
A systematic comparison of rheumatoid arthritis and ankylosing spondylitis: non-steroidal anti-inflammatory drugs

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) play different roles in the management of patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS). In RA there is minimal evidence that NSAIDs are able to alter the course of disease or prevent joint destruction and, therefore, they should mostly be used as a short-term bridging therapy. In contrast to RA, in AS NSAIDs are considered as a cornerstone of the treatment not only because of a high symptomatic efficacy, but also because they might even retard osteoproliferation and radiographic progression. Considering younger age of AS patients and lower prevalence of comorbidities, they are probably at lower risk for cardiovascular and gastrointestinal side effects of short- and long-term NSAID therapy in comparison to RA.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of sign and symptoms of musculoskeletal disorders including rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Inhibition of the enzyme cyclooxygenase (COX) that catalyses the conversion of arachidonic acid to prostaglandin G₂ and then to prostaglandin H₂ is the major mechanism of action of NSAIDs. COX exists in at least two isoforms, COX-1 and COX-2 (1). The role of a recently cloned third isoform still remains elusive. COX-1 is considered as a constitutive enzyme and is present in many cells, including platelets, cells of the gastric and intestinal mucosa, and endothelial cells. Production of COX-2 can be increased at sites of inflammation, due to the influence of pro-inflammatory cytokines and growth factors. The majority of NSAIDs (ibuprofen, diclofenac, indomethacin, etc.) realize their effects by inhibition of both

COX isoforms (non-selective NSAIDs). NSAIDs selectively inhibiting COX-2 (coxibs – celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, etc) were developed with the hope for a better safety profile, first of all, in regards to better gastrointestinal tolerability. However, increased incidence of thrombotic cardiovascular events (rofecoxib), liver toxicity (lumiracoxib), and severe allergic reactions (valdecoxib) arouse new safety concerns. As a result, to date the only one COX-2 selective NSAID (celecoxib) possesses an approved status in the US and two COX-2 selective NSAIDs (celecoxib and etoricoxib) are marketed in the EU.

Efficacy and safety of NSAIDs in rheumatoid arthritis

In the contemporary treatment of RA, NSAIDs play a limited role. Although they are usually the first drugs administered to patients with symptoms of arthritis reducing joint pain and swelling, there is only minimal evidence that NSAIDs are able to alter the course of RA or prevent joint destruction (2-4). Furthermore, various DMARDs, including the new biologics, and low dose glucocorticoids are so effective in controlling signs and symptoms and also in stopping or retarding erosive structural damage of bone that the main role of NSAIDs in the therapy of RA is a short-term bridging therapy. But even for acute early treatment, a moderately high dose of glucocorticoids given over a short period of time is probably more effective. At the same time long-term low-dose glucocorticoid therapy (in a daily dose of 5 mg or less) is probably safer than NSAID therapy with at least comparable efficacy. ACR guidelines for the management of rheumatoid arthritis underline indeed that NSAIDs should not be used as a sole treatment of RA (5). NSAIDs showed symptomatic efficacy in treating RA in a large number of clin-

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ical trials. Both non-selective NSAIDs and selective COX-2 inhibitors are significantly more effective than placebo as assessed by rates of ACR20 responders, number of tender and swollen joints, level of pain and patient global assessment in the short-term clinical trials (up to 12 weeks of therapy) (6–10). At the same time there were no significant differences in clinical efficacy between non-selective and COX-2 selective NSAIDs in patients with RA (6–11). However, there are no solid data about long-term efficacy of NSAIDs in RA and there are no results demonstrating the ability of NSAIDs to prevent or retard structural changes in RA.

Another group of factors precluding long-term use of NSAIDs in RA are side effects. Concerns about safety of long-term NSAIDs therapy have been clearly expressed in European Medicines Agency (EMA) and US Food and Drug Administration (FDA) statements. According to these recommendations the lowest effective dose for the shortest possible duration of treatment with both non-selective NSAIDs or COX-2 selective inhibitors should be used (12, 13). In general, patients with RA are nearly twice as likely as patients with osteoarthritis to have serious gastrointestinal complications from NSAID treatment (14). Several factors that increase the risk of NSAIDs-associated serious gastrointestinal events include age more than 60 years, previous history of ulcers and ulcer complications, concomitant use of glucocorticoids, anticoagulants and low dose (≤ 325 mg/day) aspirin, smoking, alcohol consumption, high doses of NSAIDs, concomitant use of 2 and more NSAIDs, and, possibly, *Helicobacter pylori* infection (15).

