Treat to Target in Axial Spondyloarthritis

Pros, Cons, and Future Directions

Jean W. Liew, MD[a], Maureen Dubreuil, MD, MSc[b,*]

KEYWORDS

• Treat to target • Disease activity • Axial spondyloarthritis • Ankylosing spondylitis

KEY POINTS

- Treat to target describes a management paradigm that involves choosing a clinically relevant target, assessment with validated measures at a prespecified frequency, and a change in therapy if the target is not met.
- The treat-to-target strategy has been used in other rheumatologic conditions, such as rheumatoid arthritis and psoriatic arthritis, and is advocated in axial spondyloarthritis.
- An ideal outcome measure for a treat-to-target strategy needs to be defined in axial spondyloarthritis, with consideration of existing or potential outcome measures and their attributes.

INTRODUCTION: TREAT TO TARGET

Treat to target describes a disease management paradigm that involves selection of a clinically relevant target, assessment with validated measures at a prespecified frequency, and a change in therapy if the target is not met. Treat-to-target strategies have been incorporated in treatment guidelines and in clinical practice for chronic medical conditions, such as hypertension,[1] type 2 diabetes mellitus,[2] and hyperlipidemia.[3] Treating these diseases to target has been demonstrated to improve important clinical outcomes, such as preventing cardiovascular events and retinopathy.[4–6]

In rheumatology, treat-to-target strategies are recommended for the management of gout, rheumatoid arthritis (RA), and spondyloarthritis (SpA), including psoriatic arthritis (PsA). In gout, the target is a serum uric acid level of less than 6 mg/dL or less than 5 mg/dL in the presence of erosive or tophaceous disease, and levels should be checked in order to titrate urate-lowering therapy.[7] The target and cutoffs were

[a] Division of Rheumatology, Department of Medicine, University of Washington, 1959 Northeast Pacific Street, BB561, Seattle, WA 98195, USA; [b] Section of Rheumatology, Boston University School of Medicine, 650 Albany Street, X201, Boston, MA 02119, USA
* Corresponding author.
E-mail address: mdubreui@bu.edu
Twitter: @rheum_cat (J.W.L.); @Spondy_MD (M.D.)

Rheum Dis Clin N Am 46 (2020) 343–356
https://doi.org/10.1016/j.rdc.2020.01.011
0889-857X/20/Published by Elsevier Inc.
rheumatic.theclinics.com

chosen based on the physiologic level at which monosodium urate precipitates in vivo and the understanding that controlled disease in gout prevents joint damage. In 2014 for RA, the European League Against Rheumatism (EULAR) released treat-to-target guidelines that included 4 overarching principles with the primary goal of optimizing quality of life through decreasing symptoms and joint damage.[8] In order to meet this goal, inflammation should be attenuated via adjusting treatment alongside regular measurements of disease activity. Shared decision making also should be used throughout this process. These guidelines have the backing of multiple randomized controlled trials (RCTs) that compared a treat-to-target or tight control strategy with standard of care in RA.[9] The connection between improved control of inflammation and prevention of joint damage also is established in RA.[10]

The first treat-to-target guidelines for SpA were introduced in 2014[11] and underwent revision in 2017.[12] Both PsA and axial SpA (axSpA) are included but the strength of evidence is greater for the former. Similar to the treat-to-target guidelines for RA, those for SpA include overarching principles and key recommendations. Like the RA guidelines, the overall goal is optimizing quality of life by decreasing symptoms, inflammation, and structural damage by regularly measuring disease activity and adjusting treatment accordingly. In contrast to the RA guidelines, the SpA guidelines include extraarticular manifestations (EAMs) of SpA as possible targets and indicate that imaging also should be considered as an adjunctive form of assessment for disease activity. All imaging modalities (conventional radiograph, computed tomography, magnetic resonance, and ultrasonography) are included, although the guidelines do not specify which sites ought to be assessed. The evidence base for the treat-to-target strategy in PsA rests on 1 RCT, the Tight Control of Psoriatic Arthritis (TICOPA) study[13]; strategy trials in axSpA have been under way but their results have not been published. Furthermore, it is not yet established that the achievement of treatment targets in axSpA would prevent structural damage, EAMs, or co-occurring conditions.

