

# Defining the target: clinical aims in axial spondyloarthritis

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## Abstract

Treat-to-target (T2T) is an emerging treatment paradigm in axial spondyloarthritis (axSpA), originally based on evidence from other inflammatory conditions, which aims to direct therapy to a clear target such as disease remission or low disease activity, with the ultimate goal of maximizing quality of life in affected individuals. The 2016 update of the Assessment of Spondyloarthritis International Society/EULAR guidelines for axSpA have recommended that treatment should be guided according to a predefined target but controversy remains as to what this target should be. An international task force has recommended remission or inactive disease as the desired outcome; however, there are many disease outcome measures developed for use in clinical practice in axSpA and the question remains of which is the most appropriate to use. Another important consideration when discussing the T2T paradigm is when to intervene. Although evidence is limited in this respect, the available data suggest that therapy should be commenced at an early stage of the disease, when the process of bone repair expected to occur after an inflammatory phase has not yet started. It has also been argued that the success of the T2T paradigm may depend more on the treatment strategy than the individual therapies utilized. This article will explore the feasibility of using a T2T approach in axSpA clinical practice, the utilization of new composite outcome measures of disease activity such as the ASDAS, and the validity of different treatment strategies to allow for a T2T intervention in these patients.

**Key words:** ankylosing spondylitis, axial spondyloarthritis, interleukin-17, TNFis, secukinumab

### Rheumatology key messages

- The main treatment goal in axial SpA is the maximization of long-term quality of life.
- Symptom control, preservation of function and social participation are key in axial SpA.
- Treat-to-target in axial SpA may depend on achieving an early state of remission with complete suppression of disease activity.

## Introduction

The treatment of axial spondyloarthritis (axSpA) requires a combination of pharmacological and non-pharmacological treatment modalities and has as its main goal the maximization of long-term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalization of function and social participation [1]. Given the variability

in the predominance of disease manifestations among patients and the multifactorial nature of the treatment goal, the measurement of its successful achievement is complex and is currently a matter of research and discussion among clinicians. In this article, we will discuss the most recent developments in the treat-to-target (T2T) paradigm and recommendations for what to target and when to intervene, as well as considerations of and the latest data on treatment strategies.

## T2T paradigm in axSpA

T2T is emerging as a new paradigm in the treatment of inflammatory arthritis, and particularly RA. This is based on evidence from other chronic conditions where it has been shown to be a pragmatic and cost-effective strategy. For example, the application of a T2T paradigm has

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resulted in the prevention of microvascular complications such as retinopathy and nephropathy in patients with type 2 diabetes mellitus, and in a significantly reduced risk of cardiovascular death in patients with hypertension [2, 3].

In chronic inflammatory arthritis, T2T aims to direct therapy to a clear target, such as disease remission or low disease activity, which should be sustained over time. This concept involves regular disease activity monitoring and a clear understanding of flares, and ideally aims at tight control. Evidence in early RA supports the benefits of this paradigm in the prevention of damage, maintenance of physical function and reduction of comorbidity risks [4]. Furthermore, emerging data support the validity of this approach in established RA, in elderly patients and to improve work capacity [4]. T2T has also been advocated for PsA, for which a validated definition of minimum disease activity is already available [5].

The 2016 update of the Assessment of Spondyloarthritis International Society (ASAS) and the EULAR guidelines included a new recommendation supporting the T2T paradigm in axSpA. There are, however, significant challenges in facilitating its implementation [6]. For example, unlike in RA, the relationship between uncontrolled inflammation and joint damage has not been unequivocally shown in axSpA, which, coupled with the scarcity of data on what the target should be and when to intervene, illustrates some of the obstacles faced by clinicians and researchers involved in the care of these patients.

The recently updated recommendations by an international task force on the T2T paradigm highlight remission or inactive disease of the musculoskeletal and extra-articular manifestations of axSpA as the desired outcome [7]. However, there is still debate as to what the ideal target should be in order to achieve the desired outcome of disease inactivity or remission.

#### Relationship between inflammation and joint damage

One of the main outcome measures in axSpA is the loss of function through bone neo-formation or joint fusion at the levels of both the SIJ and the spine. This progression appears to be generally linear over time, with a quarter of affected individuals progressing rapidly at the beginning of their disease [8]. A logical group to target would, therefore, be those with the more severe disease phenotype, who are likely to progress faster.

Data from a number of recent studies have indicated that radiographic progression is higher than average in people who have a high level of CRP at baseline [9, 10] and those who have evidence of inflammation, particularly severe SIJ bone marrow oedema (BMO) [11]. Taken together, these data indicate that there is a link between inflammation and new bone formation suggesting that both high CRP and BMO lesions are suitable targets for intervention. However, an important consideration remains that these inflammatory biomarkers are not universal, occurring only in 70–80% of patients with axSpA [12].

Further evidence suggests that individuals who have existing syndesmophytes at baseline (i.e. evidence of established bone neo-formation) progress much faster than

those without [13]; this is particularly true for men and patients who smoke [14, 15]. However, the molecular basis underpinning this process remains poorly understood and, although a relationship with inflammation has been shown, there remains uncertainty over when and how these processes of inflammation and new bone formation are linked. Indeed, prospective studies have shown progression of spinal syndesmophyte formation in the absence of MRI inflammation, despite ongoing TNF inhibitor (TNFi) therapy over 2 years [16, 17]. However, recent, long-term, retrospective analyses have suggested that long-term TNFi therapy can retard radiographic progression [18–20], while a prospective study of the Swiss Clinical Quality Management cohort of axSpA patients also demonstrated a reduced risk of radiographic progression with TNFi use, as assessed by new syndesmophyte formation and the modified Stoke Ankylosing Spondylitis Spinal Score [21].

