

Treat-to-target in Axial Spondyloarthritis: Gold Standard or Fools' Gold?

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Abstract

Purpose of review:

Treat-to-Target (T2T) is an emerging management strategy in axial spondyloarthritis (axSpA). The concept was originally based on evidence from other chronic conditions, such as hypertension, diabetes and hypothyroidism, as well as some rheumatic diseases, such as rheumatoid arthritis and gout. The purpose of this review is to discuss the arguments against and in favour of adopting a T2T strategy in the management of axSpA.

Recent findings:

International groups have recommended a T2T strategy in axSpA. Inactive disease according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) has been suggested as a potential target. Achievement of ASDAS inactive disease has been associated with less progression of radiographic damage in several studies. Evidence for the benefit of a T2T approach has been published in psoriatic arthritis, a form of spondyloarthritis.

Summary:

Observational evidence suggests that a T2T approach might be beneficial in axSpA. However, data from a prospective randomized study proving the efficacy of a T2T strategy compared to routine care is still lacking. Moreover, the cost-effectiveness of such strategy in clinical practice also needs to be tested. The target will need to be useful and feasible in both clinical practice and clinical trials.

Keywords:

Axial Spondyloarthritis, Remission, Inactive Disease, Treat-to-Target, Outcomes Research.

Introduction

The availability of biologic therapies has vastly improved the clinical outcomes for patients with axial spondyloarthritis (axSpA). Consequently, targeting clinical remission/inactive disease is now an achievable major treatment goal as outlined in international recommendations.^{1,2}

The concept of treat-to-target (T2T) was “imported” from diseases like hypertension and diabetes, where clear targets have been defined and validated, and it is defined as “a treatment strategy in which the clinician treats the patient aggressively enough to reach and maintain explicitly specified and sequentially measured goals, such as remission/inactive disease or low disease activity”.³ A proactive clear endpoint, which is the aim of the treatment, should be used as a specific target algorithm. This endpoint should be supported by findings from randomized controlled trials suggesting that early aggressive treatment approaches are advantageous.³ In rheumatoid arthritis, this treatment approach was proven to be effective for example in the Tight Control of Rheumatoid Arthritis (TICORA) trial⁴ and is now a well-established concept.⁵ In psoriatic arthritis, benefits of a T2T approach have recently been shown in the Tight Control in Psoriatic Arthritis (TICOPA) study.⁶

However, trial evidence for this approach in axSpA is lacking and there is no absolute consensus about the specific target to use. In this article we will review arguments against and in favour of a treat-to-target (T2T) approach in axSpA.

Arguments against T2T in axSpA

The T2T concept in medicine is founded on the principle that changing or escalating therapy according to a pre-defined target leads to a better outcome, compared to “routine care”, which usually aims to give relief to the patient without an agreed upon goal. As mentioned above, the field of rheumatology borrowed this concept from management of diabetes and hypertension, where its application has successfully reduced serious outcomes such as retinopathy, neuropathy, renal damage, and stroke.⁷ In the treatment of rheumatoid arthritis, T2T strategy led to

reduced erosions and better function compared to routine care.⁴ However, just because this strategy improves outcomes in one rheumatic disease, can one presume it will work in another immune-mediated rheumatic disease such as axSpA? There are several lines of reasoning which suggest that this may not be the case.

The commonest argument proponents of T2T therapy in axSpA make, is to point to the evidence that high disease activity in axSpA leads to osteoproliferation.⁸ The implied message being that, if we do not suppress the disease activity, patient will continue to progress to “bamboo spine”. Let us examine this argument a little closely. First, there is no evidence to suggest that osteoproliferation is linear in every patient, plus it is unclear if a “group-level” observation can be applied to an individual. In practice, it is not always possible to predict which axSpA patient will have rapid, function-altering radiographic progression. Patients may accrue osteoproliferation for some time, albeit slowly – usually at a mean rate of 1 modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) point over 2 years, but then the rate of progression may flatten.⁹ Second, the change of 1 or 2 points in mSASSS score in a patient with axSpA may be inconsequential, since such small changes do not translate in any loss of function,¹⁰ or affect quality of life adversely. While there is evidence of increased cardiovascular comorbidity in axSpA patients, this link is not as strong as the link between HbA1C, or blood pressure readings, and serious outcomes such as renal failure, stroke, or death; and there are no data to support T2T therapy in axSpA will diminish the cardiovascular risk. Third, if an axSpA patient is satisfactorily responding to TNF inhibitor (TNFi) therapy symptomatically, there is little point in changing therapy in an attempt to achieve an artificial “target”. We currently do not have anything better than starting either a TNFi or an IL-17 inhibitor (IL17i), and several international treatment guidelines suggest changing the medication only for failure to get symptomatic relief, not for failure to achieve a pre-specified target.¹¹