This review focuses on the background for a treat-to-target strategy in axSpA. The potential targets of treatment, which are the available validated measures of disease activity, are discussed. The association of these targets with outcomes of interest, including structural damage, physical function, spinal mobility, and EAMs, as well as the evidence that available treatments can have an impact on these outcomes, are addressed. How treat-to-target strategies have been incorporated into SpA treatment guidelines is reviewed. Finally, treat-to-target RCTs and the research agenda for future studies in axSpA are discussed.

DEFINING THE TARGET: DISEASE ACTIVITY MEASURES

The first necessary step of a treat-to-target strategy is defining the target. The target must be easily measurable in clinical practice, be validated in axSpA patients, and reflect clinical outcomes that are important to both patients and physicians. The 2 most commonly used measures for axSpA in clinical practice are the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS). The BASDAI was developed in 1994 and comprises 6 questions addressing 5 major symptoms in AS: fatigue, spinal pain, peripheral joint pain and swelling, localized tenderness, and morning stiffness.[14] Although the BASDAI correlates with other clinical outcomes of interest, such as physical function,[15] and has been used as both an eligibility criterion and outcome in clinical trials, it has major limitations. BASDAI questions pertain only to subjective, patient-reported outcomes and are not specific for symptoms related to inflammation versus other processes; 4 items are given equal weighting; and there is no assessment of extra-articular disease, such

as eye, skin, or bowel inflammation.[16] Due to the subjectivity of the items included on the BASDAI, there often is discordance between patient and clinician assessments of the disease activity.[17]

The ASDAS was developed by experts to try to overcome some of the limitations of the BASDAI. ASDAS includes some questions from BASDAI as well as patient and physical global assessments, and laboratory measures (either the C-reactive protein [CRP] or the erythrocyte sedimentation rate [ESR]).[18] The ASDAS has been validated in multiple observational databases and clinical trials as well as in different populations.[19] It has been shown to be responsive to clinical and imaging measures of disease activity, more so than the BASDAI.[20] The ASDAS remains, however, with limitations: it does not incorporate other objective measures of inflammation, such as that found on imaging; and like BASDAI it does not include any assessment of extra-articular disease.[16] ASDAS is challenging to use in US clinical practice because CRP and ESR assessments typically are not available in real time at the point of care. Although ASDAS has validated cutoffs for disease activity categories, there are no validated cutoffs for the BASDAI.

ASAS (then called Assessments in Ankylosing Spondylitis) developed a core set of 5 domains (physical function, pain, spinal mobility, spinal stiffness/inflammation, and patient global assessment) to be assessed in trials and other clinical outcomes studies. Based on this core set, Anderson and colleagues[21] developed standard ASAS response criteria using data from 3 RCTs comparing nonsteroidal anti-inflammatory drugs (NSAIDs) to placebo in AS. The final response criteria included the 4 domains of physical function (measured by the Bath Ankylosing Spondylitis Functional Index [BASFI]), pain (measured by a visual analog scale [VAS]), inflammation (measured with the proxy of morning stiffness), and patient global assessment (measured by VAS). Spinal mobility was excluded due to its poor performance. The ASAS20 and ASAS40 are the commonly used response criteria for primary outcomes in RCTs. An ASAS20 response is defined as greater than or equal to 20% improvement in at least 3 domains with no worsening in the fourth domain. The utility of these response criteria in clinical practice, however, is limited, and they suffer from issues similar to the BASDAI and ASDAS.

In response to the lack of a definition of ankylosing spondylitis (AS) disease severity, ASAS developed an instrument based on the International Classification of Functioning, Disability, and Health model of function and health.[22] The ASAS Health Index (ASAS HI) includes 17 items with dichotomous responses, meant for use in RCTs and in clinical practice. It has been shown to have construct validity, interpretability, reliability, and responsiveness in both axSpA and peripheral SpA populations.[23] A value greater than or equal to 12.0 serves as the cutoff between poor and moderate health, whereas a value less than 5.0 is the cutoff between good and moderate health. The ASAS HI serves as the primary outcome measure in an ongoing treat-to-target trial in axSpA.

