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REVIEW

Benefits and Risks of Ankylosing Spondylitis Treatment With Nonsteroidal Antiinflammatory Drugs

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease with a prevalence of 0.1–1.2%, and it normally starts in the third decade of life. In contrast to other inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), the therapeutic options are limited and confined to nonsteroidal antiinflammatory drugs (NSAIDs) and, if this treatment fails, to tumor necrosis factor (TNF) blockers. Disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids have only a limited role for peripheral arthritis but are not effective for the axial manifestations. Consequently, recently reported recommendations for the management of AS suggested NSAIDs as a first-line drug treatment for patients with symptomatic disease (1). Furthermore, a failure of previous treatment with NSAIDs should be documented before treatment with TNF blockers can be started in patients with active disease. Thus, NSAIDs play a crucial role in the management of AS and related spondylarthritides.

Efficacy of NSAIDs in the treatment of AS

The NSAIDs have been regarded as the cornerstone of pharmacologic intervention for AS since phenylbutazone in 1949; subsequently, a second generation of NSAIDs led by indomethacin in 1965 was introduced into clinical practice. This generation of NSAIDs reduces pain and stiffness rapidly, and full effect can normally be observed after 48–72 hours. A variety of NSAIDs are currently available for the treatment of AS patients (Table 1).

Several placebo-controlled trials investigating different NSAIDs convincingly showed good results compared with placebo treatment (2–4). When AS patients are asked about the level of efficacy when treated with NSAIDs, 70–80% report good or very good improvement of their symptoms (2,5,6). In contrast, this level of response is reported by only ~15% of patients with chronic low back pain of noninflammatory causes (5). Furthermore, a good response to NSAID treatment is also used in a diagnostic approach to differentiate chronic back pain in AS patients from that resulting from other causes (5). Up to 15% of patients with active AS treated with a full dose of an NSAID fulfill even the ASsessment in Ankylosing Spondylitis (ASAS) International Working Group criteria for partial remission (2,7). Finally, a maximal reduction of pain and stiffness is wanted in order to guarantee an optimal effect of physiotherapy.

Such a good efficacy indicates that the antiinflammatory properties of NSAIDs are more relevant for the treatment of AS than is the analgesic potential of these drugs. According to the ASAS International Working Group improvement criteria for clinical trials, a combination of the 4 domains of inflammation (defined by morning stiffness), patient's global assessment, back pain, and function differentiates best between NSAID and placebo (7), further supporting the concept that suppression of inflammation plays a major role in the successful treatment of AS. Two recent AS studies also showed that the C-reactive protein (CRP) level was significantly decreased by a 12-week treatment with diclofenac, naproxen, or celecoxib (4,6).

Treatment trials with NSAIDs have only been

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Table 1. Main available NSAIDs in rheumatology practice*

NSAID	Half-life	Approved maximal daily dosage for arthritis in European Union†	Label for AS in European Union	Approved maximal daily dosage for arthritis in US	Label for AS in US
Diclofenac‡	~2 hours	150 mg	Yes	125 mg	Yes
Ibuprofen	1.8–3.5 hours	2,400 mg	Yes	3,200 mg	No
Indomethacin‡	~2 hours	150 mg	Yes	200 mg	Yes
Ketoprofen	1.5–2.5 hours	200 mg	Yes	300 mg	No
Naproxen	10–18 hours	1,000 mg	Yes	1,000 mg (up to 1,500 mg for short-term treatment)	Yes
Piroxicam	30–60 hours	20 mg	Yes	20 mg	No
Meloxicam	~20 hours	15 mg	Yes	15 mg	No
Aceclofenac	~4 hours	200 mg	Yes	Not approved in US at all	No
Phenylbutazone	50–100 hours	600 mg (for short-term treatment only)	Yes	Not approved in US at all	No
Celecoxib	8–12 hours	400 mg	Yes	400 mg	Yes
Etoricoxib	~22 hours	90 mg	No	Not approved in US at all	No

* NSAIDs = nonsteroidal antiinflammatory drugs; AS = ankylosing spondylitis.
† Exemplified by approval status in Germany.
‡ Diclofenac and indomethacin are also available in slow-release form of 75–100 mg per tablet, resulting in a duration of efficacy of ~12 hours.

performed in AS patients with radiographic evidence of sacroiliitis. However, it has become clear in recent years that inflammation of the sacroiliac joint or spine is often present for years before radiographic (chronic) changes do develop (5,8). Thus, these patients with "early" AS should be treated similarly, and it can be expected, currently mainly based on clinical experience, that such patients will respond at least equally well to NSAIDs (5). Furthermore, NSAIDs also play an important role in the management of predominant peripheral spondylarthritis (1,5), which shows only a limited response to conventional DMARD therapy (1).

