Current Rheumatology Reports (2021) 23: 36
https://doi.org/10.1007/s11926-021-01003-z

SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

Value-Based Healthcare in Rheumatology: Axial Spondyloarthritis and Beyond

David F. L. Liew[1,2,3] · Jonathan Dau[4] · Philip C. Robinson[5,6]

Accepted: 23 March 2021 / Published online: 28 April 2021

Abstract

Purpose of Review This review examines axial spondyloarthritis (axSpA) and the wider field of rheumatology through a value-based healthcare (VBHC) lens. VBHC is focused on ensuring patients receive high quality care to improve outcomes and reduce unnecessary costs.

Recent Findings There are many opportunities to apply the principles of VBHC in axSpA. These include the appropriate utilization of diagnostic investigations, such as HLA-B27 and magnetic resonance imaging, assessing outcomes meaningful to patients, and optimizing care pathways. Multidisciplinary care may improve value, and reduced specialist review and medication tapering may be appropriate.

Summary Increasing the value of the care we provide to patients can occur across domains and directly and indirectly improves patient outcomes. Taking the time to integrate principles of VBHC into our practice will allow us to justifiably gain and maintain access to diagnostic and therapeutic advances for the benefit of all our patients.

Keywords Value-based healthcare · Low benefit care · Health economics · Pharmacoeconomics · Treatment strategy · Diagnosis · Axial spondyloarthritis · Ankylosing spondylitis · Rheumatology

Introduction

New technologies in the healthcare arena are expanding our understanding of the biology of disease. These new insights often flow onto new diagnostics and therapeutics which are usually more resource intensive than their predecessors. A relentless focus on evidence-based therapy is also driving an unprecedented number of clinical trials. All of this progress is extremely admirable but neglects the fact that we have been practicing medicine for thousands of years and many old and even newer practices often lack a robust evidence base.

This review aims to explore the concept of value-based healthcare (VBHC) in rheumatology through the lens of axial spondyloarthritis (axSpA). Expenditure on healthcare is growing faster than gross domestic product (GDP) in most affluent countries [1]. The inevitable conclusion of this trend is healthcare expenditure consuming the entire GDP to the exclusion of education, defense, social security, and in fact everything else. Thus, at some point, we are obligated to consider the value we get from our health dollars, and how this can be maximized. We present a number of issues, examples, and unanswered questions in the hope of precipitating thought in this important area and focus by all those who either consume, fund, or provide healthcare.

Value-Based Healthcare

Value-based healthcare is focused on ensuring patients receive high quality care to improve outcomes and reduce

This article is part of the Topical Collection on *Spondyloarthritis*

✉ Philip C. Robinson
philip.robinson@uq.edu.au

1 Department of Medicine, University of Melbourne, Parkville, Victoria, Australia

2 Department of Rheumatology, Austin Health, Heidelberg, Victoria, Australia

3 Department of Clinical Pharmacology and Therapeutics, Austin Health, Heidelberg, Victoria, Australia

4 Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Boston, MA, USA

5 Faculty of Medicine, University of Queensland School of Clinical Medicine, Herston, Queensland 4006, Australia

6 Department of Rheumatology, Royal Brisbane & Women's Hospital, Metro North Hospital & Health Service, Bowen Bridge Road, Herston, Queensland 4006, Australia

unnecessary costs [2]. Low benefit care, also referred to as low value care, is the antithesis of value-based healthcare [3]. It provides little benefit to patients, is costly, and in some cases causes patient harm. In an environment of limited health resources and increasing demands, it is imperative that we do not perform activities with little supporting evidence or evidence of harm.

Unwarranted variation in practice is a key way to identify variation in the value of care being provided. This is variation not explained by patient preference or disease characteristics [4]. It is also worthwhile noting that this does not only apply to over-provisions of services; under provisioning of services, for example, in the realm of cancer screening, can lead to patient harm. Clinical practice guidelines aim to standardize care around evidence, and when they are followed, the value of care can be improved [5].

Diagnosis and Over-Diagnosis

One of the challenges relevant to VBHC in axSpA is non-radiographic axial spondyloarthritis (nr-axSpA). There is a divergence of opinion on the requirements for classification for axSpA in the axSpA academic community [6••, 7]. Diseases which lack an objective basis for diagnosis will have to reach different thresholds for individual practitioners to assign a diagnosis. This then leads to significant variation in the diagnoses being assigned to patients across different practitioners. Part of the nidus of the issue stems from the limitations of physician diagnosis as gold standard in classification studies which is affected by circularity [8]. This is a problem not easily addressed until there are highly specific and objective disease features. Genetics may well have a role to play, as may biomarkers and other tools such as microbiome analysis [9–11].

Screening Outside of Secondary Care

Recognizing potential axSpA in the primary care setting and determining an effective referral strategy have been significant challenges for VBHC in axSpA. Diagnostic delay negatively impacts axSpA patients who are commonly younger, active, and working. Multiple diagnostic aids and tools have been developed including formal ASAS-endorsed criteria for referral to be seen by a rheumatologist [12]. Other examples include the Spondyloarthritis Diagnosis and Evaluation (SPADE) tool and the Dublin Uveitis Evaluation Tool (DUET) [13, 14]. Most referral strategies rely on these parameters: the presence of inflammatory back pain (IBP), HLA-B27 positivity, sacroiliitis on imaging, and favorable response to NSAIDs. European (RADAR and MASTER RCT) and US (ProSpA) studies have found that the inclusion of some combination (whether singular or two-criteria) strategy identifies patients with axSpA in around 40 to 50% of cases [15–17]. The combination of IBP and sacroiliitis or IBP and HLA-B27 had the highest sensitivity and specificity for axSpA [16].