For a target to be useful, there should be a clear definition of that target, as has been established for ASDAS inactive disease/remission and low disease activity (LDA). These are defined in **Table 1**. Remission refers to the absence of clinical or laboratory evidence of significant inflammatory disease over a prolonged period of time.[24] It also has been defined as a state in which the disease does not progress.[25,26] In clinical trials, the disease activity states of either inactive disease (ASDAS <1.3) or ASAS partial remission (a value <20 on a scale of 0–100 in all 4 ASAS domains) is used. The main limitation with ASAS partial remission is that it relies partly on the BASFI, and a patient with irreversible structural damage may be unable to fulfill ASAS partial remission criteria.[16]

Table 1
Definitions of remission and low or minimal disease activity

ASDAS inactive disease	ASDAS <1.3 ASDAS questions 1. How would you describe the overall level of AS neck, back, or hip pain you have had? 2. How active was your spondylitis on average? 3. How would you describe the overall level of pain/swelling in joints other than neck, back, or hips you have had? 4. How long does your morning stiffness last from the time you wake up? 5. CRP measured in milligrams per liter ASDAS calculation 0.1216 * Q1 + 0.1106 * Q2 + 0.0736 * Q3 + 0.0586 * Q4 + 0.5796 Ln (CRP + 1)
ASAS partial remission	<20 on a scale of 0–100 in 4 out of 4 domains ASAS domains 1. Physical function (BASFI) 2. Pain (by VAS) 3. Inflammation (morning stiffness) 4. Patient global assessment (by VAS)

Abbreviations: + denotes plus; * denotes times; Ln, natural log.

As conceptually defined at the Outcome Measures in Rheumatology (OMERACT) 6 conference in 2002, MDA comprises both remission and LDA and should be "a useful target of treatment by both patient and physician given current therapy and knowledge."[27,28] After this conference, MDA has been defined and validated in both RA[29] and PsA.[30] MDA for PsA was used as the primary outcome measure in the TICOPA treat-to-target RCT.[31]

WHICH OUTCOMES TO TARGET

Disease activity measures and disease states as defined by these measures are only surrogate targets for the outcomes of interest. In axSpA, a main outcome of interest is irreversible structural damage of the axial skeleton. European cohort studies of axSpA and AS have identified several variables that are independently associated with radiographic progression: baseline syndesmophytes,[32–35] male sex,[33,35] smoking,[34,35] HLA-B27 positivity,[33] and elevated CRP.[34] In long-term extension studies of tumor necrosis factor inhibitor (TNFi) trials, 2-year to 4-year follow-up has shown no benefit of TNFi on the prevention of structural damage in either AS or nonradiographic axSpA.[36–41] The comparator was a historical cohort, the Outcome in AS International Study, whose participants were TNFi-naïve for the first 4 years of follow-up. On the other hand, observational cohort studies with longer term follow-up of 5 years to 8 years have provided evidence that TNFi treatment over this longer duration may slow radiographic progression.[42–44] The data regarding whether NSAIDs have a disease-modifying effect on radiographic progression, either alone or in combination with TNFi, have been mixed.[45–47]

Available therapies for AS and nonradiographic axSpA have shown efficacy on the outcome measures of disease activity, physical function, spinal mobility, and health-related quality of life in RCTs.[48–55] The objective radiographic outcome of structural damage is associated with the outcomes of physical function and spinal mobility.[15,56,57] It is believed that spinal mobility may be determined independently by both reversible inflammation and irreversible structural damage.[57] In long-term

extension trials with over 10-year follow-up, measures of physical function and spinal mobility remained stable despite radiographic progression; however, there was no control group in this study.[58]

Magnetic resonance imaging (MRI)-detected inflammation in the sacroiliac (SI) joints and spine may serve as a surrogate for the outcome of structural damage. Whether MRI-detected inflammation should be a target of therapy requires further study. A major hypothesis is that a window of opportunity exists and that radiographic progression can be halted if disease is treated early, particularly with biologic therapy.[59] Studies have shown that the formation of new syndesmophytes at vertebral corners is predicted by the presence of prior inflammatory lesions, in particular lesions of fat infiltration or metaplasia, at the same site.[59–62] Structural lesions (fat metaplasia and ankylosis) seen in the SI joints on MRI also have been found to be associated with future spinal radiographic progression.[63] Finally, MRI-detected inflammation in both the SI joints and the spine are associated with disease activity as measured by the ASDAS and the BASDAI.[64,65] In RA, treat-to-target RCTs specifically looking at whether a target of imaging remission was superior to usual care did not show a benefit.[66,67] Whether the same is true for axSpA remains to be shown.

