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EDITORIAL

Unanswered questions in the management of axial spondyloarthritis: an opinion piece

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The major breakthrough in the treatment of ankylosing spondylitis (AS) came in 2003 with the approval of the first two TNF inhibitors (TNFi) [1]. Since then, three additional TNFi have been approved for the treatment of AS, but biologics with different mechanisms of action (e.g., anakinra, abatacept, tocilizumab) were found to be not efficacious in these patients [2]. In 2009, the Assessment of SpondyloArthritis International Society (ASAS) redefined the spectrum of axial inflammatory diseases by developing classification criteria for axial spondyloarthritis (axSpA), an umbrella term that includes AS and non-radiographic axSpA (nr-axSpA) [3]. Only a few trials since the reclassification have included subjects from the entire spectrum of axSpA or those with nr-axSpA [4–6].

Despite these advances, pharmaceutical interventions for axSpA are quite limited compared with other chronic inflammatory diseases such as rheumatoid arthritis (RA). Some major unresolved questions and possible challenges for future studies in the treatment of axSpA are shown in Table 1.

We use anti-inflammatory therapies, but are they symptom- or structure-modifying?

Although there are hardly any studies on the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) in nr-axSpA, these agents are recommended and routinely used as the first-line treatment for pain and stiffness in active, symptomatic axSpA [7]. The question of whether NSAIDs prevent osteoproliferation is still a matter of debate. The German Spondyloarthritis Inception Cohort (GESPIC) and a randomized NSAID trial showed that NSAIDs, when given in high dosages (vs. low dosage) or continuously (vs. on demand), led to a reduction in radiographic progression over 2 years in subjects with AS. This effect was most pronounced in those who presented with increased C-reactive protein (CRP) levels [8–10]. However, in the Prospective Study of Ankylosing Spondylitis (PSOAS) cohort, NSAIDs failed to show any inhibitory effect on radiographic progression in a multivariate analysis model [11]. This discrepancy in results is possibly due to a stronger and more robust TNFi effect blunting the NSAID effect on osteoproliferation in the PSOAS cohort (see below). High NSAID intake has also not been shown to have any significant effect on radiographic progression in nr-axSpA patients in the GESPIC cohort [8].

The efficacy of TNFi for clinical symptoms in patients who are not responding to NSAIDs is well established, although the effects of long-term TNFi on structure modification were shown only very recently. In 2013, two independent studies demonstrated a benefit from TNFi on radiographic progression when treatment was extended beyond 4 years. In a comparison of a TNFi trial with long-term follow-up vs. a historical cohort [12], and in a careful follow-up of a well-characterized subgroup in the PSOAS cohort [11], subjects on TNFi showed decreased rates of spinal radiographic progression compared to those treated with NSAIDs, but only after 4 years.

Osteoproliferation in axSpA occurs slowly; hence, "structure modification" studies need to be longer than 2 years' duration. Studies described above serve as a template for future investigations on osteoproliferation prevention. Long-term placebo-controlled prospective studies on any agent are unlikely to be done due to the economic (large number of subjects to be followed for several years) and ethical (placebo-administered controls) considerations. We also do not know

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Table 1 Unanswered questions in treatment of axial spondyloarthritis