The high efficacy of NSAIDs in treating signs and symptoms raises the question of whether NSAIDs are only effective for the reduction of symptoms or whether there might be an additional effect on the long-term outcome of AS. Investigators in one earlier study reported a reduction of spinal ossification after prolonged and continuous use of phenylbutazone in AS patients (9). 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 for 2 years showed significantly less radiographic progression compared with a group that received treatment on demand, suggesting that NSAIDs may indeed have disease-controlling properties (10). More data will be needed to finally answer these questions. It must also be determined whether such an effect is due to suppression of inflammation or instead to direct inhibition of osteoblast activity (11).

Dosing of NSAIDs should be adjusted to the patient's symptoms. In some AS 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 higher doses of celecoxib (400 mg/day versus 200 mg/day) (6), etoricoxib (120 mg/day versus 90 mg/day) (2), or meloxicam (22.5 mg/day versus 15 mg/day) (3).

Normally, an optimal effect of an NSAID is reached not later than after 1–2 weeks (2), but sometimes a longer treatment period is necessary to determine the optimal drug and dose (3). In some patients a full dosage is necessary to cover the entire day. If morning stiffness and pain at night are the predominant symptoms, a long-acting night time dose might be sufficient. The treating physician should be familiar with the optimal dose of at least 2–3 different NSAIDs, because patients often respond to one NSAID but not to another.

Thus, based on these considerations, NSAIDs used in the treatment of AS not only are analgesics but also have a high antiinflammatory potential and, possibly, an antiosteoproliferative potential. Consequently, at this time the primary aim of treating AS patients should be to eliminate their symptoms, while it still has to be determined whether NSAIDs should be used continuously even if patients are free of symptoms (comparable with DMARD treatment in RA).

However, this reasoning is in contrast to current daily clinical practice, mostly because of concerns of possible side effects of continuous NSAID therapy. For

example, 43% of German AS patients, under the care of rheumatologists, who had a constantly high disease activity index (Bath Ankylosing Spondylitis Disease Activity Index ≥4) (12) for 1 year were not treated with NSAIDs every day (13). Additionally, in a recent survey among European rheumatologists, concerns about long-term toxicity were mentioned by 38% as the main barrier to using NSAIDs more frequently (14). Concerns about safety of long-term NSAID therapy have also been expressed in European Medicines Evaluation Agency and US Food and Drug Administration (FDA) statements. According to these recommendations, the lowest effective dose for the shortest possible duration of treatment should be used with either nonselective NSAIDs or cyclooxygenase 2 (COX-2)–selective inhibitors (15,16).

Thus, exact knowledge about potential side effects of long-term treatment (and, in many patients, continuous treatment as well) with NSAIDs is necessary to allow the treating physician—and also the patient—to assess the benefit:risk ratio. A discussion of these side effects is especially important, because AS is probably the only chronic rheumatic disease in which continuous treatment with NSAIDs is medically justified, given their high clinical efficacy and given the absence of pharmaceutical alternatives (except for TNF blockers). In contrast, in diseases such as RA and osteoarthritis (OA), NSAIDs are considered only for symptom relief, and alternative options are available.

Side effects of NSAID therapy

In the NSAID studies in AS patients, only relatively small numbers of patients were treated, mostly for short periods of time. Therefore, information regarding side effects is rather limited if one looks at only those studies. Very good data regarding side effects of NSAIDs have recently become available from the conduction of large long-term studies assessing the efficacy and the safety of COX-2–selective inhibitors in comparison with nonselective NSAIDs and, in a few studies, also in comparison with placebo. In this review we have concentrated on reported studies with treatment duration of at least 1 year. Furthermore, in nearly all these studies a high dose of NSAIDs was used. Thus, sufficient information is available for assessing the side effects if AS patients are treated continuously with a full dose of an NSAID.