Beyond the primary outcomes of structural damage, function, mobility, and quality of life, other important outcomes have been rarely addressed in RCTs. These include EAMs and sequelae of long-standing disease, such as cardiovascular disease (CVD) and osteoporosis. The pooled lifetime prevalence of common EAMs in a meta-analysis were uveitis, 26%; psoriasis, 9%; and inflammatory bowel disease, 7%.[68] EAMs have not been studied as secondary outcomes, apart from standard safety assessments, in RCTs. Individuals with axSpA have an increased risk of CVD as well as CVD-related mortality compared with general population comparators of the same age and sex,[69–71] and it is hypothesized that chronic systemic inflammation from axSpA disease activity may be contributing. Whether anti-inflammatory therapy attenuates the CVD risk in axSpA is unclear.[72–75] The pooled prevalence of osteoporosis was 12% to 34% and that of vertebral fractures 11% to 25% in a meta-analysis.[76] In a systematic literature review, Ashany and colleagues[77] found that TNFi in long-term extension trials of 2 years' to 4 years' duration, was associated increased bone mineral density in the hip and lumbar spine but not with a significant change in fracture risk. Outcomes like CVD and osteoporosis require a long duration of follow-up, so they are not easily assessed in RCTs, although may be assessed in prospective cohort studies. Such information would prove valuable for knowing the treatment effects on long-term complications of axSpA.

TREAT-TO-TARGET TRIALS IN RHEUMATOLOGY

In RA and PsA, the treat-to-target approach compared with standard care has been evaluated in key RCTs. In both trials, the intervention arm featured frequent visits with scheduled measurement of disease activity as well as a protocol of treatment titration, addition, or switching. These trials, and their key design characteristics and outcomes, are summarized in **Table 2**.

The Tight Control for Rheumatoid Arthritis (TICORA) study, published in 2004, was conducted in the United Kingdom and included patients with active RA and disease duration of less than 5 years.[9] Subjects were randomized to either intensive therapy, in which a disease activity score (DAS) was performed at each monthly visit, or a routine management arm, in which they were followed every 3 months without measurement of disease activity. The DAS included ESR, joint tenderness, swollen joint

Table 2
Treat-to-target randomized controlled trials in rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis

	TICORA	TICOPA	TICOSPA
Study population	Active RA Disease duration <5 y	Active PsA Disease duration <24 mo	axSpA
Study sites	2 UK centers	8 UK centers	18 European sites in France, Belgium, and the Netherlands
Number randomized	111	206	160 anticipated
Duration of study	18 mo	48 wk	12 mo
Intervention group	Tight control, monitored by DAS every 4 wk	Tight control, monitored for MDA every 4 wk	Tight control, monitored for ASAS HI every 4 wk
Comparator group	Standard care, seen every 3 mo	Standard care, seen every 3 mo	Standard care
Treatment protocol for tight control group	Start with sulfasalazine monotherapy Gradually step up to combination DMARD therapy No biologic DMARDs	Start with methotrexate monotherapy Gradually step up with possibility of starting biologic DMARD (adalimumab)	Start with NSAID monotherapy Switch to biologic (TNFi) after 12–16 wk
Primary outcome	Mean decrease in DAS	Proportion with ACR20 response	ASAS HI, comparing follow-up to baseline
Secondary outcomes	EULAR remission ACR20, ACR50, and ACR50 responses Pain score by VAS Physician global assessment Health-related quality of life by HAQ and SF-12 Radiographic progression by van der Heijde-Sharp score Resource utilization analysis	ACR50 and ACR70 responses PASI75 response mNAPSI score BASDAI score Tender joint count, swollen joint count Leeds Dactylitis Index Maastricht Enthesitis Index, Leeds Enthesitis Index Pain score by VAS BASFI score Health-related quality of life by HAQ, PsAQoL, EQ-5D Radiographic progression by van der Heijde-Sharp score Cost-effectiveness analysis	ASDAS major improvement Clinically important improvement in BASDAI50 Change in ASDAS and BASDAI Change in NSAID score Health-related quality of life by WPAI, EQ-5D Resource utilization analysis

Abbreviations: EQ-5D, EuroQoL quality of life instrument; HAQ, health assessment questionnaire; mNAPSI, modified Nail Psoriasis Severity Index; PsAQoL, psoriatic arthritis quality of life; PASI75, psoriasis area severity index with improvement of 75% or greater; SF-12, Short Form 12; WPAI, Work Productivity and Activity Impairment.