Until now it is not totally clear whether the use of COX-2 selective NSAIDs can reduce the risk of serious gastrointestinal events in comparison to non-selective NSAIDs. In four large arthritis trials (VIGOR, CLASS, MEDAL and TARGET) comparing COX-2 selective with non-selective NSAIDs, a rate of serious gastrointestinal events (symptomatic gastroduodenal ulcers and ulcer complications) of 0.67–2.1 per 100 patient-years for COX-2 selective inhibitors and 0.97–4.5 per 100 patient-years

for non-selective NSAIDs was shown (16–20). At the same time, the rate of complicated events only (bleeding, perforation, gastric outlet obstruction) was about 1 or less per 100 patient-years for both COX-2 selective and non-selective NSAIDs (with the only exception: 1.4 for naproxen) with a lower, although not always significant, rate for the COX-2 selective ones (16–20).

Regarding long-term continuous intake of NSAIDs, it is an important question whether there is at any specific time point or time period an increased risk of gastrointestinal events. Several case-control studies have suggested that the risk of NSAID-associated gastrointestinal complications is highest within the first 30 days of NSAID use (21). However, large and long-term randomized controlled studies (VIGOR, CLASS, MEDAL and TARGET) have indicated that the risk of serious NSAID-induced gastrointestinal complications appears to be cumulative and linear with constant hazard ratio over time (16–19).

Serious concerns about NSAIDs safety arose after publications indicating significant increase of thrombotic cardiovascular events in patients treated with selective COX-2 inhibitor rofecoxib (16, 22). Rofecoxib was voluntarily withdrawn by the manufacturer from the market, but the discussion about cardiovascular safety of NSAIDs is ongoing until now. In the meta-analysis by Kearney *et al.* (2006) COX-2 selective inhibitors were associated with a slightly but significantly increased relative risk (RR) of 1.42 (95% confidence interval (CI) 1.13 to 1.78, $p=0.003$) for serious cardiovascular events in comparison to placebo (23). An estimation of the RR for non-selective NSAIDs revealed that ibuprofen and diclofenac showed a similar RR with 1.51 (95% CI 0.96 to 2.37) and 1.63 (95% CI 1.12 to 2.37), respectively, in comparison to placebo. However, naproxen was the only NSAID with no increased RR (RR of 0.92 (95% CI 0.67 to 1.26) (23), which can probably be explained by the capacity of naproxen to inhibit platelet aggregation. These data were confirmed in the recent population-based study by Fosbol *et al.* (2009). In this study hazard ratios for death/myocardial infarction

were 1.01 (95% CI 0.96–1.07) for ibuprofen, 1.63 (95% CI 1.52–1.76) for diclofenac, 0.97 (95% CI 0.83–1.12) for naproxen, 2.13 (95% CI 1.89–2.41) for rofecoxib, and 2.01 (95% CI 1.78–2.27) for celecoxib (24). Thus, both non-selective and COX-2 selective NSAIDs are associated with a moderate increase of unfavourable cardiovascular events. Obviously, the individual cardiovascular risk depends on numerous factors such as age, pre-existence of cardiovascular risk factors, and the NSAID dose used. Moreover, RA itself is associated with substantial increase of cardiovascular risk, most probably due to persistent systemic inflammation (25). In the MEDAL study cardiovascular risk was especially low in younger patients and patients with low baseline cardiovascular risk, less than 1 event per 100 patient-years (26). Similarly, the number of cardiovascular events during treatment with lumiracoxib, ibuprofen and naproxen was lower in patients with no baseline cardiovascular risk and lower age in the TARGET study (27).

Another important question related to long-term NSAID therapy is whether there is an increased risk if treatment continues, for example, beyond 1 year. In the MEDAL trial only a proportional increase of CV events for both etoricoxib and diclofenac during all 36 months of study period has been shown, indicating constant CV risk over time (26).

Efficacy and safety of NSAIDs in ankylosing spondylitis

In contrast to RA NSAIDs play a crucial role in the management of AS and related spondyloarthritides. Disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids have only a limited role for peripheral arthritis in AS and are not effective for the axial manifestations. Current ASAS-EULAR recommendations for the management of AS suggest NSAIDs as a first-line drug treatment for symptomatic patients (28). Furthermore, a failure of previous treatment with NSAIDs should be documented before treatment with TNF-blockers can be started in active patients (29).

NSAIDs have been regarded as the cornerstone of pharmacological intervention for AS since phenylbutazone in

1949, which is still used for short-term treatment of highly active AS patients, and, subsequently, a second generation of NSAIDs led by indomethacin in 1965 were introduced into clinical practice. They reduce pain and stiffness rapidly and a full effect can normally be observed after 48-72 hours.

Several placebo-controlled trials investigating different NSAIDs convincingly showed positive results compared to placebo treatment (30-32). When AS patients are asked about the level of efficacy, when treated with NSAIDs, 70-80% report a good or very good improvement of their symptoms (32-34). In contrast, this level of response is only reported by about 15% of patients with chronic low back pain of non-inflammatory causes (34). Furthermore, a good response to NSAID treatment is also used in a diagnostic approach to differentiate chronic back pain in AS patients from other causes (34). Up to 15% of active AS patients treated with a full dose of an NSAID fulfil even the ASAS working group criteria for partial remission (32, 35). Finally, a maximal reduction of pain and stiffness is wanted in order to guarantee an optimal effect of physiotherapy.

