The Role of Nonsteroidal Anti-inflammatory Medications and Exercise in the Treatment of Ankylosing Spondylitis

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Ankylosing spondylitis (AS) is a chronic systemic rheumatic disease that primarily affects the sacroiliac joints and spine. Even with the development of tumor necrosis factor-α inhibitors, which have revolutionized the treatment of this disease, the combination of nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and a life-long exercise program still form the first step in its management. Multiple clinical trials have addressed the efficacy and safety of both nonselective and selective NSAIDs. Gastrointestinal toxicity remains their major side effect, with increased concern about the potential of cardiovascular toxicity, especially with the selective cyclooxygenase-2 inhibitors. A specific set of recommendations has been proposed for the management of AS.

Introduction

Ankylosing spondylitis (AS) is a chronic systemic rheumatic disease that primarily affects the sacroiliac joints and spine. Its management has always been challenging. Nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise have been the mainstay of AS management for five decades. Even with the development of tumor necrosis factor-α (TNF-α) inhibitors, which have revolutionized the treatment of AS, NSAIDs, exercise, and physical therapy still form the first step in the management [1]. This combination of NSAIDs and nonpharmacologic modalities is needed to optimize the outcome of AS.

Boulos et al. [2] reviewed the literature for the evidence regarding the efficacy and safety of pharmacologic therapies available for the treatment of AS. Eight randomized clinical trials found nonselective NSAIDs and two randomized clinical trials found cyclooxygenase-2 (COX-2) selective NSAIDs to be superior to placebo for relief of pain and improvement in physical function. Twenty-nine randomized clinical trials of various NSAIDs showed comparable efficacy and safety.

Zochling et al. [3••] published specific recommendations for the management of AS as a combined effort of the Assessment in Ankylosing Spondylitis (ASAS) international working group and the European League Against Rheumatism (EULAR). Their final recommendations were based on the evidence available from the literature. They addressed, among other topics, the use of NSAIDs, selective COX-2 inhibitors, gastrointestinal-protective drugs, exercise, and physiotherapy. They also provided the strength of evidence for each of their specific recommendations [4].

The optimal treatment of AS should be chosen based on the extent and severity of the disease and general health status. The wishes of the patient also need to be taken into consideration. Patients should be followed closely during any type of treatment to monitor response to therapy and watch for the development of untoward side effects. Disease monitoring should include symptoms and signs, laboratory tests, and imaging. This should be guided by the clinical presentation and the ASAS core set [3••].

The Role of NSAIDs

NSAIDs are recommended as the first line of drug therapy for active AS patients with pain and stiffness. NSAIDs remain essential in the treatment of AS, as a significant number of patients respond to their administration [5–8] the traditional disease-modifying antirheumatic drugs are not effective in axial disease [9], and the new biologic drugs are expensive. All patients with AS must have failed

to show adequate therapeutic response to at least two different NSAIDs given for at least 3 months at maximal recommended or tolerated anti-inflammatory dose (unless NSAIDs have to be withdrawn due to intolerance, toxicity, or contraindications) prior to the use of anti-TNF therapy.

There is good quality evidence (level 1b) that supports the use of the conventional NSAIDs or selective COX-2 inhibitors to improve symptoms and decrease functional limitations in patients with AS [10–17]. NSAIDs need to be used regularly and in full therapeutic anti-inflammatory doses in order to obtain maximal benefits. Most patients experience significant improvement in back pain and stiffness within 48 hours of therapy with full-dose NSAIDs. Symptoms would typically recur within 2 days of discontinuing the NSAID [5–8]. In those with increased risk for gastrointestinal complications, the NSAID should be combined with a gastrointestinal-protective drug such as misoprostol, a prostaglandin E1 analogue, or one of the proton pump inhibitors. Alternatively, a selective COX-2 inhibitor can be used [18,19]. It remains controversial whether histamine type 2 receptor antagonists, sucralfate, and antacids are as protective against peptic ulcers, even though they reduce dyspepsia symptoms [19]. NSAIDs decrease axial and peripheral joint pain and improve function over a short period of time. Selective COX-2 inhibitors are also equally effective. Comparative studies of different NSAIDs did not show a clear therapeutic advantage of any one preparation, though there are variations in individual responses to different NSAIDs [10–16], as well as variations in their side effects profile and drug interactions [20].

