Correspondence on "ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update"

With great interest I read the recently published Assessment of Spondyloarthritis International Society (ASAS/European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of axial spondyloarthritis (axSpA,1), which included some but not many changes in comparison to the last recommendations.[1] Let me first say that I largely agree with them. However, I would like to initiate a discussion related to the recommendation related to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in order to possibly change this recommendation in the next update. NSAIDs were clearly shown to work in axSpA including ankylosing spondylitis but a large proportion of patients does not tolerate this treatment for longer periods of time.[2 3] All ASAS/EULAR recommendations for axSpA have included the recommendation to first start treatment with at least two NSAIDs within 4 weeks in patients with the correct diagnosis and high disease activity.[1 4] As a matter of fact, this step is mandatory,[2 3] and a BASDAI value >4 should be documented—as once proposed many years ago.[5] An insufficient response to this strategy is followed by a strategic step up in the sense of treat-to-target (T2T) which usually means therapy with a biological disease-modifying anti-rheumatic drug (bDMARD).[2 3 6] Even though this has been practical in the last two decades because, as an item in a trial design it can be easily fulfilled since one mainly has to tick the box 'insufficient response to NSAIDs'. However, in no study I'm aware of has it ever been controlled whether this was really performed in the way it was asked for. Thus, the first criticism of this recommendation is that this item is constructed as a precise strategic step but in daily clinical practice and in clinical studies it is clearly not. In fact, it is largely a decision made by the treating rheumatologist who wants to start bDMARD therapy.

The second point is the lack of evidence that the time period chosen is anything more than an arbitrary decision once made to ease the initiation of tumour necrosis factor inhibitors (TNFi) by making sure that these effective agents are not being given to all axSpA patients right away.[7] There is, for example, the data of the infliximab as first line therapy in patients with early active axial spondyloarthritis trial (INFAST) published some years ago[8] in which about one-third of the patients with relatively early disease reached partial remission according to the ASAS definition,[9] and the response rate did increase quite steadily.[8] However, the combination of infliximab with an NSAID was much better,[8] and, in the second part of the INFAST study starting after remission had been achieved, NSAIDs were unable to improve outcomes after discontinuation of TNFi.[10] Thus, why wait for 4 weeks? I'm certainly not advocating a longer period here, I just want to stress that the evidence for the time period chosen is very limited and that it does not make much sense to stick to it.

Third, there are patients with axSpA who have very clear signs of inflammation as indicated by a positive magnetic resonance imaging (MRI) result and/or an elevated serum level of C-reactive protein (CRP).[11 12] In non-radiographic (nr)-axSpA, having objective signs of inflammation is even mandatory before starting bDMARDs.[13] Whether NSAIDs have an influence on inflammatory changes detected by MRI is unclear, there is only one negative study performed many years ago.[14] In contrast, bDMARDs reduce axial inflammation quite rapidly and effectively.[15] Furthermore, while therapy with TNFi is clearly associated with a reduction and often normalisation of CRP values[16] this is rather limited for NSAIDs.[17 18] However, long-term treatment with TNFi is needed to show an influence on radiographic progression,[19] while the data for NSAIDs are conflicting[20–22] with a possible difference for cyclo-oxygenase-2 inhibitors versus conventional NSAIDs, and the open question of continuous versus on-demand application[19]—the former showing benefit mainly for axSpA patients with an elevated CRP.[2] In any case, the scientific reasoning to treat with TNFi or other bDMARDs for longer periods of time has a stronger basis than that for NSAIDs. Thus, why wait in cases with clear-cut systemic inflammation?

The clinical question behind this is whether an obligatory period of NSAID therapy is needed in patients with an objective sign of inflammation—given that NSAIDs will not have a major effect on this within 4 weeks—on the background of the OASIS data showing that patients with a low ASDAS have much better radiographic outcomes,[23] which provided a strong basis for promoting the T2T strategy for axSpA.[6] On that background, would one really continue treatment with NSAIDs only in patients who continue to have objective signs of inflammation but had a good symptomatic response to NSAIDs ? The good symptomatic response to NSAIDs which has been promoted as an aid to diagnosis earlier on is part of the classification criteria for axSpA[24] but whether this is still the case in more advanced disease has been recently challenged.[25]

The fourth point relates to real life data showing that many patients do not want to regularly take NSAIDs—even though this had been strongly recommended.[26] Limited compliance and adherence to NSAID medication has also been reported in other circumstances.[27]

The discussion on gastrointestinal, cardiovascular and renal adverse events of NSAIDs is beyond the scope of this viewpoint but there are published expert concerns including a recommendation to only use the smallest possible dose for only a short period of time.[28]

Finally, there is evidence that patients with axSpA may have different reasons for back pain,[29] which includes degenerative changes and fibromyalgia. While NSAIDs do also have analgetic properties, bDMARDs do not. Thus, a positive response to NSAIDs may have a different basis than assumed when prescribed.

Taken together, the basis for the NSAID recommendation in the ASAS-EULAR management recommendations for axSpA is rather weak. Since bDMARD therapy is widely considered standard of care these days there is no reason to ask for an obligatory course of NSAIDs anymore. Thus, I propose to spend some discussion on this point when it is time for the next update. If the rheumatologist in charge of the patient is convinced that a bDMARD should be given, because other approaches have not sufficiently worked, this should be good enough—and actually pretty close to how it is handled today in many centres. I predict that rheumatologists will handle patients with axSpA and objective signs of inflammation differently in this regard,[30] and I think this makes sense, but I do not see the need to document a course of NSAIDs or tick a box with questionable content.

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