

NSAIDs and radiographic progression in ankylosing spondylitis

Bagging big game with small arms?

Nigil Haroon,¹ Tae-Hwan Kim,² Robert D Inman¹

ARE NSAIDS DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)?

Non-steroidal anti-inflammatory drugs (NSAIDs), including Coxibs, are recommended as first-line drug treatment for patients with ankylosing spondylitis (AS) with inflammatory back pain and stiffness. Continuous treatment with NSAIDs is preferred for patients with persistently active, symptomatic disease.¹

Although many young patients with AS may be at lower risk of gastrointestinal and cardiac adverse events with NSAID therapy than older patients with other rheumatic diseases, patients and physicians alike continue to raise questions about the optimal role of these agents in AS.

An earlier study examined phenylbutazone in AS and concluded that this agent not only improved the symptoms of spinal pain and stiffness, but also appeared to influence progression of new bone formation in the spine.² A study by Wanders *et al* in 2005 found that the *continuous* use of celecoxib, in contrast with *on-demand* use, was also associated with less radiographic progression in AS.³ The latter was measured determining the change in the modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS) over a 2-year interval. This provocative finding heightened interest in the potential disease-modifying effects of NSAIDs. However, the study of Wanders *et al* entailed relatively small differences in total celecoxib dose between groups. The study has awaited confirmation in other AS cohorts. We recently reported a reduced rate of progression of mSASSSs in

patients who continue to take NSAIDs while being on anti-tumour necrosis factor (TNF) agents for AS.⁴

Two papers now published in the *Annals of Rheumatic Disease* provide supportive evidence that NSAIDs may slow the progression of bony change of the spine in AS.^{5,6} Data from the German Early Spondyloarthritis Inception Cohort (GESPIC) suggests that patients with AS with a high NSAID intake over 2 years demonstrated slowing of new bone formation in the spine compared with patients with low NSAID intake. Interestingly, this protective effect was nearly exclusively seen in patients with elevated C-reactive protein levels over time and the presence of syndesmophytes at baseline. A second study from the Netherlands, a post hoc analysis of the study cited above,³ reports that patients with elevated acute-phase reactants seem to benefit most from continuous treatment with NSAIDs, a finding similar to that seen in GESPIC. The application of continuous NSAID therapy in patients with elevated acute-phase reactants may lead to an improved benefit/risk ratio of these drugs, although the challenge at hand is to weigh the risks and benefits in the individual patient as discussed below.

BIOLOGICAL BASIS FOR NSAIDS INFLUENCING BONE FORMATION

The effect of NSAIDs on bone has been recognised for some time now. Earlier studies reported that NSAIDs improve bone mineral density (BMD) in postmenopausal women.⁷ This was followed by reports that propionic acid NSAIDs may preferentially have an effect on BMD compared with salicylates and that combining salicylates with cyclo-oxygenase-2-selective NSAIDs resulted in improved BMD in older women.⁸ None of these studies, however, showed a beneficial effect of NSAID use on preventing fractures. In fact, a subsequent study hinted

at a possible increase in risk of fractures in NSAID users despite an increase in BMD.⁹ Analysis of the Canadian Multicentre Osteoporosis Study on the effects of NSAIDs on BMD led to interesting findings.¹⁰ The use of NSAIDs was associated with a *decrease* in BMD in men and *increase* in postmenopausal women who did not receive oestrogen replacement.¹⁰ The authors concluded that the effect of NSAIDs seen in this study is a reflection of suppression of inflammation associated with the postmenopausal state, while the direct effect of prostaglandin inhibition on bone is manifest in men as a decrease in BMD. NSAIDs have long been considered to delay fracture healing and increase graft failure after spinal fusion.^{11–13} Inhibition of spinal fusion has been demonstrated in animal models, and in a rabbit model this was shown to be reversed by recombinant bone morphogenetic protein (BMP)-2.¹⁴ Ectopic bone formation in hamstrings of mice using the bone anabolic agent, BMP-7, was reduced by diclofenac, showing a negative influence on pathological bone formation in this model.¹⁵

NSAIDs reduce prostaglandin synthesis, and the issue of their effect on AS progression is very timely, as recent genome-wide association studies in AS have shown an association of the gene prostaglandin E receptor 4 (*PTGER4*) with AS.¹⁶ *PTGER4* is one of the four genes that encode the prostaglandin E2 receptors (EP1–EP4). The effect of the *PTGER4* polymorphisms on EP4 function is not yet known. EP4-knock-out (KO) mice—unlike EP1-, EP2- or EP3-KO mice—show reduced bone resorption with impaired generation of osteoclasts, matrix metalloproteinase (MMP)-2 and MMP-13.^{17,18} Osteoclast differentiation factor (ODF) is produced by osteoblasts in a prostaglandin-dependent and -independent manner. Lipopolysaccharide-induced, prostaglandin-dependent ODF production is decreased in EP4-KO mice and inhibited by indomethacin. Thus bone resorption can be affected by the *PTGER* gene, and this effect may be modified by NSAIDs. Corner fatty lesions in the spine are considered to predispose to syndesmophytes.¹⁹ *PTGER4* can induce bone formation in fatty areas of the marrow at the expense of adipose tissue and thus is potentially a key factor involved in syndesmophytes formation.²⁰ Prostaglandins can also stimulate osteoblast formation, but this effect appears to depend on the concentration.^{21,22} Thus differences in

¹Department of Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, Canada

²Hospital for Rheumatic Diseases, Hanyang University, Seoul, Republic of Korea

Correspondence to Professor Robert D Inman, 1E-423, 399 Bathurst Street, Toronto Western Hospital, Toronto, ON M5T 2S8, Canada; Robert.Inman@uhn.ca

local concentration of prostaglandins could explain the paradoxical new bone formation and osteoporosis seen in AS. Hence there is a reasonable biological basis to explain the NSAID effect on radiographic progression in AS. However, the effect on an individual patient may be difficult to predict, considering the complexity of bone metabolism and the multiple effects of prostaglandins.