Though numerous referral strategies have been trialled, there continues to be issues with delayed diagnosis and misdiagnosis. A 2019 study among US healthcare providers found that the majority of providers failed to recognize IBP in chronic low back pain patients. Of these patients, 41% had seen another specialist before a rheumatologist [18]. In a UK study, over one-third of patients diagnosed with axSpA took 10 years to go from initial presentation to a formal diagnosis [19]. The reasons for this significant diagnostic delay are likely multifactorial but are likely due in part to the very high prevalence of degenerative back disease and non-specific back pain in the community.

One key strategy for boosting recognition and diagnosis of axSpA is encouraging other specialists who see the extra-articular manifestations of axSpA to refer these patients for rheumatology assessment. This includes our gastroenterology, ophthalmology, and dermatology colleagues. Screening anterior uveitis patients for HLA-B27 and back pain is a relatively quick and simple strategy for an ophthalmologist. The Spanish SENTINEL study determined that 70% of patients with anterior uveitis and HLA-B27 were diagnosed with axSpA [20]. Psoriasis may be a good screening tool for SpA, though this strategy may not be as effective as anterior uveitis + HLA-B27, since only 15% of patients with psoriasis had the diagnosis of axSpA in the US NHANES cohort [21].

HLA-B27

HLA-B27 is present in 8–10% of the general Caucasian population and a lower prevalence in other ethnicities such as Asian, African, and Middle Eastern populations [22, 23]. The prevalence of radiographic axSpA in those who are HLA-B27 positive is only 1–5%. HLA-B27 is present in 70–80% of patients with r-axSpA and 50–70% of those with nr-axSpA, depending on how each individual cohort was ascertained. HLA-B27 is therefore a sensitive but poorly specific marker of axSpA. This means it has the most value in a screening context. Poddubnyy and colleagues integrated HLA-B27 into a study of referral strategies for axSpA diagnosis and found that when HLA-B27 was used as a component of screening (one of the three: HLA-B27, inflammatory back pain, or sacroiliitis was required), 42% of patients referred from primary care for rheumatology assessment were diagnosed with axSpA [17]. With the discovery and potential widespread use of genotype-based HLA-B27 testing and in fact whole genome sequencing at birth, HLA-B27 status will potentially become an easily accessible datapoint which will inform the primary care physician when a patient presents with chronic low back pain [24, 25]. It will enable the higher post-test probability that chronic back pain (CBP) and a

positive HLA-B27 portend to facilitate an appropriate referral to secondary care for assessment. Nevertheless, inappropriate utilization, including repeat testing and use of testing in non-SpA contexts, occurs frequently and can confer a substantial cost burden [26]. Furthermore, the value of HLA-B27 remains uncertain in patients who already have a high pretest probability, and encouraging conscientious ordering among clinicians could improve value-based care delivery [27]. Ordering the test in a rheumatology assessment often has little value if the other symptoms suggest a definitive imaging assessment is required anyway.

Applying the axSpA Disease Concept to the Real World

There is little disagreement about the concept of axSpA: an inflammatory arthritis affecting the spine and sacroiliac joints [6••]. It was traditionally diagnosed with plain radiography of the pelvis, but magnetic resonance imaging has demonstrated the inflammation that can subsequently cause erosions.

There remains limited understanding of the long-term natural history of non-radiographic axSpA, and there are real challenges differentiating abnormal from normal changes on SIJ MRI [6••, 28]. This leads to challenges in patients with severe symptoms who lack objective signs of inflammation like raised C-reactive protein or a clearly abnormal SIJ MRI [29].

Using the 2009 ASAS axSpA criteria, a patient can be classified as having axSpA without objective evidence of spinal inflammation in the form of a positive MRI and/or raised CRP [30]. However, this is a source of disagreement in the field of axSpA [6••, 31, 32]. It has been demonstrated that treating nr-axSpA patients with anti-TNF who lack objective signs of inflammation does not necessarily lead to a clinical improvement [33]. C-reactive protein elevation, HLA-B27, and often SIJ MRI changes are non-specific which leads to challenging decisions about who and when to recommend resource intensive therapies such as biologics or JAK inhibitors. Does this mean these patients do not have axSpA, or is it that we have not found the right techniques to identify and treat their specific sub-pathology? These questions remain to be answered, but it is clear that not all patients with axSpA benefit from biologics or JAK inhibition [29]. This leads one to ask then what level of symptoms should one have to have to justify treatment with an advanced therapy? In a single payer system like the United Kingdom, Australia, or New Zealand, these limits are set centrally. In a private insurance market, this is left to individual clinicians to negotiate with insurance industry gatekeepers. There are clear advantages and disadvantages to each of these scenarios but it is likely that the non-standardized approach in private insurance interactions would lead to significant variation in the utilization of this therapy for a number of both clinical and non-clinical factors.