count, and patient global assessment of disease activity. The intensive therapy arm followed a protocol in which patients started on sulfasalazine monotherapy and were gradually stepped up on combination disease-modifying antirheumatic drug (DMARD) therapy. Biologics were not used in this trial. The primary outcome of mean decrease in the DAS was significantly higher in the intensive therapy group versus the comparator at 18 months in an intent-to-treat analysis. Secondary outcome measures also were improved with intensive therapy, including health-related quality of life, disability, erosions, and radiographic progression. Adherence was high in this trial. Costs were lower in the intensive therapy group, although this did not reach statistical significance and did not assess subjects' productivity loss or time off work for visits. Although multiple RCTs have demonstrated the strength of a treat-to-target strategy in RA, subsequent studies show that the adoption of this strategy has lagged behind in multiple countries and settings.[78] Barriers include patient and provider adherence, limited access to care, and limited access to biologic medications.

The TICOPA study was also conducted in the United Kingdom, and included PsA patients with disease duration of less than 24 months.[31] Subjects were randomized to a tight control group, which was assessed monthly for MDA criteria, compared with a group receiving standard care assessed every 3 months. The tight control protocol started with methotrexate monotherapy, and, in contrast to TICORA, this did include the possibility of switching to TNFi. The primary finding was that tight control was associated with approximately twice the odds of American College of Rheumatology (ACR) 20 response (odds ratio [OR] 1.91; 95% CI, 1.03–3.55) compared with the standard care. Secondary outcomes, including the more stringent ACR50 and ACR70 response criteria, other measures of disease activity and function, and measures of health-related quality of life, also were significantly different favoring the tight control group. Radiographic progression was similar, however, at follow-up between the 2 groups, likely due to early disease in the study population, with low radiographic damage scores at baseline. Serious adverse events were more common in the tight control group. A cost-effectiveness analysis found that costs of the tight control strategy exceeded the threshold typically allowable by UK guidelines. Ultimately, the use of the treat-to-target strategy from TICOPA received only a conditionally recommendation in ACR treatment guidelines[79] and there are few data on adoption of this strategy in clinical practice.

There have been 2 treat-to-target trials of axSpA. STRIKE (NCT02897115) was a German RCT of axSpA patients meeting the ASAS criteria with symptom duration less than 5 years, who were randomized to treat-to-target versus standard of care. In the treat-to-target arm, they were assessed monthly and the protocol involved starting with an NSAID and escalating to adalimumab. The primary outcome was ASDAS inactive disease at 32 weeks. This trial was unfortunately terminated due to slow recruitment.

TICOSPA (NCT03043846) is a European randomized cluster trial of axSpA patients, comparing tight control with monthly assessments to usual care. The primary outcome is change in the ASAS HI over 1 year. Secondary outcome measures include ASDAS, BASDAI, quality of life, and resource utilization. Enrollment began in 2016 and results are expected in 2020.

TREAT TO TARGET IN SPONDYLOARTHRITIS MANAGEMENT GUIDELINES

In 2017, an international task force published revised recommendations regarding the use of treat to target in SpA .[12] Several recommendations were based on low-level evidence and expert opinion, including the primary recommendation that the target of

SpA management should be clinical remission/inactive disease, including the musculoskeletal disease and EAMs. LDA/MDA was considered allowable as an alternative target of treatment. The recommendations also encouraged consideration of comorbidities, patient factors and drug-related risks, and the results of laboratory or imaging tests in management decisions.

Updated axial SpA treatment guidelines were published by the ACR in collaboration with the Spondylitis Association of America, the Spondyloarthritis Research and Treatment Network in 2019.[80] These updated guidelines did not change the earlier (2015) recommendation to use a validated AS disease activity measure at a regular interval.[81] The 2019 updated guidelines, however, conditionally recommended against use of a treat-to-target strategy in axSpA using a target of ASDAS less than 1.3. The panel noted that a treat-to-target approach in axSpA was supported indirectly by the association of lower disease activity with lesser radiographic progression but lacked direct evidence. The panel cited the costs of a treat-to-target strategy, including the burden on patients and clinicians, as 1 cause for concern.

The most recent PsA treatment guidelines from ACR and the National Psoriasis Foundation (NPF) conditionally recommend use of a treat-to-target strategy for patients with active PsA.[79] The recommendation provided for clinicians to consider not using a treat-to-target strategy among patients for whom a greater burden of adverse events, higher treatment costs, or greater medication burden with tighter control would be a concern. The ACR/NPF guideline development process included a patient panel meeting, during which patients expressed concern for the potential costs of treat to target, including financial (eg, additional copayments) and productivity loss (eg, travel and appointment time).

