

NSAIDs in axial spondyloarthritis: to be continued ...?

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Phenylbutazone was discovered in 1946 and promptly exhibited efficacy in various rheumatic diseases in the early 1950s. Its efficacy on pain and general well-being was especially present in ankylosing spondylitis (AS), which was then known as 'rheumatoid spondylitis'.^{1 2} However, even in the early days, non-steroidal anti-inflammatory drugs (NSAIDs) were not considered harmless drugs, as the toxic properties on bone marrow or the gastrointestinal tract, and the appearance of oedema or skin rash, although commonly reversible, were already apparent from the start. Up until now, a various range of NSAIDs have taken centre stage and have been the cornerstone of treatment of patients with spondyloarthritis (SpA).^{3 4} Despite the common use of these drugs for almost seven decades, there are still a number of unanswered questions, such as which type of NSAIDs we should preferentially use in axial SpA (AxSpA) and whether these agents should be given continuously or on demand.

All NSAIDs are effective anti-inflammatory drugs because of their ability to inhibit the biosynthesis of prostaglandins at the level of the cyclo-oxygenase (COX) enzyme; however, this mode of action also explains a number of side effects. While selective COX-2 inhibitors have claimed to induce fewer side effects through the omission of COX-1 inhibition, large meta-analyses have failed to demonstrate this superiority of COX selectivity in vascular and complicated gastrointestinal outcomes compared with conventional NSAIDs.^{5 6} Furthermore, head-to-head comparisons of efficacy in AxSpA regarding the available NSAIDs are scarce. In AS, the treatment effect of piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg did not differ significantly after 1 year of treatment regarding the patient's overall assessment,⁷ and Sieper *et al*⁸

reported that the efficacy of diclofenac compared with celecoxib was non-inferior regarding symptom relief. In contrast, other studies have demonstrated superior efficacy of etoricoxib compared with naproxen regarding spinal pain, disease activity and function.^{9 10} Nevertheless, a recent meta-analysis reported comparable short-term efficacy for all NSAIDs in active AS.¹¹ Besides pain relief and suppression of inflammation, treatment goals in AxSpA have also focused on the potential deceleration—and preferably the arrest—of structural damage. The primary choice of NSAID in pain relief and modulation of radiographic progression has remained ambiguous and the need for chronic NSAID therapy in patients with SpA has been the reason for debate between patients and clinicians, and also among clinicians themselves.

Sieper *et al*¹² adds challenging data to our knowledge of continuous versus intermittent NSAID intake on radiographic progression after 2 years in AS with the Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis (ENRADAS) trial. The ENRADAS trial provides us with a prospective trial of high quality with transparent statistical analysis, in a clinically homogeneous population with well-defined NSAID intake. In 2005, Wanders *et al*¹³ published a landmark paper, demonstrating that continuous intake of NSAIDs yielded a better outcome regarding structural damage over a 2-year period, compared with intermittent NSAID use. The Wanders trial has impacted clinical practice, as this was the first prospective randomised controlled trial (RCT) addressing a possible beneficial effect of continuous NSAID intake, regardless of patient symptoms and flares. The favourable effect of NSAIDs on radiographic progression in AS had already been postulated in a small retrospective study by Boersma.¹⁴ Later on, a few years after the study by Wanders *et al*, a retrospective analysis within the German Spondyloarthritis Inception Cohort (GESPIC) cohort found an association between higher NSAID intake and less radiographic progression. However, this was based on a NSAID index of ≥ 50 , which is the mean daily intake of the patient expressed as the percentage of the

optimal daily dose of NSAIDs during the period of interest, rather than a true continuous intake.^{15 16} In contrast, in a multivariate analysis by Haroon *et al*,¹⁷ NSAID intake was not associated with radiographic progression in AS, regardless of systemic inflammation.

Both in the GESPIC cohort and in the subanalysis by Kroon *et al*¹⁸ within the same study population described in the paper by Wanders *et al*, this structural effect was mainly attributable to an effect in patients with elevated inflammatory parameters.¹⁵ Due to these recent findings, the idea grew among rheumatologists that continuous intake of NSAIDs could be proposed in patients with a high inflammatory burden, regardless of their clinical symptoms. At present, extrapolation to non-radiographic AxSpA is not exceptional in clinical practice, although this effect has not been demonstrated in early disease.¹⁵

The investigators of the ENRADAS trial compared diclofenac 150 mg daily with on-demand NSAID intake in a numerically equivalent sample of patients with AS, but could not demonstrate a difference in radiographic progression between continuous or intermittent intake of NSAID, not even when considering the subgroups of patients that had been identified previously as more prone to radiographic progression, such as patients with elevated C-reactive protein, baseline syndesmophytes or smokers.^{12 17 19} In fact, although not significant, a numerically higher progression was seen in the patients with continuous intake. Another recent study by Maksymowych *et al*²⁰ has also identified the presence of inflammation of the spine on MRI as a risk factor for radiographic progression. However, data on baseline MRI inflammation are lacking in both prospective trials and consequently may have been a potential drawback in patient stratification within the trials and patient comparability across the trials. The ENRADAS trial describes a modified Stoke Ankylosing Spondylitis Spine Score progression of 1.3 (95% CI 0.7 to 1.9) in the continuous intake group compared with the on-demand group, in which 0.8 (95% CI 0.2 to 1.4) progression was observed. However, Wanders *et al* detected a progression of 0.4 (± 1.7) in the group with continuous intake compared with 1.5 (± 2.5) in patients on demand, which is more or less the opposite. In contrast to the use of a classic NSAID, such as diclofenac, the trial by Wanders *et al*¹³ employed the COX-2-selective agent celecoxib.