Specific side effects. *Cardiovascular.* Triggered by the observed cardiovascular side effects of rofecoxib, which was subsequently withdrawn from the market, a discussion was started to address the questions of whether there is a difference regarding the risk of cardiovascular disease among the COX-2–selective drugs, whether there is a difference between COX-2–selective and –nonselective NSAIDs, and, finally, what the relative risk (RR) is compared with placebo.

In the long-term placebo-controlled trial with celecoxib (the APC [Adenoma Prevention with Celecoxib] study), a 2.8-fold excess in serious cardiovascular events was found in the group receiving 400 mg/day celecoxib, and a 3.4-fold increase was found in the group receiving 800 mg/day celecoxib (a dose not used in rheumatology practice) (17,18) (Table 2). In contrast, in 2 other long-term preventional trials, the PreSAP (Prevention of Spontaneous Adenomatous Polyps) and the ADAPT (Alzheimer's Disease Anti-Inflammatory Prevention Trial) studies, such an increased risk was not observed for 400 mg/day celecoxib (19,20). Celecoxib at 800 mg/day did not increase the risk of cardiovascular disease in comparison with the nonselective NSAIDs diclofenac and ibuprofen, as shown in the CLASS (Celecoxib Long-Term Arthritis Safety Study) trial (21,22) (Table 2). There are no long-term placebo-controlled trials of celecoxib with a daily dosage of 200 mg, but results of observational studies suggest that this dosage is not associated with an increased risk of cardiovascular disease (23).

Currently, there are no results available from long-term placebo-controlled studies of other COX-2–selective inhibitors such as etoricoxib or lumiracoxib. Data regarding their cardiovascular safety came from long-term studies with nonselective NSAIDs used as active comparators. In the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term [program]) study, 34,701 patients with RA and OA were treated either with 60 mg/day or 90 mg/day etoricoxib or with 150 mg/day diclofenac for up to 3 years. There was no significant difference in the rate of cardiovascular events (myocardial infarction, stroke, death from cardiovascular cause) between the etoricoxib groups and the diclofenac group (0.83 and 0.82 events, respectively, per 100 patient-years) (24). The cardiovascular safety of 400 mg/day lumiracoxib was evaluated in comparison with that of 1,000 mg/day naproxen and 2,400 mg/day ibuprofen in the large TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) (25) study, in which altogether 18,244 patients were treated for 12 months. Serious cardiovascular events occurred less frequently in the lumiracoxib group than in the ibuprofen group (0.59 and 0.74 events, respectively, per 100 patient-years) and more frequently in the lumiracoxib

Table 2. Serious cardiovascular events (myocardial infarction, stroke, and death from cardiovascular cause) in long-term trials of COX-2–selective inhibitors*

Study (ref.)	Duration, months	COX-2 inhibitor	Comparator	No. of events/total no. of patients (%)		Rate per 100 patient-years		RR (95% CI)
				COX-2 inhibitor	Comparator	COX-2 inhibitor	Comparator	
APC (17,18)	37	Celecoxib, 200 mg BID	Placebo	17/685 (2.5)	6/679 (0.9)	0.82	0.29	2.81 (1.11–7.08)†
		Celecoxib, 400 mg BID	Placebo	20/671 (3.0)	6/679 (0.9)	0.99	0.29	3.37 (1.36–8.35)‡
PreSAP (18,19)	37	Celecoxib, 400 mg QD	Placebo	21/933 (2.3)	12/628 (1.9)	0.86	0.72	1.18 (0.58–2.38)
ADAPT (20)	36	Celecoxib, 200 mg BID	Placebo	17/717 (2.4)	22/1,070 (2.1)	–	–	1.15 (0.62–2.16)
		Celecoxib, 200 mg BID	Naproxen, 220 mg BID	17/717 (2.4)	23/713 (3.2)	–	–	0.74 (0.40–1.36)
CLASS (21)	12	Celecoxib, 400 mg BID	Diclofenac, 75 mg BID	26/3,987 (0.7)	16/1,996 (0.8)	1.12	1.48	0.81 (0.44–1.51)
		Celecoxib, 400 mg BID	Ibuprofen, 800 mg TID	26/3,987 (0.7)	17/1,985 (0.9)	1.12	1.52	0.76 (0.41–1.40)
MEDAL (24)	36	Etoricoxib, 60/90 mg QD	Diclofenac, 75 mg BID	332/17,412 (1.9)	325/17,289 (1.9)	0.83	0.82	1.01 (0.87–1.18)
TARGET (25)	12	Lumiracoxib, 400 mg QD	Ibuprofen, 800 mg TID	19/4,376 (0.4)	23/4,397 (0.5)	0.59	0.74	0.83 (0.45–1.52)
		Lumiracoxib, 400 mg QD	Naproxen, 500 mg BID	40/4,741 (0.8)	27/4,730 (0.6)	1.10	0.76	1.48 (0.91–2.40)

