Therapeutic Controversies in Spondyloarthritis

Nonsteroidal Anti-Inflammatory Drugs

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KEYWORDS

• Spondyloarthritis • Ankylosing spondylitis • ASAS
• Nonsteroidal anti-inflammatory drugs • Therapy

KEY POINTS

- Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a first-line therapy in axial spondyloarthritis, including ankylosing spondylitis.
- NSAIDs are highly effective in reduction of spondyloarthritis symptoms, including pain and stiffness.
- NSAIDs also reduce activity of systemic inflammation and might have a (small) impact on the activity of local inflammatory lesions in the sacroiliac joints and the spine.
- NSAIDs are able to reduce progression of structural damage in the spine if administered continuously, especially in patients who already have signs of structural damage (syndesmophytes) and elevated C-reactive protein and/or erythrocyte sedimentation rate.
- Cardiovascular, gastrointestinal, renal, and hepatic risks should be taken into account if an NSAID is administered, especially if a long-term and continuous treatment is anticipated.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered a first-line therapy in patients with axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS).[1] Beyond NSAIDs, only tumor necrosis factor α (TNF-α) blockers are currently available and effective for treating axial signs and symptoms of patients with active axSpA.[1,2] In contrast to rheumatoid arthritis, for example, disease-modifying antirheumatic drugs and corticosteroids play only a minor role in the management of axSpA, and only in the case of peripheral joint involvement.[3,4] In the joint ASAS (Assessment of SpondyloArthritis international Society) and EULAR (European League Against Rheumatism) recommendations for the management of axSpA, continuous treatment with NSAIDs

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is preferred for patients with persistently active symptomatic disease.[1] Continuous treatment with NSAIDs, however, raises safety issues. In a survey on the application of the ASAS/EULAR recommendations, 38% of European rheumatologists mentioned safety concerns as the main barrier for not using NSAIDs more consistently in patients with AS.[5]

This article discusses the current role of NSAIDs in axSpA treatment, including the risks and benefits of NSAID use and current trends for more individualized treatment strategies.

CLINICAL EFFICACY OF NSAIDS

So far, clinical trials with NSAIDs have only been performed in patients with established AS. However, based mainly on clinical experience, NSAIDs can be expected also to be highly effective in patients with nonradiographic axSpA (nr-axSpA), or those with axSpA who did not develop (yet) radiographic sacroiliitis. Thus, patients with nr-axSpA should be treated with NSAIDs similarly to those with AS.[6] Furthermore, NSAIDs also play an important role in the management of patients with predominant peripheral spondyloarthritis,[1,7] who show only a limited response to conventional disease-modifying antirheumatic drugs.[1]

High clinical efficacy of NSAIDs for treating axial signs and symptoms of active axSpA/AS was shown (against placebo and an active comparator) in several clinical trials with nonselective cyclooxygenase (COX) inhibitors and selective COX-2 antagonists.[8–11] All NSAIDs, independently from their COX selectivity, are nearly equally effective in their therapeutic doses for reducing pain and stiffness in axSpA/AS. Nonetheless, great individual variation exists in response to and tolerability of NSAIDs. In general, trying at least one NSAID, but frequently several others, is worthwhile in case one is found to be ineffective. This sampling is also frequently performed in clinical practice: more than 20% of 1080 patients with AS who participated in a survey on NSAID use in Germany reported that they used at least 2 different NSAIDs (5% used $\geq$3 NSAIDs) within the past year.[12]

Good or very good improvement of AS symptoms is usually reported by 60% to 80% of patients treated with NSAIDs.[7,8,11] In contrast, this level of response is only reported by approximately 15% of patients with chronic low back pain from noninflammatory causes.[7] Furthermore, a good response to NSAID treatment is also used as a diagnostic approach to differentiate chronic back pain of inflammatory origin from other causes.[7] Moreover, good pain control is necessary to perform physiotherapy effectively. Many clinical trials showed that reduction of pain and stiffness during NSAID therapy was associated with improvement of functional status in patients with AS measured using the Bath Ankylosing Spondylitis Functional Index.[8,11,13] Up to 35% of active patients with AS treated with a full dose of an NSAID can fulfill even the ASAS criteria for partial remission.[8,14] In a survey performed in Germany, almost 20% of the patients with AS reported complete pain control with NSAIDs, and another 60% of the patients reported a reduction in pain level from one-quarter to one-half.[12]

In most cases, NSAIDs reduce pain and stiffness rapidly, and a full effect can normally be observed after 48 to 72 hours. In some cases, a longer treatment period (up to 2 weeks) is necessary to achieve the complete anti-inflammatory and analgesic effect of an NSAID.[8] However, if a response is not experienced within 2 weeks, it is unlikely to occur with continued treatment.

To judge the therapeutic effect of an NSAID in a patient with axSpA/AS, a full therapeutic (inflammatory) dose is usually required. The dose and the intake frequency could be, however, adjusted based on the patient's symptom intensity. In some patients with AS, a moderate dose might be sufficient for long-term treatment,