Therapies

Treatment of axSpA remains a substantial driver of cost burden in axSpA. While axSpA clinicians have been more vocal than other rheumatic diseases in assessing and valuing non-pharmacological therapy as a core part of standard care [34, 35, 36••], the constant evolution of pharmacotherapeutics in terms of both new agents and treatment strategies means that determining the path to best value care during treatment remains challenging. While it might remain easy to retain the status quo, are there better ways to deliver axSpA care which optimizes value, particularly in the face of evolution in healthcare treatment?

The Importance of Pharmacoeconomic Data in Defining Therapeutic Treatment Strategies

As effective therapies in rheumatology have facilitated a revolution in effective treatment and brought with it substantial gains in the function of patients, the importance of therapeutics has increased. Correspondingly, the actual and potential cost has escalated [37]. There may remain a temptation for clinicians, as an instinctive default, to use newer drugs earlier without consideration of the effectiveness of older therapies or non-pharmacological therapies. While long-term economic benefit can be derived from biologic therapy use and can even prove economically beneficial in times of fiscal stress, clinical response and overall cost burden are usually broadly linked. As such, blanket adoption of new therapies may not always represent a cost-effective intervention [38–41]. Balanced against this, drug costs remain the primary driver of the disease-related cost burden in axSpA patients, and funded access to therapies too often remains a substantial impediment to achieving best patient outcomes [42–46]. There consequently remains an imperative to structure therapeutic approaches around cost-effectiveness and to explore cost-effectiveness of therapies wherever possible.

Reflecting this, therapeutic approaches in axSpA have sought to incorporate considerations regarding drug costs into therapeutic algorithm recommendations, as they have in other rheumatic diseases [47, 48]. Given the effectiveness of NSAID therapy in axSpA and in the absence of alternative pharmacoeconomic justification, the restraint of only considering biologic therapies until after other therapies have failed in axSpA has been commendable compared to that sometimes proposed in other inflammatory arthropathies [34, 49–51]. It should be recognized that, in the absence of definitively proven long-term disease modification from early treatment or a treat-to-target strategy, and therefore the absence of any

associated pharmacoeconomic benefit projected into the future, pharmacoeconomic analysis is simpler for axSpA than for RA [52]. This may evolve in the future, particularly with the emergence of alternative therapeutics such as non-TNF inhibitor biologics and JAK inhibitors, changes in the disease characteristics of diagnosed patients, and the evolution in disease characterization [53–57]. Alternative treatment strategies may be justifiable with appropriate cost-effectiveness data, including the potential that early therapy may lead to higher drug-free remission rates [28], and this is particularly the case if biosimilars are able to yield substantive price reductions in TNF inhibitors in the near future as structural barriers to price reduction are overcome [58]. Better justification can facilitate better treatment, and the clinical evolution of therapeutic strategies in axSpA therefore necessitates a focus on pharmacoeconomic research [59–61].

The importance of pharmacoeconomic assessment has been clearly demonstrated in axSpA with the evolution of biologic therapy in nr-axSpA. While previously treatment of disease outside of ankylosing spondylitis might have been practically inconceivable, even though the presence of radiographic disease has not necessarily delineated the likelihood of response to NSAIDS, cost-effectiveness data derived in recent years was able to justify to payers the extension of indication of biologic agents to nr-axSpA [60, 62–64]. Usefully, such data have been incorporated in treatment guidelines to determine the cost-effective rationale of biologic therapies in patients' refractory to more than one NSAID, strengthening the likelihood of alignment of therapeutic guidelines with funded clinical practice. Further evolution will only be able to yield changes in real-world practice with further cost-effectiveness data.

Advanced Therapy Tapering

Reduction of any unnecessary therapy is a key mechanism to promote VBHC, and consequently, tapering and discontinuation of biologic therapy is a key consideration in VBHC in axSpA [65]. If patients can similarly maintain remission or low disease activity on lower doses of biologic therapy, then adverse events are reduced and precious resources are saved by discontinuing therapy. Pharmacokinetic variability means that a fixed dosing schedule is plausibly supratherapeutic in a substantial proportion of patients, supporting the justification to trial tapering [66]. Both industry trials and investigator initiated work have demonstrated that tapering of biologic agents in axSpA is able to retain good disease control while achieving reductions in medication use [67••, 68–70]. In contrast, studies examining biologic discontinuation have almost universally led to significant flare rates [71–76], suggesting that while patients may be able to optimize their dose, they do still benefit from ongoing therapy. In the same way as a pragmatic approach on the basis of available data would currently support cautious tapering dependent on the clinical scenario, future optimal treatment algorithms should incorporate a movement towards dose optimization, and further research on dose prediction would likely yield improved value delivery.

Maintaining Care

Outcomes

One important aspect of care planning in axSpA regards the goals used to design the therapeutic strategy. In the absence of being able to prove the impact of therapies on radiographic progression, the threshold to utility focuses on symptom control [50]. This then leads one to compare the relative value of outcome measures such as ASAS40 or ASDAS to measures addressing quality of life, but unfortunately, few outcome measures capture all aspects of disease, and there is a relative absence of definition regarding remission [77]. It is very pleasing to see the enthusiastic uptake of patient reported outcomes in industry trials, and the design and validation of outcome measures such as the ASAS Health Index (ASAS-HI) [78]. Whether they will take a more important place in outcome hierarchies in clinical trials is dependent on the emphasis of regulators, but a patient focus in guiding therapy escalation might be more likely to be impactful in routine clinical practice — a fundamental tenet of VBHC, and one that bears consideration in initiating therapeutic escalation [65]. Listening to our patients about the things that matter to them, particularly regarding domains not well addressed by our current therapies (such as fatigue), is key to further lifting the health status and functional ability of our patients, and consequently the value of the care we deliver to them.