* Some data (e.g., relative risk [RR]) were calculated by the authors on the basis of originally reported study results. COX-2 = cyclooxygenase 2; 95% CI = 95% confidence interval; APC = Adenoma Prevention with Celecoxib; BID = twice a day; PreSAP = Prevention of Spontaneous Adenomatous Polyps; QD = once a day; ADAPT = Alzheimer's Disease Anti-Inflammatory Prevention Trial; CLASS = Celecoxib Long-Term Arthritis Safety Study; TID = three times a day; MEDAL = Multinational Etoricoxib and Diclofenac Arthritis Long-term (program); TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial.
† $P < 0.05$.
‡ $P < 0.01$.

group than in the naproxen group (1.10 and 0.76 events, respectively, per 100 patient-years), but neither of the comparisons yielded a significant difference (Table 2).

In addition to these reports, a recent meta-analysis of short- and long-term trials compared COX-2–selective inhibitors and COX-2–nonselective NSAIDs with placebo treatment. COX-2–selective inhibitors were associated with a slightly but significantly increased RR of 1.42 (95% confidence interval [95% CI] 1.13–1.78) ($P = 0.003$) for serious cardiovascular events in comparison with placebo (26). An estimation of the RR for nonselective NSAIDs revealed that ibuprofen and diclofenac showed similar RRs of 1.51 (95% CI 0.96–2.37) and 1.63 (95% CI 1.12–2.37), respectively, in comparison with placebo. However, naproxen was the only NSAID with no increased RR (RR 0.92 [95% CI 0.67–1.26]) (26), which can probably be explained by the capacity of naproxen to inhibit platelet aggregation. Therefore, all NSAIDs, with the probable exception of naproxen, are associated with a slightly increased risk of cardiovascular disease.

Obviously, the individual risk of cardiovascular disease depends on numerous factors such as age, preexisting risk of cardiovascular disease, and the NSAID dose used. As shown in Figure 1, rates of serious cardiovascular events during NSAID treatment in the APC and the MEDAL studies were especially low in younger patients and in patients with low baseline risk of cardiovascular disease (<1 event per 100 patient-years) (17,24). It has to be stressed that AS is a disease of young people that starts normally in the third decade of life, and AS patients have a mean age of ~40 years in most of the reported treatment trials. Thus, the risk of cardiovascular disease is probably even lower than that shown for the groups age <60 years in Figure 1A or age <65 years in Figure 1B. Similarly, the number of cardiovascular events during treatment with lumiracoxib, ibuprofen, and naproxen was lower in patients with no baseline risk of cardiovascular disease and lower age in the TARGET study (25).

Currently, chronic systemic inflammation is recognized as a new risk factor for cardiovascular disease.