Unanswered questions	Type of therapy	Hurdles in investigations	What is likely to be achieved	What is unlikely to be done or known
Does this therapy even work?	• DMARDs (MTX, LEF, combination regimens) • Biosimilars and new agents (inhibitors of IL-17A, JAK, and PDE4)	Sample size, funding, ethical issues in performing placebo-controlled DMARD trials	Trials of newer agents because of pharmaceutical companies' interests	Large placebo-controlled DMARD trial of adequate duration
What is the optimum dose?	• Physical therapy • Existing biologics • New biologics	Sample size, funding, controlling for concomitant therapy	Biologic dose trials because they are attractive from an economic standpoint	Comparative physical therapy trials or "dose of physical therapy" trials
Is this therapy "structure modifying" (prevents, slows, or stops osteoproliferation)?	• NSAIDs • Biologics • Biologics + NSAIDs • Bisphosphonates • New agents	Sample size, duration of trial, ethical issues with control arms, using historical control group, novel molecule discovery	• Indirect answer generated by following large cohorts of patients in registries • MRI, not X-ray, will be used in studies	Study with a placebo group followed for a long enough period to get direct evidence
Could combining the treatment with another class benefit the patient?	• NSAIDs + biologics or • DMARDs + biologics vs. individual agents	Sample size, funding	NSAIDs + biologics trial (interest in prevention of osteoproliferation is high)	Adequately sized prospective trial of DMARDs + biologics
What types of patients are appropriate for this therapy and what types are not? (predictors of response)	• Physical therapy • DMARDs • TNFi • Non-TNFi biologics	Funding issues for physical therapy and DMARD trials, better understanding of genetics of axSpA	Likelihood ratios of "response" to biologics based on genetics plus baseline clinical characteristics	• Physical therapy trials • DMARD trials • Definitive answers from baseline clinical characteristics alone
Will this therapy prevent long-term complications?	• Biologics (TNFi and others)	Funding for large national registries, or inception cohorts followed prospectively	Trends in complication rates compared to historical rates	"Cause-and-effect" relationship between changing complication rates and new therapies
Can this therapy be withdrawn after remission is reached?	• Biologics and novel agents	Discontinuation study design, ethical issues	Pharmaco-economics may force these studies	Long-term drug-free remission
What is the role of MRI in monitoring disease progression and response to treatment?	• Biologics • DMARDs • NSAIDs	Funding issues for serial MRIs	New imaging techniques for predicting response to treatment and identifying possible non-responders	–

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *DMARD* disease-modifying anti-rheumatic drug, *IL* interleukin, *JAK* Janus kinase, *LEF* leflunomide, *MRI* magnetic resonance imaging, *MTX* methotrexate, *NSAID* non-steroidal anti-inflammatory drug, *PDE* phosphodiesterase, *TNFi* tumor necrosis factor inhibitor

whether treatment with either NSAIDs or TNFi, if prescribed at an early disease stage, is able to prevent progression of nr-axSpA to AS, or if the combination of NSAIDs and TNFi leads to even better radiographic outcomes.

Data on conventional disease-modifying anti-rheumatic drugs (DMARDs) in the management of AS are limited, and there are only a couple of studies in subjects with nr-axSpA. Sulfasalazine is the only DMARD to show some efficacy for the peripheral manifestations of AS [13]. However, it does not appear to have an effect on early spinal manifestations of SpA. A placebo-controlled trial in patients with inflammatory back pain due to undifferentiated SpA and early AS showed that sulfasalazine was no better than placebo for the treatment of the signs and symptoms of undifferentiated SpA [14]. Methotrexate is the most commonly used DMARD in RA, but it has not been found effective in a few small AS trials at doses ranging from 7.5 to 20 mg/week [15, 16] (doses used in RA) and there are no large, placebo-controlled trials of this agent either in AS or axSpA. Regardless, methotrexate is widely used for axSpA in many parts of the world [17], which suggests patients may draw some benefits from it. Pamidronate, a bisphosphonate with both anti-osteoclastic and anti-inflammatory properties [18], has demonstrated clinical efficacy in AS [19], but not in nr-axSpA or in TNFi-refractory AS. In a small, open-label, short-term trial of another bisphosphonate, neridronate was found to be equally effective as infliximab in reducing disease symptoms in AS [20].

In the absence of well-designed studies, DMARDs remain undervalued in the management of axSpA and are likely to remain so as there is little economic incentive for such studies to be conducted.