Service Delivery: Who and How Often

The accessibility and cost burden of rheumatology specialist care remains a challenge to rheumatic disease patients in general, particularly in the context of a rheumatology workforce shortage in many regions. Researchers within axSpA have actively embraced sustainable healthcare model improvements which simultaneously not only improve the quality of care to patients but also reduce this cost burden to the broader health system.

One challenge remains the optimal intensity of specialist involvement. While the introduction of "treat-to-target" has led to marked improvements in patient disability and the cost of care compared to a "pyramid approach" of slow intensification, it remains uncertain as to whether the modern status quo in specialist follow-up represents clinical and financial value. The recent TICOSPA study found no significant improvement in ASAS-HI with an increase in rheumatologist

review from 12-weekly to 4-weekly, despite improvements in corresponding biological measures. Insights such as this either mean our outcome measures need improvement or, in fact, more intensive care does not deliver value for our patients [79].

This quandary about intensity of care also extends to the challenges of diagnosis, where system-wide speed and accuracy remain elusive [19, 80]. Traditional approaches remain rooted in ready accessibility of specialist rheumatologists to make a definitive clinical diagnosis. However, the evolution of systems which can initiate interim care consistent with a provisional diagnosis while more efficiently utilizing rheumatologists' time specifically at critical junctures of the diagnostic process may not only lead to overall healthcare savings but also improved early access for patients [81]. Overcoming challenges in recognition and referral at both primary and secondary care level might not only lead to better patient outcomes but also reduced healthcare practitioner involvement at each stage [82]. Targeted education may be useful given poor recognition, although in practice, it is very difficult to change primary care practitioner care strategies substantially without introducing incentives [12, 83–85]. Improved screening tools, which have long been proposed but are largely underused, can provide crucial base information to non-specialists and, by virtue of directing better understanding, reduce clinician time and cost necessary at each stage to reach the point of accurate diagnosis [19, 80, 86, 87]. Broader adoption of electronic aids, such as the SPADE tool (http://www.spadetool.co.uk/), may be a practical bridge to achieving this but their implementation is often challenging [82].

Similarly, multidisciplinary cooperation can yield benefits in speed and cost of care, while reducing dependence on specialist care and the costs associated with it, particularly given the multiple diagnoses clustered around superficially similar presentations to axSpA. Multidisciplinary clinics, engaging orthopedic surgeons and nurse practitioners, have been shown to improve the speed of diagnosis [88]. Engagement across disciplines may also be necessary to educate other healthcare workers about diagnosing axSpA; by nature of its presentation, axSpA may be initially seen by a variety of different clinicians with limited diagnostic capacity, including general physiotherapists, chiropractors, and osteopaths [89, 90]. This leads to diagnostic delays, and clinical waste in patients presenting to these clinicians would likely be reduced by better interdisciplinary communication [91]. Unfortunately, reimbursement structures often drive the design of clinical care pathways, and funding for multidisciplinary rheumatology care is not widespread.

Finally, given the nature of chronic specialized care necessary to maintain targeted therapies in axSpA, better value care may be derived from health services research in axSpA designed to determine the optimal frequency of review. Of note, on demand rather than scheduled review may deliver equivalent care and outcomes at reduced cost in rheumatoid arthritis, and the success of such an approach is equally plausible in axSpA [92, 93]. Although this needs further investigation, reimbursement via capitation rather than fee-for-service may assist rationalization of clinician involvement and instead encourage patient-directed measures in axSpA [94].

Research Agenda

The exciting developments in basic science and new modes of action necessitate appropriate promotion and use of our current therapies [65, 95]. How can this be done better? First, genuine improvements in prediction of the disease course could provide improved value care. It is clear that there is enormous potential in a personalized medicine approach, using a patient's individual characteristics like their genome or microbiome to direct therapy choice. If judiciously deployed and accompanied by justifying health economics research, such innovations could both improve outcomes and save precious health resources, and the first studies of this kind are now being published [96••]. Prioritising patient reported outcomes has a huge potential to improve the value of care, and further work in this area is vital. Secondly, health services research should be considered integral to any potential practice change: further work into understanding the impacts of frequency and access to care will allow us to safely structure care pathways while conserving resources. Thirdly, we need to do more with less: repurposing and optimizing existing tools to address new problems are critical, both in terms of extensions of indications, such as nr-axSpA, and also in applying axSpA solutions to broader health challenges [97–99]. Finally, the long diagnostic delay represents both a challenge and an opportunity to patients and axSpA clinicians. Imaging needs to also be a continuing focus as it is so critical to diagnosis; the importance of MRI changes and the value of new techniques is still being clarified [100, 101, 102••]. Reduced diagnostic delay confers the potential to improve outcomes for a longer period of time, and like most aspects of VBHC in axSpA, the potential to synchronously improve individual functional and economic outcomes for our patients.