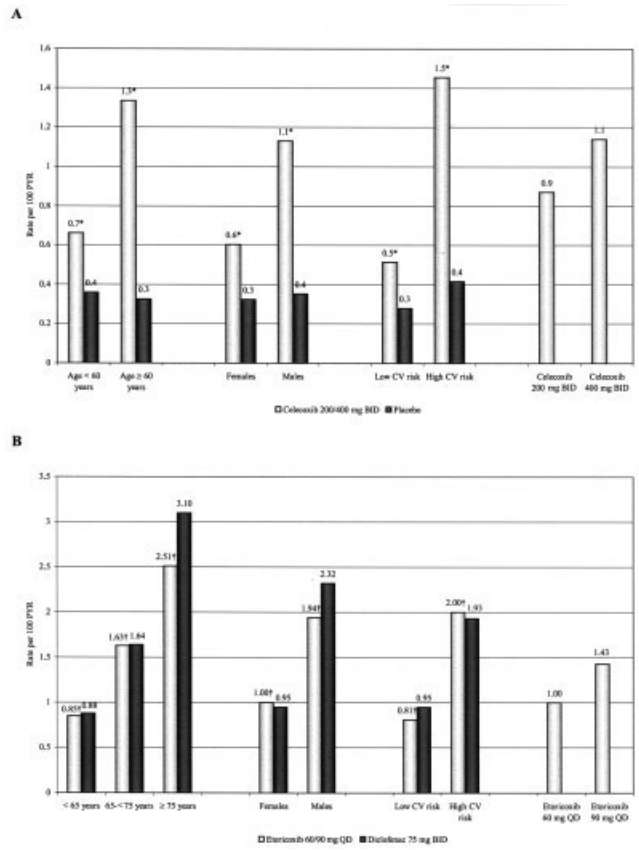

Figure 1. A, Rates of cardiovascular events (myocardial infarction, stroke, death from cardiovascular cause, hospitalization for heart failure) in the Adenoma Prevention with Celecoxib study in different patient subgroups. Rates were significantly higher only in the subgroups of patients with higher age and higher risk of cardiovascular disease (CV risk) within the celecoxib group (as calculated by the authors on the basis of the originally reported data). * indicates combined data from patients treated with 200 mg celecoxib twice a day (BID) and 400 mg celecoxib BID. **B,** Rates of all thrombotic cardiovascular events in the Multinational Etoricoxib and Diclofenac Arthritis Long-term program in different patient subgroups. Levels of significance for the differences between subgroups were not presented in the original report. † indicates combined data from patients treated with 60 mg etoricoxib once a day (QD) and 90 mg etoricoxib QD. PYR = patient-years.

One of the most sensitive markers of systemic inflammation, CRP, was found to be a strong independent predictor of major cardiovascular events (cardiovascular disease, myocardial infarction, stroke, peripheral vascular disease) in a number of prospective studies (27). Therefore, an effective antiinflammatory treatment in patients with chronic inflammatory disease can potentially reduce the risk of cardiovascular disease. In 2 recent studies, it was shown that the CRP level could be significantly reduced in AS patients treated with NSAIDs (4,6). Such an effect might at least partly counterbalance the small increase in the risk of cardiovascular disease in patients treated with NSAIDs.

Because long-term and continuous treatment of AS patients with NSAIDs is a relevant treatment option, it is an important question whether there is an increased risk if treatment continues, for example, beyond 1 year. In the APC study, divergence of Kaplan-Meier curves did not start before 12 months of treatment, resulting in significantly higher rates of cardiovascular events in the celecoxib groups after 36 months (17). In contrast, in the PreSAP study, which had nearly the same design as the APC trial, a proportional increase in the number of cardiovascular events was observed during all 36 weeks of celecoxib treatment (19). Similarly, the MEDAL trial showed only a proportional increase of cardiovascular events for both etoricoxib and diclofenac during all 36 months of the study period, indicating constant risk of cardiovascular disease over time (24).

Gastrointestinal (GI) side effects. GI toxicity, a well-known adverse effect during NSAID treatment, is related to inhibition of prostaglandin synthesis in the gastric mucosa and to some non–prostaglandin-dependent effects. Dyspepsia has been found to be increased in patients treated with NSAIDs, but it correlates only poorly with endoscopic ulcers and with clinical events such as ulcer bleeding (28). Up to two-thirds of long-term NSAID (especially nonselective) users have gastric lesions identified at endoscopy, and these are significantly reduced in patients treated with COX-2–selective NSAIDs (29).