Such a good efficacy suggests that the anti-inflammatory properties of NSAIDs are more relevant for the treatment of AS than the analgesic capacity. According to the ASAS improvement criteria for clinical trials a combination of the four domains inflammation (defined by morning stiffness), patient global assessment, back pain, and function differentiates best between NSAID and placebo (35), further supporting the concept that suppression of inflammation plays a major role for successful treatment of AS. Two recent AS studies could also show that the C-reactive protein (CRP) level was significantly decreased by a 12 week treatment with either diclofenac, naproxen or celecoxib (31, 33).

The high efficacy of NSAIDs in treating signs and symptoms raises the question whether NSAIDs are effective only for the reduction of symptoms or whether there might be an additional effect on the long-term outcome of AS. One earlier study reported a reduction of spinal

ossification after prolonged and continuous use of phenylbutazone in AS patients (36). More recent data support the concept that NSAIDs might indeed have an additional disease modifying effect. Patients who were treated with a daily dose of an NSAID continuously over two years showed significantly less radiographic progression in comparison to an on-demand treatment group, suggesting indeed that NSAIDs may have disease-controlling properties (37). More data are needed in the future to finally answer these questions. A currently ongoing trial in Germany, ENRADAS (Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis), was designed to test and possibly confirm the ability of NSAIDs to retard radiographic progression over two years of treatment in patients with ankylosing spondylitis.

Response to NSAIDs in patients with AS is dose-dependent. In some patients a moderate dose might be sufficient, while in others the highest tolerated dose of a single NSAID is necessary to achieve an optimal effect. On the group level, a higher efficacy could also be demonstrated for some of the outcome parameters in patients treated with a higher dose of celecoxib (400 mg vs. 200 mg per day) (33), etoricoxib (120 mg vs. 90 mg per day) (32), or meloxicam (22.5 mg vs. 15 mg per day) (30) in comparison to a lower dose.

Normally, an optimal effect of an NSAID is reached not later than after 1-2 weeks (32), but sometimes a longer treatment period is necessary to determine the optimal drug and dose (30). In some patients a full dosage is necessary to cover the entire day. If morning stiffness and pain at night are predominant symptoms a long-acting night time dose might be sufficient. The treating physician should be familiar with the optimal dose of at least two to three different NSAIDs because patients often respond to one NSAID but not to another one.

Thus, based on these considerations, NSAIDs used in the treatment of AS are not just analgesics but have a high anti-inflammatory and, possibly, also an anti-osteoproliferative potential. Consequently, at this moment the primary aim of treating AS patients

should be to enable the patient to be free of symptoms, while it has still to be determined whether NSAIDs should be used continuously even if patients are free of symptoms (comparable to disease modifying antirheumatic drugs treatment in rheumatoid arthritis).

However, this reasoning is in contrast to the current daily clinical practice, mostly because of concerns of possible side effects of continuous NSAIDs therapy. For example, 43% of German AS patients, taken care by rheumatologists, who had a constantly high disease activity index (BASDAI ≥ 4) over 1 year were not treated with NSAIDs every day (38). Additionally, in a survey among European rheumatologists, concerns about long-term toxicity were mentioned by 38% as the main barrier for not using NSAIDs more consistently (39).

To date, the results of three long-term (≥ 1 year) NSAID trials in AS are available. Although they were not specially powered to identify differences in rates of cardiovascular, gastrointestinal and other side effects, no toxicity signals different from those discussed above were reported and the incidences of adverse events or discontinuations due to adverse events did not differ significantly within treatment groups as well as between treatment and placebo groups (30, 32, 37). It is very important to emphasize that patients with AS, in comparison to patients with RA, are normally of younger age, have low prevalence of co-morbidities, usually do not use glucocorticoids concomitantly and, therefore, are most probably at lower risk for gastrointestinal and cardiovascular complications.

Conclusion

NSAIDs play different roles in the management of patients with RA and AS. In RA, NSAIDs are considered only as symptomatic drugs and should not be used as a sole treatment, because they do not prevent structural damage of joints. In AS, NSAIDs are drugs of first choice, not only because of the high symptomatic efficacy, but also because of the possible potential to retard radiographic progression in the spine (and maybe elsewhere) when used

continuously. Considering younger age of AS patients, lower prevalence of comorbidities and concomitant medication intake (e.g., glucocorticoids) in comparison to RA in general, patients with AS have probably lower risk of NSAID side effects during short- and long-term therapy. Thus, based on the available data, AS patients considered for long-term treatment with NSAIDs can and should be informed about the potential risk of such a treatment, which is relatively low (16).

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