PERSONALISED MANAGEMENT OF AS

The recent studies of NSAID effect on AS progression raise important questions for the optimal management of AS for the clinician. Key elements that should be factored into the decision on the use of NSAIDs in the management of the individual AS patient can be stated as a series of questions.

1. *What is the symptomatic state of this patient at present?* This domain must figure importantly in the management of the patient with AS, as improved quality of life is the ultimate treatment goal for any intervention, pharmacological or non-pharmacological. ASAS-EULAR guidelines place optimal NSAID therapy as the cornerstone of the management plan for AS.¹ This remains a sound approach since NSAIDs have proved to be effective in control of symptoms for many patients with AS. Indeed, NSAID responsiveness has been considered to be a defining feature of inflammatory back pain, in contrast with mechanical back pain.²³
2. *What is the likelihood of radiographic progression in this patient?* This fundamental issue of prognosis in AS continues to be a work in progress, and numerous studies indicate (as reflected in cumulative probability plots) that the great majority of patients will fall into the non-progressor category. The current study of Kroon *et al* suggests that elevated erythrocyte sedimentation rate (ESR) is an important predictor of progression. However, there are other important clinical associations with radiographic progression such as smoking and age of onset.^{24 25} Serum biomarkers such as MMP-3,²⁶ dickkopf-1,²⁷ Wnt3a²⁸ and sclerostin²⁹ have been examined as prognostic indicators in several cohorts. A recent development is the application of genetic polymorphisms to predictive models of progression.³⁰ As further candidate genes are identified in genome-wide association studies, those related to bone-forming pathways will be of particular interest for

application in predictive models. At present, the most robust predictor of structural progression is the presence of syndesmophytes at baseline,³¹ so this constitutes a useful stratifying factor for the clinician. It is of interest that baseline mSASSs in the study of Kroon *et al* proved to be predictive of progression as expected, but this did not alter the influence of ESR or the NSAID treatment effect, although further studies in this regard would be informative.

3. *What are the risks of continuous NSAID treatment in this patient?* Traditionally, concerns about safety of NSAIDs have related primarily to gastrointestinal or cardiovascular adverse events. Recent studies in AS have heightened concerns in both these areas. The recognition that the same polymorphisms in the interleukin (IL)-23 receptor confer susceptibility to AS and inflammatory bowel disease has led to further investigation of the role of occult bowel inflammation in AS. In the studies of Ciccia *et al*,³² it was found that the upregulation of IL-23 seen in gut tissues of patients with Crohn's disease is also seen in patients with AS with no gastrointestinal symptoms. This follows the earlier pioneering studies of Mielants and Veys demonstrating that subclinical gut inflammation is a common occurrence in AS. With respect to cardiovascular disease, there is increasing recognition that cardiovascular events occur with increased frequency in AS,³³ which may be related to disease activity.³⁴ In the context of inflammatory joint disease, NSAIDs may not confer an increased risk of cardiovascular mortality, but this area needs further study in large cohorts with long-term follow-up.³⁵ In psoriatic arthritis, concerns about cardiovascular and gastrointestinal risks have led to a conservative approach to the use of NSAIDs, with the recommendation being the lowest dose and the shortest treatment duration possible with NSAIDs, in view of their potential toxicity.³⁶
4. *What treatment alternatives are available for this patient?* Using the ASAS-EULAR guidelines, the NSAID-unresponsive or NSAID-intolerant patient is on the threshold of biological therapy. One of the central ironies of AS management is that the anti-TNF agents have proved effective for improvement of symptoms of AS, but have not been shown to retard radiographic progression in the

disease. The fact that these agents predictably normalise the ESR in AS highlights the complexities, as the current studies on NSAID effect identify elevated ESR as a robust predictor of progression. From the patient's perspective, it is symptomatic improvement in the pain, stiffness and fatigue of the disease that are the primary concerns. And these correlate poorly with mSASS. But symptomatic status (as reflected by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) turns out to be a poor predictor of the NSAID 'protective' effect with respect to radiographic progression. Similarly, there are few studies to inform the decision on whether NSAIDs should be continued when a biological agent is administered, although our recent experience provides supportive evidence for this approach.⁴ Both for the pivotal phase 3 random control trials of biological agents in AS and current third-party coverage, inadequate control of symptoms by NSAIDs has become the criteria for use of anti-TNF agents. Thus the published literature on the effects of anti-TNF agents on bone formation is based largely on experience with NSAID non-responders.

In the final analysis, treatment of AS must be customised to the individual patient, as set out as the first principle of the ASAS-EULAR Recommendations.¹

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