New agents with different mechanisms of action are currently in clinical evaluation in AS. Apremilast is a small-molecule inhibitor of phosphodiesterase 4, which modulates pro-inflammatory and anti-inflammatory mediator production. Secukinumab is a fully human anti–interleukin (IL)-17A monoclonal antibody. Increasing evidence suggests that IL-17A is involved in AS pathogenesis [21] and may be a mediator of joint destruction in animal models of arthritis [22]. In a recent mouse model of SpA, IL-23 and entheseal-resident T cells were found to promote enthesitis and bone remodeling through IL-17 and IL-22 [23]. Both apremilast and secukinumab are being tested in phase III clinical trials for AS (but not nr-axSpA). Ustekinumab, a fully human monoclonal antibody that inhibits the IL-12/23 pathway, very recently showed reduction of clinical and imaging signs and symptoms in a small open-label proof-of-concept study of subjects with active AS [24]. Because of the commercial potential of these new agents, we are likely to learn more about their efficacy than the efficacy of DMARDs and NSAIDs in the treatment of axSpA.

Biosimilars—is interchangeability justified in axSpA?

With health care costs skyrocketing, there is a huge unmet need for less-expensive biologic therapies. Biosimilars, expected to have similar quality, safety, and efficacy, but lower cost to reference biologics, may provide a window of opportunity to alleviate economic pressures.

Data from the first studies with biosimilars have been published very recently for both AS and RA, and both studies met their primary endpoints, demonstrating similar clinical responses as the innovator biologic infliximab [25, 26]. Neither long-term safety data nor convincing radiographic data in either disease have been provided so far. Nevertheless, based on the early data, the Korean Ministry of Food and Drug Safety and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) not only recommended this particular biosimilar for the treatment of both AS and RA but also extrapolated these results for approval in other diseases like ulcerative colitis, Crohn's disease, and psoriasis [27]. Whether approval will be extended to nr-axSpA and whether the efficacy and safety data of biosimilars will be comparable to those of innovator biologics in the long term will have to be shown in the future.

What is the optimum dose of therapies we currently use and can they be withdrawn after patients reach remission?

Non-pharmacological treatment options for AS center around patient education and physical therapy (PT) [2], based on expert opinion and decades of collective experience. While the nature of these interventions prevents double-blind, placebo-controlled studies, the available clinical trials of physical therapy in AS are not standardized and mostly not well designed. There are very few comparative studies on the efficacy of well-defined physiotherapy interventions and those that exist lack adequate information on exercise frequency (or the "dose" of physical therapy) [28, 29].

Is additional physiotherapy even required in an axSpA patient whose disease is well-controlled on pharmacotherapy? In one study in AS subjects, physical rehabilitation added to existing TNFi therapy improved all clinically relevant outcomes [30]. In clinical practice, our experience shows that adherence to exercise dwindles in most patients after they start TNFi. If exercises add substantial value over and above the new pharmacotherapy, we need more evidence to convince our patients.

As noted earlier, there is little evidence for the efficacy of DMARDs in AS. An unexplored possibility is that DMARD doses higher than those conventionally used in RA might work in axSpA. The use of higher dose DMARDs in combination with TNFi in TNFi-inadequate responders is another area that will be economically prohibitive to investigate, considering the large number of subjects required and the possible toxicity of the compounds used in such a scenario.

While the efficacy of TNFi for the treatment of active AS is well established, the optimal dose and frequency of administration of TNFi in AS is not known. In the past, TNFi trials in AS generally evaluated a single dose, mostly the same dose used in RA trials. Most non-responders to a conventional infliximab regimen did respond to dose escalation in one study [31], similar to the clinical experience of practicing rheumatologists. Recent studies of TNFi have evaluated the differences in efficacy of different doses (golimumab and etanercept) or dosing intervals (certolizumab) in patients with axSpA, but the findings were negative [5, 32, 33]. Dose de-escalation of TNFi in patients who are in remission would have important economic implications. A recent small study of etanercept in AS showed that remission appeared to be maintained in most patients after halving of the dose [34]. Large TNFi dose titration studies (up and down) based on clinical symptoms would mimic a real-life scenario, but such data are most likely to be generated from cohort studies rather than in the setting of a controlled trial.

It has been shown that disease activity returns within months if long-term TNFi therapy is discontinued in patients with established AS [35]. However, in patients with early, active axSpA, the INFAST study showed the encouraging result that partial remission could be maintained in almost half of the patients at 6 months after stopping the treatment (infliximab/placebo+naproxen); improvements in several less-stringent measures of disease activity were generally maintained with very few patients experiencing disease flares [36]. Whether this low level of disease activity could be maintained beyond 6 months has not been studied. Nevertheless, these results

suggest that drug-free remission in axSpA might become an achievable goal with early and aggressive treatment.