Conclusions

While there is inevitably a focus on new developments, the only way to be able to afford new developments is to do what we already do in a better and more efficient way. For the doctor to truly derive the best care for their patients, they must consider not just the patient in front of them but also the sustainability of the system that supports all patients, the allocation of resources, and the cost-effective utilization of

investigations, therapies, and human resources. In this way, all clinicians need to have a working understanding of health economics and pharmacoeconomics for a simple reason: to ignore this consideration is to invite an unworkable or untenable situation being forced upon them. It behooves us all to start conversations about how we can be using our current knowledge to optimize care and build our future knowledge in rheumatology to ensure we can treat not only the patient we have today but also the one who arrives tomorrow, next month, and next year.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest PCR reports personal fees from AbbVie, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Roche, and UCB. Research grant funding from UCB, Janssen, and Novartis; nonfinancial support from Pfizer and BristolMyers Squibb. DL and JD declare no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Watson R. Health spending rising faster than GDP in most rich countries. BMJ. 2006;333:60.
2. Gray M. Value based healthcare. BMJ. 2017;356:j437.
3. Elshaug AG, Watt AM, Mundy L, Willis CD. Over 150 potentially low-value health care practices: an Australian study. Med J Aust. AMPCo. 2012;197:556–60.
4. Wennberg JE. Unwarranted variations in healthcare delivery: implications for academic medical centres. BMJ. 2002;325:961–4.
5. Rutten GM, Degen S, Hendriks EJ, Braspenning JC, Harting J, Oostendorp RA. Adherence to clinical practice guidelines for low back pain in physical therapy: do patients benefit? Phys Ther. 2010;90:1111–22.
6. •• Robinson PC, van der Linden S, Khan MA, Taylor WJ. Axial spondyloarthritis: concept, construct, classification and implications for therapy. Nat Rev Rheumatol. 2021;17:109–18 **This paper discusses the issues with diagnosis and the challenges of using imaging for diagnosis.**
7. Robinson PC, Sengupta R, Siebert S. Non-radiographic axial spondyloarthritis (nr-axSpA): advances in classification, imaging and therapy. Rheumatol Ther. 2019;6:165–77.
8. Taylor WJ, Robinson PC. Classification criteria: peripheral spondyloarthropathy and psoriatic arthritis. Curr Rheumatol Rep. 2013;15:317.
9. Thomas GP, Willner D, Robinson PC, Cortes A, Duan R, Rudwaleit M, et al. Genetic diagnostic profiling in axial spondyloarthritis: a real world study. Clin Exp Rheumatol. 2017;35:229–33.
10. Costello M-E, Robinson PC, Benham H, Brown MA. The intestinal microbiome in human disease and how it relates to arthritis and spondyloarthritis. Best Pract Res Clin Rheumatol. 2015;29:202–12.
11. Costello M-E, Ciccia F, Willner D, Warrington N, Robinson PC, Gardiner B, et al. Brief report: intestinal dysbiosis in ankylosing spondylitis. Arthritis Rheumatol. 2015;67:686–91.
12. Poddubnyy D, van Tubergen A, Landewé R, Sieper J, van der Heijde D. Assessment of SpondyloArthritis international Society (ASAS). Development of an ASAS-endorsed recommendation for the early referral of patients with a suspicion of axial spondyloarthritis. Ann Rheum Dis. 2015;74:1483–7.
13. Haroon M, O'Rourke M, Ramasamy P, Murphy CC, FitzGerald O. A novel evidence-based detection of undiagnosed spondyloarthritis in patients presenting with acute anterior uveitis: the DUET (Dublin Uveitis Evaluation Tool). Ann Rheum Dis. 2015;74:1990–5.
14. Habibi S, Doshi S, Sengupta R. THU0413 utility of the spade tool to identify axial spondyloarthritis in patients with chronic backpain. 2016. ard.bmj.com. Available from: https://ard.bmj.com/content/75/Suppl_2/338.2.abstract.
15. Poddubnyy D, Sieper J. Treatment of axial spondyloarthritis: what does the future hold? Curr Rheumatol Rep. 2020;22:47.
16. Sieper J, Srinivasan S, Zamani O, Mielants H, Choquette D, Pavelka K, et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. Ann Rheum Dis. 2013;72:1621–7.
17. Poddubnyy D, Vahldiek J, Spiller I, Buss B, Listing J, Rudwaleit M, et al. Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol. 2011;38:2452–60.
18. Magrey M, Yi E, Wolin D, Price M, Chirila C, Davenport E, et al. Recognition of inflammatory back pain by US healthcare providers and barriers to specialist referral. Arthritis Rheumatol. Wiley 111 River St, Hoboken 07030-5774, NJ USA; 2019.
19. Derakhshan MH, Pathak H, Cook D, Dickinson S, Siebert S, Gaffney K, et al. Services for spondyloarthritis: a survey of patients and rheumatologists. Rheumatology. 2018;57:987–96.
20. Juanola X, Loza Santamaría E, Cordero-Coma M, SENTINEL Working Group. Description and prevalence of spondyloarthritis in patients with anterior uveitis: the SENTINEL interdisciplinary collaborative project. Ophthalmology. 2016;123:1632–6.
21. Thom N, Ritchlin CT, Zhang X, Reveille J, Weisman MH. Prevalence of chronic axial pain, inflammatory back pain, and spondyloarthritis in diagnosed psoriasis. Arthritis Care Res. 2015;67:829–35.
22. Robinson PC, Brown MA. The genetics of ankylosing spondylitis and axial spondyloarthritis. Rheum Dis Clin North Am. 2012;38:539–53.
23. Robinson PC, Brown MA. Genetics of ankylosing spondylitis. Mol Immunol. 2014;57:2–11.
24. International Genetics of Ankylosing Spondylitis Consortium (IGAS), Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. Nat Genet. 2013;45:730–8.
25. Huang X-F, Li Z, De Guzman E, Robinson P, Gensler L, Ward MM, et al. Genomewide association study of acute anterior uveitis identifies new susceptibility loci. Invest Ophthalmol Vis Sci. 2020;61:3.
26. Nolan MW, Brown MM, Gertner E. Choosing unwisely: HLA-B27 testing and adherence to choosing wisely practices in a large integrated academic healthcare system. Arthritis Rheumatol. Wiley 111 River St, Hoboken 07030-5774, NJ USA; 2017.