However, the most important aspect of GI safety with NSAID treatment is the risk of serious events such as bleeding, perforation, or gastric outlet obstruction. Symptomatic ulcers are often also counted as an important outcome parameter in NSAID safety trials. The risk of GI events is clearly highlighted by the following statement of the US FDA from the year 2005 summarizing the reported studies: "Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk" (16). The background rate of serious GI events has been estimated in observational studies as 0.1–0.2% per 1 year in people not exposed to NSAID treatment (30). Thus, based on these indirect data, NSAID intake can

Table 3. Serious GI adverse events in long-term studies of NSAIDs (COX-2–selective inhibitors versus nonselective NSAIDs)*

Event type, study (ref.)	Duration, months	COX-2 inhibitor	Comparator	No. of events/total no. of patients (%)		Rate per 100 patient-years		RR (95% CI)
				COX-2 inhibitor	Comparator	COX-2 inhibitor	Comparator	
Complicated GI events plus symptomatic ulcers								
CLASS (22)	12	Celecoxib, 400 mg BID	Diclofenac, 75 mg BID	43/3,987 (1.05)	26/1,996 (1.30)	1.85	2.41	0.83 (0.51–1.34)
		Celecoxib, 400 mg BID	Ibuprofen, 800 mg TID	43/3,987 (1.05)	36/1,985 (1.76)	1.85	3.21	0.59 (0.38–0.92)†
MEDAL (32)	36	Etoricoxib, 60/90 mg QD	Diclofenac, 75 mg BID	176/17,412 (1.01)	246/17,289 (1.42)	0.67	0.97	0.71 (0.59–0.86)‡
TARGET (33)§	12	Lumiracoxib, 400 mg QD	Ibuprofen, 800 mg TID and naproxen, 500 mg BID	87/9,117 (0.95)	186/9,127 (2.04)	1.27	2.79	0.47 (0.36–0.60)‡
Complicated GI events only								
CLASS (22)	12	Celecoxib, 400 mg BID	Diclofenac, 75 mg BID	17/3,987 (0.43)	10/1,996 (0.50)	0.73	0.93	0.85 (0.39–1.86)
		Celecoxib, 400 mg BID	Ibuprofen, 800 mg TID	17/3,987 (0.43)	11/1,985 (0.55)	0.73	0.98	0.77 (0.36–1.64)
MEDAL (32)	36	Etoricoxib, 60/90 mg QD	Diclofenac, 75 mg BID	84/17,412 (0.48)	86/17,289 (0.50)	0.32	0.34	0.97 (0.72–1.31)
TARGET (33)	12	Lumiracoxib, 400 mg QD	Ibuprofen, 800 mg TID	10/4,376 (0.23)	33/4,397 (0.75)	0.31	1.06	0.30 (0.15–0.62)¶
		Lumiracoxib, 400 mg QD	Naproxen, 500 mg BID	19/4,741 (0.40)	50/4,730 (1.06)	0.52	1.41	0.38 (0.22–0.64)‡

* Complicated gastrointestinal (GI) events included bleeding, perforation, and gastric outlet obstruction. Some data (e.g., RR) were calculated by the authors on the basis of originally reported study results. NSAIDs = nonsteroidal antiinflammatory drugs (see Table 2 for other definitions).
† $P < 0.05$.
‡ $P < 0.001$.
§ Substudy separation was not possible for this outcome on the basis of reported data.
¶ $P < 0.01$.

increase the risk of serious GI events 5–10-fold. This calculation is consistent with results of a recent meta-analysis of 16 randomized controlled trials showing that the odds ratio (OR) for serious GI events is as high as 5.36 (95% CI 1.79–16.1) for NSAIDs (mainly nonselective) in comparison with placebo (31).

In 3 large trials comparing COX-2–selective NSAIDs with nonselective NSAIDs, rates of serious GI events (symptomatic gastroduodenal ulcers and ulcer complications) of 0.67–1.85 per 100 patient-years for COX-2–selective inhibitors and of 0.97–3.21 per 100 patient-years for nonselective NSAIDs were shown, with an RR in favor of COX-2 inhibitors that indicated a significantly lower risk of serious GI events in most comparisons (22,32,33) (Table 3). At the same time, the rate of complicated events only (without symptomatic ulcers) was ~1 or <1 per 100 patient-years for both COX-2–selective and –nonselective NSAIDs (the only exception was 1.41 per 100 patient-years for naproxen), with a lower (although not always significantly different) rate for the COX-2–selective NSAIDs (Table 3). Furthermore, in the 2 placebo-controlled long-term preventional trials APC and PreSAP, the relative risk for GI ulceration and hemorrhage was not increased for celecoxib (400 mg/day or 800 mg/day) compared with placebo treatment (19,34). However, the COX-2–selective NSAID rofecoxib (at 25 mg/day), which was withdrawn worldwide, was associated with a significantly higher rate of serious GI events (GI ulcers and complications) in comparison with placebo (35).