Which patients are appropriate for the different therapies?

Not all patients improve and many experience significant side effects after using NSAIDs, such as exacerbation of inflammatory bowel disease or increased risk of myocardial infarction [37, 38]. Consequently, a risk–benefit analysis of the long-term use of NSAIDs in axSpA is essential, but has not been studied so far in a controlled manner in clinical registries.

Predictive factors such as genetic markers, serum biomarkers, or advanced imaging are not yet sophisticated enough to identify "pre-AS" patients within the nr-axSpA population who will develop structural changes as defined by the modified New York criteria for AS (Fig. 1) [3]. As we do not know definitively if any of the available therapies will be able to prevent the progression of nr-axSpA to AS, this is only of theoretical interest currently. Predictors of response to TNFi therapy in AS have been identified; a model combining age, HLA-B27 genotype, CRP level, and functional status and presence of enthesitis at baseline appears to predict the outcomes of TNFi therapy [39]. However, pharmacogenomic data regarding genetic factors (other than HLA-B27) that predict the most efficacious and least toxic therapy for individual patients (true "personalized medicine") remain elusive. As the economic value of treatment becomes increasingly important to payers, progress in the field of personalized medicine with stress on pharmaco-economics is likely to make inroads in this area.

Do the approved therapies prevent long-term complications associated with axSpA?

The effects of TNFi on important long-term complications associated with axSpA (e.g., amyloidosis, pulmonary apical fibrosis, cauda equina syndrome, aortic valve disease), long-term work

