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Response to: correspondence on "ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update " by Ramiro et al

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We read with interest the letter by Braun[1] pertaining to the 2022 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA).[2] Braun questions whether having non-steroidal anti-inflammatory drugs (NSAIDs) as the first mandatory pharmacological treatment is still appropriate. First, doubt is raised whether an insufficient response to NSAIDs, which is required in daily clinical practice and in clinical studies before the start of biological disease-modifying antirheumatic drugs (bDMARDs), is ever formally checked. Whether this is the case or not, we remain firmly of the opinion that this could not, at least without a proof against, be an argument used to delete this from our recommendations. This opinion is based on the well documented and extensive evidence on the efficacy of NSAIDs in axSpA, over long periods of time.

Furthermore, Braun indicates that tumour necrosis factor inhibitors (TNFi) reduce axial inflammation while NSAIDs do not.[1] However, it is worth noting that NSAIDs have also shown to decrease axial inflammation to some extent: a decrease in signal intensity of bone marrow oedema of the sacroiliac joints was measured as an early response to 6 weeks of optimal NSAID therapy in patients newly presenting with axSpA.[3] Nevertheless, we agree that this is an aspect of studies with NSAIDs that has been less frequently examined, as compared to TNFi and other bDMARDs.

Moreover, the question is raised around the time period (4 weeks) chosen for the treatment with NSAIDs necessary to observe clinical response. We accept that the evidence on this is very limited and arguably, a 4-week trial duration is indeed arbitrary. However, there was clear consensus to recommend an NSAID trial first, which also allows time to consider patients with axSpA who truly need to progress to bDMARDs, versus those who do not.[1 4] This strategy has indeed proven to be successful since, as also acknowledged by Braun, an important proportion of patients reach very good clinical outcomes while only on NSAIDs.[5] For example, in newly diagnosed patients in the TICOSPA trial, whereby there was indeed a 4-week visit to check efficacy, 44% of the patients in one arm and 63% in the other arm did not start a bDMARD within the first year of treatment.[6] This suggests that bDMARDs are not necessarily needed for every single patient with axSpA. It should also be noted that 4 weeks is not a very long period in comparison to the 3-month minimum window used for conventional synthetic DMARDs in rheumatoid arthritis.[7]

There are other relevant generic considerations pertaining to the content of recommendations. As in the case of classification criteria, recommendations should be conservative, not too sensitive to *Zeitgeist*, and consider the entire spectrum of patients in different regions of the world. Essentially, this means that the patients with the severest disease should be treated with the most efficacious drugs as soon as possible, while those with less severe disease could still be offered a chance of good clinical outcomes with other drugs, such as NSAIDs for axSpA, or with non-pharmacological treatment alone. In addition, there are patients with an even milder form of the disease who do not wish to be followed up long term, with the option to reach out to a specialist 'on demand'. Treatment recommendations should serve the entire spectrum of axSpA. Despite the decreasing costs of bDMARDs in some countries through more effective market-competition and the availability of biosimilars, we all must recognise that they remain considerably more expensive than NSAIDs. ASAS-EULAR recommendations for the management of axSpA aim to be used universally and their content needs to address and reflect worldwide axSpA-care including ease of access to drug treatment.[8 9]

Finally, the suggestion raised to treat patients with axSpA with bDMARDs alone as first line has so far not been formally investigated. Such a comparative (pragmatic) trial with bDMARDs first versus NSAIDs first followed by bDMARDs only if needed, would be very challenging to design and conduct properly, and sensitive to all sorts of bias. To consider such a paradigm-change in the ASAS-EULAR management recommendations for axSpA, at least some evidence favouring it would be necessary to overcome the arguments previously given and the strong rationale for keeping NSAIDs as first-line treatment in axSpA.

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