These findings challenge the underlying idea that the deceleration of structural

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damage would be an overall NSAID class effect. The question could be raised whether a possible differential effect of COX-2-selective versus conventional NSAIDs on bone is present, and more specifically the formation of syndesmophytes. There is some evidence of this differential effect of NSAIDs in rodents, while in humans, this differentiation has been studied in the field of heterotopic bone ossification (HO) and fracture healing. Yet, these results are equivocal. Provided that research in these other conditions of new bone formation would serve as a model for syndesmophyte formation in AS, literature states that indomethacin, ketolorac and naproxen would be more effective in the prevention of bone formation. On the other hand, piroxicam, flurbiprofen and rofecoxib would be ineffective.^{21–25} The published trials regarding celecoxib exhibited contradictory results.^{26–27} In conclusion, to date, meta-analysis could not support a differential effect of NSAIDs on HO,²⁸ and it is clear that the effect of NSAIDs on bone formation in patients with AS—whether conventional or COX-2-selective—has yet to be uncovered.

Second, we must take into account that the aforementioned results of Wanders *et al* might be numerical findings, rather than true effect. In this regard, the rather limited statistical effect size of 0.07 has been pointed out by Guellec *et al*.²⁹ Additionally, although continuous intake was defined as daily intake in both trials, the NSAID indexes in both RCTs are quite different. In the trial by Sieper *et al*, the NSAID index in the continuous and on-demand group was 75 and 44, respectively. However, the difference in overall NSAID intake between continuous and on-demand intake in the trial by Wanders *et al* can be calculated as being respectively 60.75 (243/400) and 50.25 (201/400), which represents a rather marginal difference between the treatment groups. One could hypothesise that a greater difference in NSAID intake over time should have amplified the previous observed effect, but this is definitely not supported by the findings of the ENRADAS study.

Up until now, only one prospective RCT pointed towards a more favourable effect of continuous NSAID intake on radiographic progression; the new data from a comparable, well-designed RCT, fail to confirm this. Considering these conflicting data, there is currently insufficient evidence that continuous intake of NSAIDs would alter the radiographic progression in AS over a 2-year time period compared with intermittent use. It

remains to be demonstrated whether this effect might be present after a longer follow-up, comparable to the data with antitumour necrosis factor- α (anti-TNF- α) agents, which were considered disappointing in the light of the prior NSAID results.³⁰ Due to the inability of anti-TNF- α to slow down radiographic progression over 2–4 years, the hypothesis was generated that NSAIDs exerted their effect on bone formation through another mode of action than the resolution of inflammatory lesions. However, in the light of these novel findings, both drugs might display a similar effect on radiographic progression through modulation of inflammation.

A final, but important consideration that has to be taken into account when discussing continuous versus on-demand NSAID treatment, is the issue of feasibility of such an approach in daily practice. A small prospective cohort study in AxSpA—studying the effect of continuous optimal NSAID intake on bone marrow oedema of the sacroiliac joints on MRI—has addressed the difficulties of maintaining a continuous full-dose NSAID, even in patients with symptomatic AxSpA. Although the mandatory intake of NSAIDs was only 6 weeks, one-third of the patients were either not compliant or experienced side effects that limited continuous intake.³¹ Therefore, achieving compliance in asymptomatic patients for prevention of structural damage might be an illusion and currently insufficiently substantiated by evidence.

At present, NSAIDs remain the cornerstone of first-line symptomatic treatment in patients suffering from AxSpA. It is self-evident that the decision whether to use NSAIDs continuously or on demand can be driven by multiple considerations, independent of a potential structure-modifying effect. Beside obvious symptom relief, this anti-inflammatory treatment might facilitate regular physiotherapy, which is also recognised as an important part of disease management. We may also not have grasped all the beneficial consequences of adequate control of chronic inflammation on the global burden of the disease. For example, Bakland *et al*³² showed more cardiovascular mortality, which was attributed to higher inflammatory load, in patients with AS who had taken NSAIDs less than once a month (OR 4.35). In another recent publication, Haroon *et al*³³ found a comparable ‘protective’ effect in a population-based study, as the use of NSAIDs and statins was associated with a decreased risk for vascular mortality in patients with AS.

The new data by Sieper *et al* challenge the notion that continuous anti-inflammatory treatment could have a potential structure-modifying effect, and prompt the clinician, who has to decide on a specific treatment strategy that involves NSAIDs, to be guided by symptoms and objective measures of inflammation.

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