The choice of an individual NSAID should be based on its potential efficacy, possible side effects, cost, compliance of the patient (less frequent regimen enhances compliance), individual response, and possible interactions with other medications. The choice of NSAIDs versus selective COX-2 inhibitors should be based on the patient's risk for development of gastrointestinal complications. The types of NSAIDs untoward events reported in the AS studies were similar to those reported in the other rheumatologic diseases studies. NSAIDs (and even selective COX-2 inhibitors) cause an increased risk of gastrointestinal bleeding, which is dose dependent [21], although selective COX-2 inhibitors have a lower risk of serious gastrointestinal events than traditional NSAIDs [22]. The cardiovascular toxicity related to all NSAIDs is of concern among health care professionals and patients. Although initially seen as a cardiovascular toxicity signal with rofecoxib [23,24•,25•], this has also been described in large trials of other selective COX-2 inhibitor preparations in various settings [26•–28•], with evidence suggesting that this is not restricted to selective COX-2 inhibitors but is possibly also an NSAID class effect [24•,25•]. In general, caution should be applied when prescribing any of these medications for patients with risk factors for cardiovascular disease.

In a recent survey by Zochling et al. [29] AS patients were generally rather satisfied with the efficacy of their therapy, but one quarter of them reported severe side effects, most commonly abdominal pain, headache and dizziness, and nausea. Almost 80% of the patients reported at least 50% reduction in their pain. The pain relief was complete in 19% of patients. It is important to note that at least 20% of patients taking NSAIDs report insufficient pain control and more than 40% change their NSAID due to lack of efficacy.

Wanders et al. [30•] recently conducted a randomized clinical trial comparing the efficacy of continuous therapy with an NSAID, usually celecoxib, to intermittent "on demand" use for AS. They demonstrated that continuous NSAIDs therapy retards radiographic disease progression at 2 years. It is the first study to show, in a prospective manner, a possible disease-modifying effect of continuous NSAIDs therapy. Ward [31••] has nicely editorialized the strengths and weaknesses of this study. Further studies are needed before NSAIDs can be labelled as disease-modifying drugs for AS.

NSAIDs are used for their analgesic effect and their anti-inflammatory effect in post-traumatic and postoperative situations, in addition to their effect in inhibiting heterotopic bone formation after hip arthroplasty [32]. Based mostly on animal studies, Beck et al. [32] cautions against their use in the presence of other risk factors such as smoking, diabetes mellitus, or peripheral arterial occlusive disease, which may adversely affect fracture healing.

The Role of Exercise and Physical Therapy

The nonpharmacologic therapy of AS includes patient education and regular exercise. The experts' consensus has been that nonpharmacologic and pharmacologic treatment modalities complement each other and that they are important in all stages of AS [3••], irrespective of disease duration and type of articular involvement (axial vs peripheral) [33]. The nonpharmacologic therapy improves function (level 1–2). The Cochrane review on the effectiveness of physiotherapy interventions in the management of AS has been updated by Dagfinrud et al. [34••]. Available evidence suggests that physiotherapy is beneficial for people with AS. However, it is still not clear which treatment protocol should be recommended. The best available evidence comes from randomized controlled trials, which have shown that physical therapy is cost-effective in this disease (level 1b) [35–38]. It has been demonstrated that an individual program of therapeutic exercise combined with patient education significantly improves function but not pain at 4 months compared with no intervention [22,37]. After the 4-month trial, this improvement in function can be maintained by minimal maintenance therapy.

Hidding et al. [38] compared group physical therapy and home exercises with home exercises alone after an

intensive training program for both groups, and they found that both intervention groups had equally significant improvement in pain and functioning. Patient global assessment of improvement and spinal mobility were found to be statistically higher in the group physiotherapy arm. Helliwell et al. [39] compared intensive in-patient physiotherapy, hydrotherapy with home exercises, and home exercise alone, but did not specify pain or function as separate outcome measures. There was significant short-term improvement in pain and stiffness in the in-patient treatment group at 6 weeks, but there was no difference among the three groups at 6 months. Analay et al. [40] compared an intensive group exercise program with unsupervised home exercise and found that neither pain nor function was significantly better in the group physiotherapy arm than in the home exercise arm. A home-based exercise and education package were not shown to improve pain or function compared with controls over 6 months [41]. However, a recent small randomized clinical trial of home exercise showed significant improvements after 8 weeks in both pain and function in young AS patients who had previously been sedentary [42].