#### Outcomes and targets

Despite a growing number of outcome measures developed for use in clinical practice on subjects with axSpA, the majority fail to incorporate all aspects of the disease, such as its impact on quality of life or extra-articular manifestations.

The recently developed ASDAS has been shown to have good discriminatory capacity and sensitivity to change and incorporates an objective measure of disease activity such as CRP or ESR [22, 23]. In addition, ASDAS has well-validated cut-offs: inactive disease (<1.3), moderate (1.3–2.0), high (2.1–3.5) and very high disease activity (>3.5), with evidence suggesting that ASDAS inactive disease (<1.3) can be considered a possible target and remission criterion in axSpA [24]. ASDAS has a possible advantage over the ASAS response criteria because the latter incorporate a function domain (the BASFI) that makes them less sensitive to change in advanced disease, when improvements in physical function are likely to be limited [25]. Yet, clinical trials show that only a small proportion of patients achieve ASDAS inactive disease after treatment with biologics, that is, patients with more advanced disease [26–29].

#### T2T paradigm in axSpA: when to intervene

An important consideration when discussing the T2T paradigm in axSpA is when to intervene. Emerging data point towards the importance of targeting disease activity, as this leads to progression with further syndesmophyte formation [10, 15]. However, this approach may only be relevant in established AS cases with not only SIJ but also spinal involvement, as these are the cases for which new syndesmophyte formation has been proven to be linked to existing baseline syndesmophytes [30]. These data cannot yet be extrapolated to earlier disease stages in axSpA or to those patients who have radiographic sacroiliitis but may never develop spinal syndesmophytes.

Studies and analyses have been conducted to determine the effect of duration and stage of disease on response to treatment with TNFis. Among these is a study by Haibel *et al.* [31] investigating adalimumab in 46 patients with active axSpA, which demonstrated that 80% (12/15 patients) with a disease duration of  $\leq 3$  years at baseline vs 14.3% (1/7 patients) with a disease duration of  $> 10$  years at baseline achieved a BASDAI 50 response and 73.3% (11/15 patients) vs 0% of patients, respectively, achieved an ASAS 40 response [31]. A study by Barkham *et al.* [32] was the first to demonstrate that infliximab is effective for reducing clinical and imaging evidence of disease activity in a cohort of patients with very early non-radiographic axial SpA (nr-axSpA) in whom progression to AS is highly likely. Furthermore, when results from this study were compared with those of a study of infliximab in established AS, it was shown that the proportion of patients reaching the ASAS partial remission criteria was higher for early axSpA (55.6 vs 22.4%) [32, 33]. Taken together, these data suggest that the extent of disease and the point of diagnosis are relevant to the success of the treatment.

Further indirect support for earlier intervention comes from imaging studies exploring the relationship between oedematous and fatty lesions in the SIJ and spine, which suggest that fat deposition is a post-inflammatory event [34]. However, data suggest that resolution of acute inflammatory lesions of BMO does not stop radiographic progression when fat metaplasia deposition occurs after resolution of inflammation [35]. Indeed new bone formation appears more likely to occur if there is fat development at any point, independent of treatment, rather than in the presence of BMO lesions that resolve completely [36]. Studies utilizing PET-CT have revealed osteoblastic activity in these fatty lesions [37]. These observations were confirmed in a recent study that analysed biopsies obtained by spinal surgery: MRI-determined fatty lesions were indeed shown to correspond to fatty cells in the bone marrow with the potential to develop osteoblastic activity [38]. These data would point towards BMO MRI lesions as a valid target for early intervention, before the process of fat transformation has started.

## Treatment strategies

It has been argued that the T2T paradigm may depend on the treatment strategy employed more than the individual therapies, and also on the achievement of an early state of remission with complete suppression of disease activity. This is supported by the results of a study, showing that patients with axSpA including AS with a disease duration of  $< 2$  years who received combination treatment of infliximab and NSAIDs were twice as likely to achieve clinical remission as patients who received NSAIDs alone [39]. A subsequent study in the same patient population confirmed that 50% of patients who had achieved partial remission after 28 weeks of treatment remained in remission after 6 months regardless of the treatment strategy used [40]. A further study suggested that the combination of a TNFi and high-dose NSAIDs led to better outcomes

and less progression over time compared with single therapy, whether that is a TNFi or NSAID [41].

To confirm these findings, validated definitions of remission and flare are needed. In addition, a greater understanding of whether remission of clinical symptoms and signs correlates with complete arrest of disease progression is required. For example, recent studies have shown conflicting data on the ability of NSAIDs to slow radiographic progression in AS despite a good clinical response [42]. Imaging studies have shown the efficacy of TNFis in reducing inflammation, correlating with significant improvements in subjective and objective measures of disease activity [43], while a growing body of evidence suggests that they also effectively inhibit radiographic progression [21, 44, 45]. Similar results have been shown with other biologic agents such as the IL-17A inhibitor secukinumab, although importantly the MEASURE studies lacked either a long-term placebo or standard-of-care control [46–48].

Nevertheless, it is noteworthy that radiographic progression occurs slowly and may only be relevant in a subset of patients with so-called poor prognostic factors, meaning it may not be a useful universal outcome measure in AS.

## Conclusions

The treatment armamentarium for AS continues to expand. Although clinical guidelines recommend the application of a T2T paradigm for the treatment of axSpA, much debate and uncertainty remain on what an adequate target should be, when intervention should occur and what role treatment strategy will play. Further research is needed to clarify these points and validated definitions of remission and flare are needed; however, the current evidence suggests that therapy should be aimed at an early stage of disease before the processes of fat transformation and new bone formation have started. It is important that the assessments used to monitor long-term response in routine clinical practice reflect the overarching goals of treatment.

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