Although not reviewed by the ACR/NPF panel, patient concerns about the burden of a treat-to-target strategy in PsA were confirmed by a cost-effectiveness analysis by O'Dwyer and colleagues.[82] This study of the PsA treat-to-target strategy from TICOPA from the perspective of the UK National Health System found that the costs of tight control relative to standard care were likely to exceed the threshold allowable by the NHS. The analysis did not incorporate indirect costs to patients, such as productivity loss; incorporating such costs likely would make tight control even less favorable due to its expense. Study investigators suggested that fewer rheumatologist visits would be one strategy to mitigate the costs of tight control.

To date, cost-effectiveness analyses of treat-to-target strategies in axSpA have not been possible, owing to the lack of primary data on the efficacy of such strategies. These remains an unmet need in axSpA.

FUTURE DIRECTIONS AND RESEARCH AGENDA

The goals of a treat-to-target strategy in axSpA require further consideration and evaluation. Existing axial SpA disease activity measures may be used within a treat-to-target framework, but data supporting their use are limited. The inclusion of clinically important disease features, beyond patient-reported outcomes and laboratory measures of inflammation, also should be considered in a treat-to-target approach. This includes discussion of whether imaging evidence of inflammation as well as disease activity in EAMs should be included as targets.

AxSpA researchers should continue to evaluate whether current therapeutic tools are sufficient to reach these targets. As the results of TICOSPA are awaited, which will provide data on whether or not a treat-to-target strategy is superior to standard of care in the management of axSpA, the following questions must be considered:

Is 1 protocol of therapy superior to another? How frequently should disease activity be assessed, and with which measures? If disease is active in 1 domain but not another, how should therapy be adjusted? and Can the costs of tight control and burden to patients be minimized? The most compelling treat-to-target strategies should be assessed in both observational data and with future treat-to-target strategy trials. The challenges to implementing an effective treat-to-target strategy and how to overcome barriers to optimize outcomes in axSpA additionally must be considered.

DISCLOSURE

Dr. J.W. Liew: National Institutes of Health (NIH) T32AR007108. Dr.M. Dubreuil: NIH AR069127 and the Spondylitis Association of America (Bruckel Early Career Investigator Award).

REFERENCES

1. Whelton P, Carey R, Aronow W, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. J Am Coll Cardiol 2018;71:e127–248.
2. Standards of medical care in diabetes 2019. Diabetes Care 2019;42(Supplement 1):S1–2.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;73:e285–350.
4. The ALLHAT Officers, Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. JAMA 2002;288:2981–97.
5. Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233–44.
6. Ridker P, Danielson E, Fonseca F, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reative protein. N Engl J Med 2008;359:1543–54.
7. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46.
8. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.
9. Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364:263–9.
10. Breedveld FC, Han C, Bala M, et al. Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:52–5.
11. Smolen JS, Braun J, Dougados M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: Recommendations of an international task force. Ann Rheum Dis 2014;73:6–16.

12. Smolen J, Schols M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018;77:3–17.
13. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): A UK multicentre, open-label, randomised controlled trial. Lancet 2015;386:2489–98.
14. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
15. Landewé R, Dougados M, Mielants H, et al. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. Ann Rheum Dis 2009;68:863–7.
16. Machado P, van der Heijde D. How to measure disease activity in axial spondyloarthritis? Curr Opin Rheumatol 2011;23:339–45.
17. Spoorenberg A, van Tubergen A, Landewé R, et al. Measuring disease activity in ankylosing spondylitis: Patient and physician have different perspectives. Rheumatology 2005;44:789–95.
18. Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.
19. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–8.
20. Pedersen SJ, Sørensen IJ, Hermann KGA, et al. Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS) and clinical and MRI measures of disease activity in a 1-year follow-up study of patients with axial spondyloarthritis treated with tumour necrosis factor α inhibitors. Ann Rheum Dis 2010;69:1065–71.
21. Anderson JJ, Baron G, van der Heijde D, et al. Ankylosing Spondylitis Assessment Group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876–86.
22. Kiltz U, van der Heijde D, Boonen A, et al. The ASAS health index (ASAS HI) - A new tool to assess the health status of patients with spondyloarthritis. Clin Exp Rheumatol 2014;32:S105–8.
23. Kiltz U, van der Heijde D, Boonen A, et al. Measurement properties of the ASAS Health Index: Results of a global study in patients with axial and peripheral spondyloarthritis. Ann Rheum Dis 2018;77:1311–7.
24. Baraliakos X, Berenbaum F, Favalli E, et al. Challenges and advances in targeting remission in axial spondyloarthritis. J Rheumatol 2018;45:153–7.
25. Wendling D, Prati C. Remission in axial spondyloarthritis: the ultimate treatment goal? Joint Bone Spine 2016;83:117–9.
26. Sieper J. How to define remission in ankylosing spondylitis? Ann Rheum Dis 2012;71(Suppl 2):i93–5.
27. Kirwan J, Heiberg T, Hewlett S, et al. Outcomes from the Patient Perspective Workshop at OMERACT 6. J Rheumatol 2003;30:868–72.
28. Saag KG. OMERACT 6 brings new perspectives to rheumatology measurement research. J Rheumatol 2003;30:639–41.
29. Wells GA, Boers M, Shea B, et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. J Rheumatol 2005;32:2016–24.

30. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48–53.
31. Coates LC, Helliwell PS. Treat to target in psoriatic arthritis—evidence, target, research agenda. Curr Rheumatol Rep 2015;17:15–20.
32. Ramiro S, Sepriano A, De Lisboa UN, et al. Spinal radiographic progression in early axial spondyloarthritis: Five-year results from the DESIR cohort. Arthritis Care Res (Hoboken) 2018. https://doi.org/10.1002/acr.23796.
33. Ramiro S, Stolwijk C, Van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: A 12 year prospective follow-up of the OASIS study. Ann Rheum Dis 2015;74:52–9.
34. Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012;64:1388–98.
35. Maas F, Arends S, Wink FR, et al. Ankylosing spondylitis patients at risk of poor radiographic outcome show diminishing spinal radiographic progression during long-term treatment with TNF-α inhibitors. PLoS One 2017;12:1–12.
36. van der Heijde D, Landewé R, Baraliakos X, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063–70.
37. van der Heijde D, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009;11:1–8.
38. van der Heijde D, Breban M, Halter D, et al. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. Rheumatology 2015;54:1210–9.
39. Braun J, Baraliakos X, Hermann KGA, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: Results through 4 years of the GO-RAISE trial. Ann Rheum Dis 2014;73:1107–13.
40. van der Heijde D, Baraliakos X, Hermann KGA, et al. Limited radiographic progression and sustained reductions in MRI inflammation in patients with axial spondyloarthritis: 4-year imaging outcomes from the RAPID-axSpA phase III randomised trial. Ann Rheum Dis 2018;77:699–705.
41. Braun J, Baraliakos X, Deodhar A, et al. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4-year results from the MEASURE 1 study. Rheumatology 2018;58(5):859–68.
42. Maas F, Arends S, Brouwer E, et al. Reduction in spinal radiographic progression in ankylosing spondylitis patients receiving prolonged treatment with tumor necrosis factor inhibitors. Arthritis Care Res (Hoboken) 2017;69:1011–9.
43. Molnar C, Scherer A, Baraliakos X, et al. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss Clinical Quality Management cohort. Ann Rheum Dis 2018;77:63–9.
44. Mease P, van der Heijde D, Karki C, et al. Tumor necrosis factor inhibition discontinuation in patients with ankylosing spondylitis: an observational study from the US-based Corrona Registry. Rheumatol Ther 2018;5:537–50.
45. Wanders A, van der Heijde D, Landewé R, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005;52:1756–65.

46. Sieper J, Listing J, Poddubnyy D, et al. Effect of continuous versus on-demand treatment of ankylosing spondylitis with diclofenac over 2 years on radiographic progression of the spine: Results from a randomised multicentre trial (ENRADAS). Ann Rheum Dis 2016;75:1438–43.
47. Haroon N, Inman RD, Learch TJ, et al. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645–54.
48. Davis JC, van der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis. Arthritis Rheum 2003;48:3230–6.
49. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582–91.
50. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: Results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013;72:815–22.
51. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39–47.
52. Inman RD, Davis JC, Van Der Heijde D, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: Results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58:3402–12.
53. Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015;67:2702–12.
54. Maksymowych WP, Dougados M, van der Heijde D, et al. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. Ann Rheum Dis 2016;75:1328–35.
55. Baeten D, Sieper J, Braun J, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534–48.
56. Wanders A, Landewé R, Dougados M, et al. Association between radiographic damage of the spine and spinal mobility for individual patients with ankylosing spondylitis: Can assessment of spinal mobility be a proxy for radiographic evaluation? Ann Rheum Dis 2005;64:988–94.
57. Machado P, Landewé R, Braun J, et al. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 2010;69:1465–70.
58. Poddubnyy D, Fedorova A, Listing J, et al. Physical function and spinal mobility remain stable despite radiographic spinal progression in patients with ankylosing spondylitis treated with TNF-α inhibitors for up to 10 years. J Rheumatol 2016;43:2142–8.
59. Maksymowych WP, Morency N, Conner-Spady B, et al. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: Evidence for a window of opportunity in disease modification. Ann Rheum Dis 2013;72:23–8.
60. van der Heijde D, Machado P, Braun J, et al. MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71:369–73.
61. Baraliakos X, Heldmann F, Callhoff J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with

anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819–25.
62. Machado PM, Baraliakos X, van der Heijde D, et al. MRI vertebral corner inflammation followed by fat deposition is the strongest contributor to the development of new bone at the same vertebral corner: a multilevel longitudinal analysis in patients with ankylosing spondylitis. Ann Rheum Dis 2016;75:1486–93.
63. Maksymowych WP, Wichuk S, Chiowchanwisawakit P, et al. Fat metaplasia on MRI of the sacroiliac joints increases the propensity for disease progression in the spine of patients with spondyloarthritis. RMD Open 2017;3:23.
64. Machado P, Landewé RBM, Braun J, et al. MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor. Ann Rheum Dis 2012;71:2002–5.
65. Navarro-Compán V, Ramiro S, Landewé R, et al. Disease activity is longitudinally related to sacroiliac inflammation on MRI in male patients with axial spondyloarthritis:2-years of the DESIR cohort. Ann Rheum Dis 2016;75:874–8.
66. Haavardsholm EA, Aga AB, Olsen IC, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ 2016; 354:i4205.
67. Dale J, Stirling A, Zhang R, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Ann Rheum Dis 2016;75:1043–50.
68. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, et al. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: A systematic review and meta-analysis. Ann Rheum Dis 2015;74:65–73.
69. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70:1921–5.
70. Haroon NN, Paterson JM, Li P, et al. Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. Ann Intern Med 2015;163:409–16.
71. Mathieu S, Soubrier M. Cardiovascular events in ankylosing spondylitis: a 2018 meta-analysis. Ann Rheum Dis 2019;78:e57.
72. Dubreuil M, Louie-Gao Q, Peloquin CE, et al. Risk of myocardial infarction with use of selected non-steroidal anti-inflammatory drugs in patients with spondyloarthritis and osteoarthritis. Ann Rheum Dis 2018;77:1137–42.
73. Lee J, Sinnathurai P, Buchbinder R, et al. Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. Arthritis Res Ther 2018;20:171.
74. Tsai WC, Ou TT, Yen JH, et al. Long-term frequent use of non-steroidal anti-inflammatory drugs might protect patients with ankylosing spondylitis from cardiovascular diseases: a nationwide case-control study. PLoS One 2015;10:1–13.
75. Kristensen LE, Jakobsen AK, Askling J, et al. Safety of etoricoxib, celecoxib, and nonselective nonsteroidal antiinflammatory drugs in ankylosing spondylitis and other spondyloarthritis patients: a swedish national population-based cohort study. Arthritis Care Res 2015;67:1137–49.
76. Ramírez J, Nieto-González JC, Curbelo Rodríguez R, et al. Prevalence and risk factors for osteoporosis and fractures in axial spondyloarthritis: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;48:44–52.
77. Ashany D, Stein EM, Goto R, et al. The effect of TNF inhibition on bone density and fracture risk and of IL17 inhibition on radiographic progression and bone

density in patients with axial spondyloarthritis: A systematic literature review. Curr Rheumatol Rep 2019;21. https://doi.org/10.1007/s11926-019-0818-9.
78. van Vollenhoven R. Treat-to-target in rheumatoid arthritis — are we there yet? Nat Rev Rheumatol 2019;15:180–6.
79. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Rheumatol 2019;71:5–32.
80. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019; 71(10):1–15.
81. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondylitis. Arthritis Rheumatol 2016;68:282–98.
82. O'Dwyer JL, Meads DM, Hulme CT, et al. Cost-effectiveness of tight control of inflammation in early psoriatic arthritis: economic analysis of a multicenter randomized controlled trial. Arthritis Care Res 2018;70:462–8.