There are several factors that increase the risk of NSAID-associated serious GI events, such as age >60 years, 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 NSAIDs, and, possibly, *Helicobacter pylori* infection (36). Most of the reports of large studies do not give detailed

values for the risk of these subgroups compared with that of the whole group. Again, however, as discussed above regarding the risk of cardiovascular disease, AS patients are normally of younger age and are therefore most probably at lower risk for GI complications.

In the MEDAL study, proton pump inhibitors were able to decrease the rate of complicated events, even when given in combination with a COX-2–selective inhibitor. The rates of complicated events in the etoricoxib group were 0.38 per 100 patient-years among proton pump inhibitor nonusers and 0.20 per 100 patient-years among proton pump inhibitor users, while in the diclofenac group these rates were 0.36 and 0.27, respectively, per 100 patient-years (differences did not reach statistical significance) (32). These data were confirmed in another recent study in which proton pump inhibitor use resulted in statistically significant reduction of the gastroduodenal ulcer rate in patients taking COX-2–selective inhibitors as well as nonselective NSAIDs (37).

Regarding long-term continuous intake of NSAIDs in patients with active AS, an important question is whether there is an increased risk of GI events at any specific time point or during any specific time period. Several case–control studies have suggested that the risk of NSAID-associated GI complications is highest within the first 30 days of NSAID use (38). However, large and long-term randomized controlled studies (CLASS, MEDAL, and TARGET) have indicated that the risk of serious NSAID-induced GI complications appears to be cumulative and linear with constant hazard ratio over time (22,32,33).

Possible damage of the lower parts of the intestine (beyond the duodenum) by NSAID intake has also been a concern for some time. Goldstein et al observed mucosal lesions in the small intestine by video capsule endoscopy after 2 weeks of treatment in 7% of subjects treated with placebo, in 55% of subjects treated with 1,000 mg/day naproxen plus 20 mg/day omeprazole, but in only 16% of subjects treated with 400 mg/day celecoxib (39). There are also data indicating that NSAID use can cause ulceration and ulcer complications in the large bowel. Moreover, exacerbation of inflammatory bowel diseases (IBDs) and even de novo disease induction have sometimes, but not always, been reported as side effects of NSAID therapy (40). A recent study showed that 3 months of treatment with 60–120 mg/day etoricoxib was not associated with an increased rate of IBD flares (10.5%) compared with the rate in the placebo group (11.4%) (41). Thus, these early data indicate that COX-2–selective inhibitors might be less harmful for the lower intestine than nonselective NSAIDs, although the exact clinical relevance of these findings has yet to be determined.

Renal-related side effects and hypertension. Several renal-related side effects can be caused by treatment with NSAIDs, including fluid and electrolyte abnormalities, acute renal failure, nephrotic syndrome with interstitial nephritis, and renal papillary necrosis. Moreover, NSAIDs may adversely influence blood pressure control in individuals with hypertension. Most of these events are rare, and in general the nonselective NSAIDs and COX-2–selective inhibitors seem to have a similar safety profile.

Edema, related to fluid and sodium retention, occurs in up to 5% of NSAID-treated patients and is supposed to be caused primarily by inhibition of prostaglandin E_2 renal synthesis (42). Edema and fluid retention are usually mild. Although NSAIDs rarely cause clinical problems in patients with normal renal function, their use may result in renal hemodynamic decompensation in individuals with volume-contracted states or any clinical condition leading to decreased renal perfusion or diminished organ perfusion. Thus, elderly patients as well as patients with hypovolemia, chronic heart failure, cirrhosis, and chronic renal disease are at risk of acute deterioration of renal function related to NSAIDs (42). Results of a recent nested case–control population-based study showed that the OR for worsening of chronic heart failure was between 1.58 and 2.04 for treatment with various NSAIDs (43).