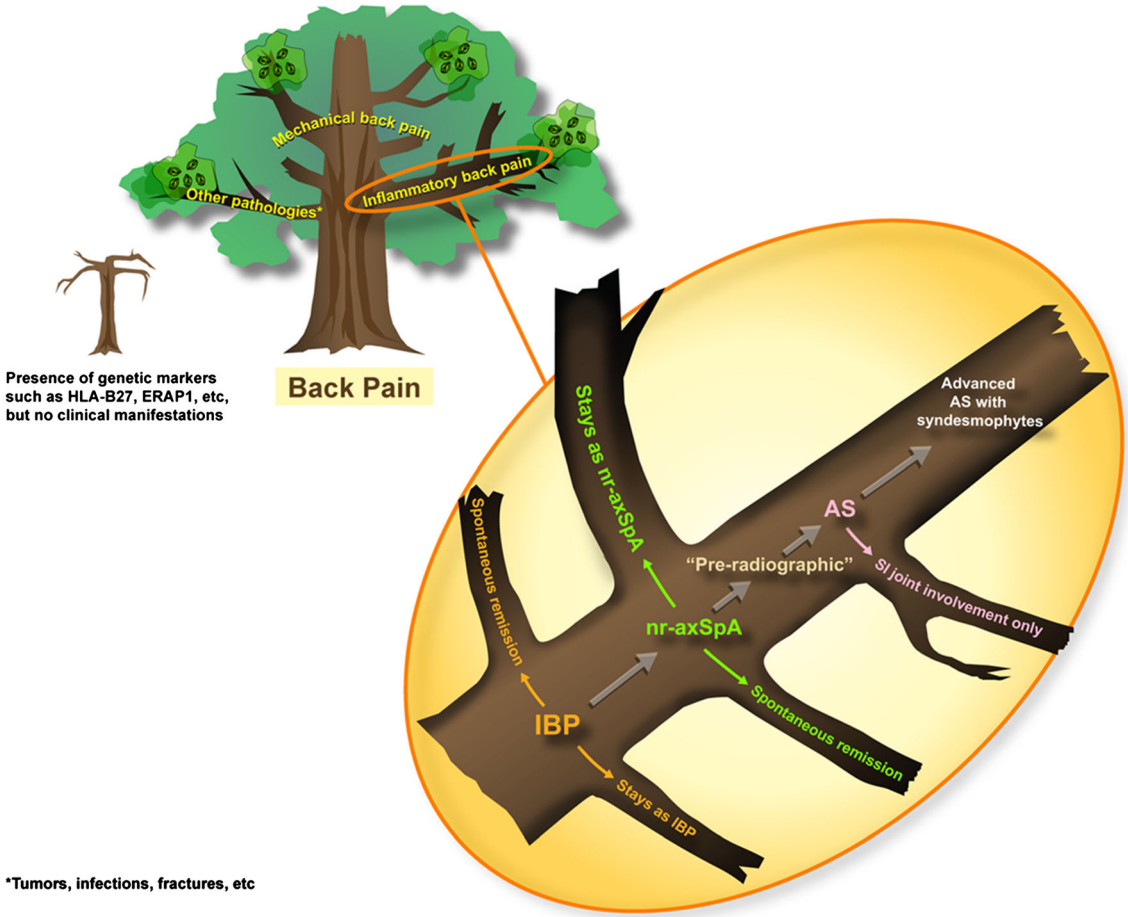

Fig. 1 Expanded concept of axSpA. The spectrum of axSpA includes non-radiographic axSpA. It remains unclear what proportion of patients with non-radiographic disease is likely to progress to AS and how to distinguish such patients (i.e., those with pre-radiographic axSpA) from patients who are unlikely to progress. The smaller tree indicates that axSpA may not develop in the presence of genetic predisposition alone. *AS*, ankylosing spondylitis; *ERAP1*, endoplasmic reticulum aminopeptidase 1; *HLA*, human leukocyte antigen; *IBP*, inflammatory back pain; *SI*, sacroiliac

productivity, disability, and mortality remain to be investigated. The effect of TNFi on malignancy risk in patients with RA is controversial and not adequately studied in patients with AS [40]. In a recent long-term safety analysis, adalimumab was not associated with significantly higher risk of total malignancy, lymphoma, melanoma, or non-melanoma skin cancer in the subset of 1,684 AS patients compared with the age- and sex-matched general population [41]. Patient registry data can better define this risk in AS patients in comparison to the general population and determine whether TNFi use influences these risks. AS patients in everyday clinical practice usually have more comorbidities than those in clinical trials. Registry data will therefore also capture the risks associated with treatment in real-world settings.

What is the role of MRI in monitoring disease progression?

Inflammatory activity in the sacroiliac joints or the spine, as shown by MRI, precedes structural changes and can be related to osteoproliferation in axSpA [42]. In AS, the degree of spinal inflammation can predict the efficacy of TNFi [43]. TNFi, but not NSAID [44], treatment significantly decreases inflammation in nr-axSpA [45] and AS [46]. In addition, it is becoming increasingly clear that not only inflammation but also its combination with fatty lesions are significantly related to future syndesmophyte progression [47]. The role of MRI is therefore considered especially important in this regard because it is the only imaging modality that can depict both abnormalities, either alone or in combination [47]. The use of MRI beyond the diagnosis and prediction of disease course or treatment response, such as to monitor patients treated with TNFi, remains unexplored. There is also no guidance on how to proceed when a disparity occurs between treatment response (i.e., improved signs and symptoms) and MRI findings (i.e., ongoing inflammatory activity). Long-term follow-up studies with serial MRI examinations are necessary to answer these questions, but the economic cost may prevent such studies from being performed.

Conclusion

Current treatment strategies for axSpA are based on studies predominantly conducted in AS, and few data exist for nr-axSpA and advanced AS. NSAIDs and TNFi are effective in reducing the signs and symptoms of axSpA, but evidence is lacking regarding the effect of anti-inflammatory treatment on the progression of nr-axSpA to AS. The data on inhibition of radiographic progression in patients with established AS is emerging for NSAIDs as well as for TNFi. There is insufficient data on a possible additional effect of physiotherapy or the use of conventional DMARDs at any disease stage. Several investigational agents are in late-stage evaluation and, if shown to be safe and effective, will face many of the same questions raised about existing therapies.

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