27. Chow SL, Carter Thorne J, Bell MJ, Ferrari R, Bagheri Z, Boyd T, et al. Choosing wisely: the Canadian Rheumatology Association's list of 5 items physicians and patients should question. J Rheumatol. 2015;42:682–9.
28. Robinson PC, Brown MA. The window of opportunity: a relevant concept for axial spondyloarthritis. Arthritis Res Ther. 2014;16:109.
29. Brown MA, Bird PA, Robinson PC, Mease PJ, van den Bosch F, Surian C, et al. Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study. Ann Rheum Dis. 2018;77:1091–3.
30. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777–83.
31. van der Linden S, Akkoc N, Brown MA, Robinson PC, Khan MA. The ASAS criteria for axial spondyloarthritis: strengths, weaknesses, and proposals for a way forward. Curr Rheumatol Rep. 2015;17:62.
32. Robinson PC, Wordsworth BP, Reveille JD, Brown MA. Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. Ann Rheum Dis. 2013;72:162–4.
33. Rusman T, van der Weijden MAC, Nurmohamed MT, Landewé RBM, de Winter JJH, Boden BJH, et al. Is treatment in patients suspected of non-radiographic axial spondyloarthritis effective? Six months results of a placebo-controlled trial. Arthritis Rheumatol. 2020; Available from: https://doi.org/10.1002/art.41607.
34. Regel A, Sepriano A, Baraliakos X, van der Heijde D, Braun J, Landewé R, et al. Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open. 2017;e000397.
35. Millner JR, Barron JS, Beinke KM, Butterworth RH, Chasle BE, Dutton LJ, et al. Exercise for ankylosing spondylitis: an evidence-based consensus statement. Semin Arthritis Rheum. 2016;45:411–27.
36.•• Sveaas SH, Bilberg A, Berg IJ, Provan SA, Rollefstad S, Semb AG, et al. High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of 100 patients. Br J Sports Med. 2020;54:292–7 **This paper demonstrates the value of non-pharmacological therapy in axSpA.**
37. Hopkins AM, Proudman SM, Vitry AI, Sorich MJ, Cleland LG, Wiese MD. Ten years of publicly funded biological disease-modifying antirheumatic drugs in Australia. Med J Aust. 2016;204:64–8.
38. Tran-Duy A, Boonen A, van de Laar MAFJ, Franke AC, Severens JL. A discrete event modelling framework for simulation of long-term outcomes of sequential treatment strategies for ankylosing spondylitis. Ann Rheum Dis. 2011;70:2111–8.
39. Tsifetaki N, Migkos MP, Papagoras C, Voulgari PV, Athanasakis K, Drosos AA. Counting costs under severe financial constraints: a cost-of-illness analysis of spondyloarthropathies in a Tertiary Hospital in Greece. J Rheumatol. 2015;42:963–7.
40. Grabner M, Boytsov NN, Huang Q, Zhang X, Yan T, Curtis JR. Costs associated with failure to respond to treatment among patients with rheumatoid arthritis initiating TNFi therapy: a retrospective claims analysis. Arthritis Res Ther. 2017;19:92.
41. Scott DL. Developing new therapeutic approaches for rheumatoid arthritis: the continuing challenges of clinical assessments. F1000Res. 2016;5. Available from: https://doi.org/10.12688/f1000research.8812.1
42. Greenberg JD, Palmer JB, Li Y, Herrera V, Tsang Y, Liao M. Healthcare resource use and direct costs in patients with ankylosing spondylitis and psoriatic arthritis in a large US cohort. J Rheumatol. 2016;43:88–96.
43. Krüger K, von Hinüber U, Meier F, Tian H, Böhm K, Jugl SM, et al. Ankylosing spondylitis causes high burden to patients and the healthcare system: results from a German claims database analysis. Rheumatol Int. 2018;38:2121–31.
44. Walsh JA, Song X, Kim G, Park Y. Healthcare utilization and direct costs in patients with ankylosing spondylitis using a large US administrative claims database. Rheumatol Ther. 2018;5:463–74.
45. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis. 2014;73:198–206.
46. Yazdany J, Dudley RA, Chen R, Lin GA, Tseng C-W. Coverage for high-cost specialty drugs for rheumatoid arthritis in Medicare Part D. Arthritis Rheumatol. 2015;67:1474–80.
47. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, 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;71:1599–613.
48. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 Update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978–91.
49. Kroon FPB, van der Burg LRA, Ramiro S, Landewé RBM, Buchbinder R, Falzon L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database Syst Rev. 2015;CD010952.
50. Fragoulis GE, Siebert S. Treatment strategies in axial spondyloarthritis: what, when and how? Rheumatology. 2020;59:iv79–89.
51. Landewé RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. Ann Rheum Dis. 2018;77:1394–6.
52. Machado PM, Deodhar A. Treat-to-target in axial spondyloarthritis: gold standard or fools' gold? Curr Opin Rheumatol. 2019;31:344–8.
53. Goeree R, Chiva-Razavi S, Gunda P, Jain M, Jugl SM. Cost-effectiveness analysis of secukinumab in ankylosing spondylitis from the Canadian perspective. J Med Econ. 2019;22:45–52.
54. Emery P, Van Keep M, Beard S, Graham C, Miles L, Jugl SM, et al. Cost effectiveness of secukinumab for the treatment of active ankylosing spondylitis in the UK. Pharmacoeconomics. 2018;36:1015–27.
55. Lubrano E, Perrotta FM, Manara M, D'Angelo S, Addimanda O, Ramonda R, et al. The sex influence on response to tumor necrosis factor-α inhibitors and remission in axial spondyloarthritis. J Rheumatol. 2018;45:195–201.
56. Micheroli R, Hebeisen M, Wildi LM, Exer P, Tamborrini G, Bernhard J, et al. Impact of obesity on the response to tumor necrosis factor inhibitors in axial spondyloarthritis. Arthritis Res Ther. 2017;19:164.
57. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis. 2008;67:1276–81.
58. Moorkens E, Jonker-Exler C, Huys I, Declerck P, Simoens S, Vulto AG. Overcoming barriers to the market access of biosimilars in the European Union: the case of biosimilar monoclonal antibodies. Front Pharmacol. 2016;7:193.

