiving treatment? Is individual variability taken into account when assessing disease activity? What is the best disease management approach for patients who do not achieve remission while taking biologic therapy? What is the optimal treatment strategy for patients who achieve remission while taking biologic therapy for remission to be sustained?
Cost-benefit	What is the cost-benefit ratio of achieving remission if it is not sustained for at least 2 years?

axSpA: axial spondyloarthritis; CRP: C-reactive protein; MRI: magnetic resonance imaging.

axSpA may be an evolution of the treat-to-target approach to focus on comprehensive disease control, including remission and prevention of structural damage. The ultimate aim is to develop a strategy, using the best available treatments to ensure the optimal outcome for patients with axSpA.

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