Let us now consider if T2T for axSpA is even realistic. How many arrows do we have in our armamentarium to hit the target of inactive disease or low disease activity? Unlike rheumatoid arthritis where multiple classes of advanced therapy are offered, there are only three classes of medicines, namely NSAIDs, TNFi and IL-17 inhibitors,

available to treat axSpA.² Studies show that even with the best biologics we have, only 25% to 35% patients reach Ankylosing Spondylitis Disease Activity Score (ASDAS)^{12,13} inactive disease or Assessment of SpondyloArthritis international Society (ASAS) partial remission.^{14,15} Since vast majority of patients treated with the best available agents may not even reach the pre-defined target, is it advisable to expose all patients to intensive therapy, with the inherent risks and expenses, to achieve the “target” in a small minority? Probably not.

Implementing T2T therapy in axSpA can be very burdensome to the patient, and to the providers. By definition, T2T therapy needs a “buy-in” from the patient at the very onset, frequent and close follow up visits, more investigations than “standard of care”, and finally multiple changes and/or escalation in therapy irrespective of symptomatic relief if the target is not reached. In countries such as the United States, where health care expenses are highly regulated by insurance companies, this care path would be arduous to both – the patient and the rheumatologist – because of the sheer time, money and the efforts involved. This is the main reason why the recently revised ACR-SAA-SPARTAN treatment guidelines recommend against implementing T2T therapy for axSpA (*Ward et al, submitted manuscript*).

T2T strategy can easily lead to “over-treatment”, and more treatment is not always better. This will increase societal cost, could waste precious health care funds, and may lead to more adverse effects.¹⁶ The only T2T trial in spondyloarthritis was conducted in psoriatic arthritis.⁶ The “Tight COntrol of Psoriatic Arthritis” (TICOPA) study compared the T2T strategy versus the routine care strategy in a multi-center study in the United Kingdom. The use of biologics was much higher in the T2T group compared to the “routine care” group,⁶ but the benefits were modest: ACR20 responses were 62% vs 44%, and the PASI75 responses were 59% vs 33%. On the flip side, the T2T group had a much higher incidence of adverse effects (14% vs 6%), and the strategy failed to reduce radiographic progression. When this strategy was applied in a nation-wide sample, the incremental cost-effective ratio (ICER) was £54,000 pounds (\$70,200) per quality adjusted life years, which made the authors conclude that T2T strategy in psoriatic arthritis was not cost-effective, and should not be recommended for general use.¹⁷

Perhaps the most important argument against applying T2T strategy in axSpA is the lack of prospective randomized study proving its efficacy compared to routine care. With no experimental scientific data to back T2T in axSpA, it is premature to apply it in daily practice.

Arguments in favour of T2T in axSpA

The first article that showed a longitudinal association between disease activity and progression of radiographic damage in AS was published in 2014.⁸ This study included patients from the Outcome in AS International Study (OASIS) cohort that were clinically and radiographically evaluated every 2 years up to a period of 12 years. Radiographic progression increased in parallel with increase in the ASDAS disease activity state with for example a patient with very high disease activity (ASDAS>3.5) being estimated to have an additional progression of 2.3 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) units in the subsequent 2 years in comparison to a patient with inactive disease (ASDAS<1.3). Several measures of disease activity (ASDAS, BASDAI, CRP) were significantly associated with an increase in the mSASSS but the ASDAS statistical model was the one that best fitted the data. A subsequent study with data from the GERman SPondyloarthritis Inception Cohort (GESPIC) showed similar findings.¹⁸ In the GESPIC study, the authors also found that disease activity was associated with radiographic spinal progression in a population in an earlier disease stage compared to OASIS. Time-averaged ASDAS was significantly associated both with mSASSS worsening by ≥ 2 points and syndesmophyte formation/bridging over 2 years.¹⁸

A more recent study used data from patients with AS from the Swiss Clinical Quality Management cohort with up to 10 years of follow-up and radiographic assessments every 2 years.¹⁹ The authors demonstrated an association between TNFi use and reduced risk of spinal structural damage. Importantly, the pattern of correlations in this study demonstrated that the impact of TNFi on spinal radiographic progression was mediated by its (decreasing) effect on disease activity (ASDAS, BASDAI or CRP). ASDAS outperformed BASDAI and CRP alone for the association of disease activity with radiographic progression, confirming data from OASIS and GESPIC.