59. Harvard S, Guh D, Bansback N, Richette P, Saraux A, Fautrel B, et al. Access criteria for anti-TNF agents in spondyloarthritis: influence on comparative 1-year cost-effectiveness estimates. Cost Eff Resour Alloc. 2017;15:20.
60. Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health Technol Assess. 2016;20: 1–334 v – vi.
61. Inman R, Sieper J. Oxford textbook of axial spondyloarthritis: Oxford University Press; 2016.
62. Baraliakos X, Kiltz U, Peters S, Appel H, Dybowski F, Igelmann M, et al. Efficiency of treatment with non-steroidal anti-inflammatory drugs according to current recommendations in patients with radiographic and non-radiographic axial spondyloarthritis. Rheumatology. 2017;56:95–102.
63. Borse RH, Kachroo S, Brown C, McCann E, Insinga RP. Cost-effectiveness analysis of golimumab in the treatment of non-radiographic axial spondyloarthritis in Scotland. Rheumatol Ther. 2018;5:57–73.
64. Sideris E, Soares M, Palmer S. The cost effectiveness of tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Value Health. 2016;A539. Available from: https://doi.org/10.1016/j.jval.2016.09.1116.
65. Landewé RBM. The unsustainable bubble of disease-modifying antirheumatic drugs in rheumatology. Lancet Rheumatol. 2021; Available from: https://www.sciencedirect.com/science/article/pii/S2665991321000138.
66. Ternant D, Mulleman D, Lauféron F, Vignault C, Ducourau E, Wendling D, et al. Influence of methotrexate on infliximab pharmacokinetics and pharmacodynamics in ankylosing spondylitis. Br J Clin Pharmacol. 2012;73:55–65.
67.•• Landewé R, van der Heijde D, Dougados M, Baraliakos X, Van den Bosch F, Gaffney K, et al. Induction of sustained clinical remission in early axial spondyloarthritis following certolizumab pegol treatment: 48-week outcomes from C-OPTIMISE. Rheumatol Ther. 2020;7:581–99 **This paper demonstrates the value of biologic tapering in the context of a controlled trial.**
68. Landewé RB, van der Heijde D, Dougados M, Baraliakos X, Van den Bosch FE, Gaffney K, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis. 2020;79:920–8.
69. Park JW, Kim H-A, Shin K, Park Y-B, Kim T-H, Song YW, et al. Effects of tapering tumor necrosis factor inhibitor on the achievement of inactive disease in patients with axial spondyloarthritis: a nationwide cohort study. Arthritis Res Ther. 2019;21:163.
70. Plasencia C, Kneepkens EL, Wolbink G, Krieckaert CLM, Turk S, Navarro-Compán V, et al. Comparing tapering strategy to standard dosing regimen of tumor necrosis factor inhibitors in patients with spondyloarthritis in low disease activity. J Rheumatol. 2015;42:1638–46.
71. Landewé R, Sieper J, Mease P, Inman RD, Lambert RG, Deodhar A, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet. Elsevier. 2018;392:134–44.
72. Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, Balsa A, Martín-Mola E, Seoane-Mato D, et al. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. Rheumatology. 2016;55:1188–94.
73. Brandt J, Khariouzov A, Listing J, Haibel H, Sörensen H, Grassnickel L, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum. 2003;48:1667–75.
74. Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther. 2005;7:R439–44.
75. Song I-H, Althoff CE, Haibel H, Hermann K-GA, Poddubnyy D, Listing J, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis. 2012;71:1212–5.
76. Haibel H, Heldmann F, Braun J, Listing J, Kupper H, Sieper J. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial spondyloarthritis who experience a flare. Arthritis Rheum. 2013;65:2211–3.
77. Marzo-Ortega H, Gaffney KM, Gaffney K. Defining the target: clinical aims in axial spondyloarthritis. Rheumatology. 2018;57: vi18–22.
78. Kiltz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis. 2015;74: 830–5.
79. Moltó A, López-Medina C, Van den Bosch F, Boonen A, Webers C, Dernis E, et al. THU0370 cluster-randomized pragmatic clinical trial evaluating the potential benefit of a tight-control and treat-to-target strategy in axial spondyloarthritis: the results of the TICOSPA trial. BMJ Publishing Group Ltd; 2020. Available from: https://ard.bmj.com/content/79/Suppl_1/413.1.abstract.
80. Poddubnyy D, Sieper J. Current unmet needs in spondyloarthritis. Curr Rheumatol Rep. 2019;21:43.
81. Sieper J. How to screen for axial spondyloarthritis in primary care? Curr Opin Rheumatol. 2012;24:359–62.
82. Barnett R, Ingram T, Sengupta R. Axial spondyloarthritis 10 years on: still looking for the lost tribe. Rheumatology. 2020;59:iv25–37.
83. van Onna M, Gorter S, Maiburg B, Waagenaar G, van Tubergen A. Education improves referral of patients suspected of having spondyloarthritis by general practitioners: a study with unannounced standardised patients in daily practice. RMD Open. 2015;1:e000152.
84. Jois RN, Macgregor AJ, Gaffney K. Recognition of inflammatory back pain and ankylosing spondylitis in primary care. Rheumatology. 2008;47:1364–6.
85. Sykes MP, Doll H, Sengupta R, Gaffney K. Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? Rheumatology. 2015;54:2283–4.
86. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol. 2012;8:262–8.
87. Sieper J, Rudwaleit M. Early referral recommendations for ankylosing spondylitis (including pre-radiographic and radiographic forms) in primary care. Ann Rheum Dis. 2005;64:659–63.
88. Li J, Xu Y, Chen Y, Ye C, Huang J, Qian L, et al. A multidisciplinary clinic approach to improve physician-related diagnostic delay for patients with axial spondyloarthritis: a retrospective study. J Int Med Res. 2019;47:2483–91.
89. Steen E, McCrum C, Cairns M. Physiotherapists' awareness, knowledge and confidence in screening and referral of suspected axial spondyloarthritis: a survey of UK clinical practice. Musculoskeletal Care. 2021; Available from: https://doi.org/10.1002/msc.1537.
90. Yong CY, Hamilton J, Benepal J, Griffiths K, Clark ZE, Rush A, et al. Awareness of axial spondyloarthritis among chiropractors and osteopaths: findings from a UK web-based survey. Rheumatol Adv Pract. 2019;3:rkz034.
91. McCrum C, Kenyon K, Cleaton J, Dudley T. An unrecognised masquerader: a retrospective review of people presenting to