Acute renal failure is a rare complication. As shown in a recent population-based nested case–control study, risk for acute renal failure in patients age >65 years was highest within 30 days of NSAID treatment initiation (RR 2.05 [95% CI 1.61–2.60] in comparison with non–NSAID-treated population) and receded thereafter (44). A deterioration of renal function (as determined by urea nitrogen increase ≥40 mg/dl and/or serum creatinine increase ≥1.8 mg/dl) was found in 0.97% and 1.56% of patients treated with celecoxib or nonselective NSAIDs, respectively, in the CLASS trial (45). The discontinuation rate due to renal dysfunction was similar in patients receiving etoricoxib (between 0.4% and 2.3% in different treatment subgroups) and diclofenac (between 0.4% and 1.8%) in the MEDAL study (24).

All NSAIDs (COX-2–selective and –nonselective inhibitors) have approximately the same ability to elevate blood pressure. Moreover, all NSAIDs can potentially attenuate the effect of the majority of antihypertensive drugs (except, possibly, calcium channel

blockers). Meta-analyses have demonstrated that not only nonselective (46) but also COX-2–selective (47) NSAIDs are associated with an increase in mean arterial blood pressure of 3–5 mm Hg. Even such a small difference in blood pressure might increase the risk of cardiovascular events.

Liver-related side effects. For nearly all NSAIDs, it has been reported that they can cause an asymptomatic elevation in aminotransferases that is often not clinically relevant and that returns to normal upon cessation of treatment. No mechanism has been determined to explain how NSAIDs cause liver damage. It seems that the mechanism of injury is not linked to prostaglandin biosynthesis or to the ability of an NSAID to inhibit cyclooxygenase (48).

In their systematic review of randomized controlled trials, Rostom et al showed that rates of aminotranferase elevation >3-fold the upper limit of normal were similar among patients receiving ibuprofen, naproxen, meloxicam, and celecoxib (range 0.19–0.43%) and were close to the rate in patients receiving placebo (0.29%). In that study, only 2 NSAIDs were associated with significantly higher rates of aminotransferase elevation (rofecoxib [1.80%] and diclofenac [3.55%]). One liver-related death was reported among 51,942 patients taking NSAIDs (1.9 per 100,000 patients) (49). Recently, serious liver-related side effects were also reported for lumiracoxib (50). In most cases, NSAID-induced hepatotoxicity (especially fatal) is related to idiosyncratic reactions (48) and, therefore, seems to be unpredictable.

Skin side effects. Skin side effects of NSAID therapy are usually related to allergic or pseudoallergic reactions (51). The most common skin reactions such as urticaria with or without angioderma usually appear in susceptible subjects with hypersensitivity, and in the majority of cases they are rather mild and disappear after drug discontinuation. Severe and potentially life-threatening skin reactions are rare.

Side effects of long-term treatment with NSAIDs in AS trials. In discussing side effects of NSAIDs in AS trials, it is important to note that even long-term AS studies were not specially powered to recognize differences in rates of cardiovascular, GI, and other side effects. Nevertheless, in the 3 reported long-term trials (≥1 year) of NSAIDs in AS patients, no signs of toxicity different from those discussed above were observed, and the incidences of adverse events or discontinuations due to adverse events did not differ significantly within treatment groups or between treatment and placebo groups (2,3,10).

Conclusions

NSAIDs are highly effective for the treatment of AS patients. In a substantial proportion of patients, continuous therapy with NSAIDs is necessary to reach an optimal clinical effect. Sufficient data about side effects are available from long-term studies with continuous NSAID treatment to assess the benefit:risk ratio for these patients. Taking into account the relatively young age and the low comorbidity in AS patients, serious adverse events can be expected to occur in ~1% or <1% of patients per year if patients are treated with a full dose of an NSAID. An NSAID should be selected according to its efficacy in a given patient and according to the patient's risk profile. There are no clear recommendations regarding the frequency of safety investigations in patients receiving long-term NSAID therapy. We suggest performing urinalysis and checking liver enzymes, serum creatinine levels, and blood pressure the first month after starting NSAID therapy and then every 3–6 months thereafter. The patient should be informed about possible cardiovascular and GI symptoms and other adverse events.

AUTHOR CONTRIBUTIONS

Dr. Sieper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Rudwaleit, Sieper.
Acquisition of data. Song, Poddubnyy.
Analysis and interpretation of data. Song, Poddubnyy, Rudwaleit, Sieper.
Manuscript preparation. Song, Poddubnyy, Rudwaleit, Sieper.
Statistical analysis. Song, Poddubnyy.

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