Achievement of an inactive disease status (ASDAS ≤ 1.3) while on treatment with TNFi resulted in almost complete inhibition of radiographic spinal progression during the following 2-year radiographic interval.

Data from the above three studies add to the validity (and predictive value in terms of progression of structural damage) of the ASDAS and provide compelling arguments to pursue a T2T strategy in axSpA, with ASDAS inactive disease potentially being the best target, particularly if the goal of treatment is inhibition of further spinal radiographic damage in addition to control of signs and symptoms, provided that the target seems realistic based on the clinical context.

Furthermore, for the purpose of defining a remission-like state in axSpA, ASDAS inactive disease seems to provide a more appropriate definition than the ASAS partial remission criteria because ASDAS inactive disease is independent of physical function, while ASAS partial remission criteria include physical function as one of its items, which implies that some patients with long-standing disease and severe structural damage and physical limitations may never fulfil ASAS partial remission criteria despite the disease being clinically and biologically inactive.²⁰ Interestingly, in AS, baseline CRP and ASDAS have also been associated with future elevated arterial stiffness measured as Augmentation Index (Aix), a risk marker of cardiovascular disease, supporting that disease activity is related to future risk of cardiovascular disease in this population.²¹

Finally, improvement in clinical disease activity and achieving inactive or low disease activity status is clearly associated with better health outcomes. For example, in a recent study (from the GO-RAISE cohort) reporting the outcomes of TNFi treatment over a period of 2 years, achievement of ASDAS inactive disease or ASDAS major improvement was significantly associated with greater improvements in the 36-Item Short Form Survey (SF-36) physical and mental component scores' as well as in work productivity compared to patients that did not meet these treatment targets.²² In another trial population with nr-axSpA (ABILITY-1), ASDAS responses, including achievement of ASDAS-ID, were also associated with statistically significant and clinically meaningful improvements in physical function, health-related quality of life and work productivity in a higher percentage of patients.²³ These data again suggest

that achieving ASDAS inactive disease should be considered a major treatment goal in patients with axSpA.

Conclusion

Observational evidence suggests that a T2T approach might be beneficial in axSpA, which has led to the recommendation of its use by experts in the field, namely in an international consensus exercise, with ASDAS-ID being suggested as the most adequate target in axSpA.¹ The 2016 update of the ASAS/European League Against Rheumatism (EULAR) guidelines for axSpA have also recommended that “treatment should be guided according to a predefined treatment target” but controversy remains as to what this target should be. The ASAS/EULAR recommendations also state that the target should be a shared decision between patient and rheumatologist, taking all relevant situational factors into consideration.

However, data from a prospective randomized study proving the efficacy of a T2T strategy compared to routine care are still lacking. The cost-effectiveness of such strategy in clinical practice will also need to be tested. Two randomized studies were addressing this issue in axSpA: an investigator-led French/Dutch/Belgian study (TICOSPA, NCT03043846) and a German pharma-sponsored study (STRIKE, NCT02897115). These studies differed between themselves in terms of the overall trial design (e.g. inclusion criteria and collection of imaging outcomes) and the T2T strategy in the tight control arm of the study (e.g. frequency of visits and treatment escalation algorithm). However, the STRIKE trial was recently prematurely terminated due to slow recruitment. Results from the TICOSPA study will help to clarify the role of T2T in axSpA.

Key points:

- Treat-to-Target (T2T) is an emerging management strategy in axial spondyloarthritis (axSpA).
- Observational evidence suggests that a T2T approach might be beneficial in axSpA.
- International groups of experts have recommended a T2T strategy in axSpA.
- Evidence from randomised controlled trials for a T2T approach in axSpA is still lacking.
- The feasibility and cost-effectiveness of such strategy in clinical practice will also need to be tested.

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Conflicts of interest

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Papers of particular interest have been highlighted as:

*of special interest

**of outstanding interest

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