musculoskeletal physiotherapy with undiagnosed spondyloarthritis. Physiotherapy. Elsevier. 2019;105:e102–3.
92. Hurst NP, Lambert CM, Forbes J, Lochhead A, Major K, Lock P. Does waiting matter? A randomized controlled trial of new non-urgent rheumatology out-patient referrals. Rheumatology. 2000;39:369–76.
93. Hewlett S, Kirwan J, Pollock J, Mitchell K, Hehir M, Blair PS, et al. Patient initiated outpatient follow up in rheumatoid arthritis: six year randomised controlled trial. BMJ. 2005;330:171.
94. Jia L, Meng Q, Scott A, Yuan B, Zhang L. Payment methods for healthcare providers working in outpatient healthcare settings. Cochrane Database Syst Rev. 2021;1:CD011865.
95. Scher JU, Schett G. Key opinion leaders — a critical perspective. Nat Rev Rheumatol. 2021;119–24. Available from: https://doi.org/10.1038/s41584-020-00539-1.
96.•• Humby F, Durez P, Buch MH, Lewis MJ, Rizvi H, Rivellese F, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. Lancet. 2021;397:305–17 **This is a seminal paper which describes a personalised approach to biologic selection.**
97. Robinson PC, Liew DFL, Liew JW, Monaco C, Richards D, Shivakumar S, et al. The potential for repurposing anti-TNF as a therapy for the treatment of COVID-19. Med (N Y). 2020;1:90–102.
98. Shivakumar S, Smibert OC, Trubiano JA, Frauman AG, Liew DF. Immunosuppression for COVID-19: repurposing medicines in a pandemic. Aust Prescr. 2020;43:106–7.
99. Robinson PC, Richards D, Tanner HL, Feldmann M. Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. The Lancet Rheumatology. Elsevier; 2020; Available from: https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30309-X/fulltext.
100. Bradbury LA, Hollis KA, Gautier B, Shankaranarayana S, Robinson PC, Saad N, et al. Diffusion-weighted imaging is a sensitive and specific magnetic resonance sequence in the diagnosis of ankylosing spondylitis. J Rheumatol. 2018;45:771–8.
101. Baraliakos X, Braun J. Opinion: perspectives on imaging in axial spondyloarthritis. Nat Rev Rheumatol. 2013;9:498–502.
102.•• Maksymowych WP. The role of imaging in the diagnosis and management of axial spondyloarthritis. Nat Rev Rheumatol. 2019;15:657–72 **This is an excellent comprehensive review of imaging in axSpA.**