Specific physical therapy modalities have not been as well studied in AS. In a controlled study, passive stretching has been shown to improve range of movement at the hip joint [43], but pain and function were not evaluated. Level 1b evidence supports spa therapy for physical functioning in AS patients over the period of 3 months but not longer, which was shown to be cost-effective [44,45]. Short-term intensive physical therapy and exercise has been shown to be effective on spine, hip, and shoulder mobility measurements [46]. Unsupervised recreational exercise helps alleviate pain and stiffness and improve function, as do specific back exercises in patients with AS, especially in younger individuals. This was shown in a cohort of 220 patients with AS; patients' health status improved when they did recreational exercise at least for 30 minutes daily and back exercises at least five times weekly [47]. A Korean study [48] (Level 3 evidence based on a cross-sectional study) showed that patients who exercise have significantly lower pain, greater perceived family support, and increased quality of life compared with their sedentary peers. A randomized clinical trial from Spain [49] evaluated the impact of a 4-month comprehensive protocol of strengthening and flexibility exercises versus conventional exercises for patients with AS on functional and mobility outcomes. Both groups showed an improvement in all the outcome measures, the Bath Ankylosing Spondylitis Metrology Index (BASMI) (tragus to wall distance, modified Schober test, cervical rotation, lumbar side flexion, and intermalleolar distance), the Bath Ankylosing Spondylitis Disease Activity Index (BASDI), and the Bath Ankylosing Spondylitis Functional Index (BASFI). In the control group, only the improvement in tragus to wall distance and lumbar side flexion was statistically significant. In the experimental group, the improvement in all the clinical measures of the BASMI and in the BASFI were statistically significant. The experimental group obtained a greater improvement than the control group in all the clinical measures of the BASMI and in the BASFI, except in tragus to wall distance.

A program of regular exercise should be implemented from the time of the diagnosis as an essential measure in managing AS patients. Patients should be instructed to perform specific exercises, which include spinal extension and deep breathing exercises twice daily; this would help retain a good posture with reasonable spinal mobility and chest expansion. It is important to instruct patients on proper posture upon walking, sitting and sleeping in bed. Patients should be advised to sleep on a firm mattress without a pillow or with a thin pillow to minimize the chances of development of spinal deformities. The patient should walk erect, keeping the spine as straight as possible. Physical activities that cause back muscles to strain, such as prolonged stooping or bending, should be avoided. Formal physical therapy sessions can be used to teach patients proper posture and suitable exercises. Patients should be encouraged to participate in regular swimming and/or hydrotherapy. Unfortunately, formal sessions of group physical therapy and hydrotherapy are still generally underutilized by both health care professionals and patients.

Conclusions

The management of AS requires pharmacologic and nonpharmacologic modalities for a better outcome. NSAIDs and physical therapy remain the first line of management despite the development of TNF-α inhibitors. A program of regular exercise should be prescribed once the diagnosis is made with specific instructions including spinal extension, deep breathing exercises, proper posture and gait. Physical therapy and life-long exercise along with patient education are important, regardless of disease duration or extent of disease, due to their benefit in improving function and quality of life while being cost-effective. It remains unclear which modality of physical therapy should be prescribed.

The literature provides evidence regarding the efficacy and safety of NSAIDs, both nonselective and COX-2 selective, for the relief of pain and improvement of physical function.

In patients with increased risk for peptic ulcer disease, the NSAID therapy needs to be combined with a gastrointestinal-protective drug, or a selective COX-2 inhibitor should be preferred. The choice of selective COX-2 inhibitors versus nonselective NSAIDs should be based on the patient's risk for gastrointestinal complications. Caution should be applied when prescribing any of these medications for patients with risk factors for cardiovascular disease.

There is preliminary evidence suggesting that continuous NSAID therapy retards radiographic disease

progression. However, further studies are needed before NSAIDs could be considered to have a possible disease modifying effect on AS.

There are now specific ASAS/EULAR recommendations for the management of AS, but the optimal treatment regimen should be individualized. The patient must have failed to show adequate therapeutic response to at least two different NSAIDs given over a period of at least 3 months at maximal recommended or tolerated anti-inflammatory dose prior to the initiation of anti-TNF therapy. Close follow-up is imperative to monitor response to therapy and watch for possible untoward effects.

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