

Patient benefit–risk in arthritis—a rheumatologist’s perspective

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Abstract

There is a range of pharmacological options available to the rheumatologist for treating arthritis. Non-selective NSAIDs or Cox-2 selective inhibitors are widely prescribed to reduce inflammation and alleviate pain; however, they must be used with caution in individuals with an increased cardiovascular, renal or gastrointestinal (GI) risk. The potential cardiovascular risks of Cox-2 selective inhibitors came to light over a decade ago. The conflicting nature of the study data reflects some context dependency, but the evidence shows a varying degree of cardiovascular risk with both Cox-2 selective inhibitors and non-selective NSAIDs. This risk appears to be dose dependent, which may have important ramifications for arthritis patients who require long-term treatment with high doses of anti-inflammatory drugs. The renal effects of non-selective NSAIDs have been well characterized. An increased risk of adverse renal events was found with rofecoxib but not celecoxib, suggesting that this is not a class effect of Cox-2 selective inhibitors. Upper GI effects of non-selective NSAID treatment, ranging from abdominal pain to ulceration and bleeding are extensively documented. Concomitant prescription of a proton pump inhibitor can help in the upper GI tract, but probably not in the lower. Evidence suggests that Cox-2 selective inhibitors are better tolerated in the entire GI tract. More evidence is required, and a composite end-point is being evaluated. Appropriate treatment strategies are needed depending on the level of upper and lower GI risk. Rheumatologists must be vigilant in assessing benefit–risk when prescribing a Cox-2 selective inhibitor or non-selective NSAID and should choose appropriate agents for each individual patient.

Key words: Gastrointestinal bleeding, Cox-2 selective inhibitors, NSAID, Celecoxib, Diclofenac, Ibuprofen, Cardiovascular risk, Renal risk, Ulcers, Proton pump inhibitors.

Introduction

Patients suffering from RA or OA require a combination of non-pharmacological and pharmacological treatment modalities to manage their condition.

As physicians, our aim is to control pain, optimize function and modify the disease process as much as we are able to. In RA, we aim to stop disease progression as well as reducing pain and maintaining functionality. In OA, although there is, as yet, no treatment to halt the processes of degeneration and inflammation, we can aim to reduce joint pain and inflammation while improving and maintaining joint function. We have a range of options

at our disposal to help us achieve these goals: ranging from exercise and weight loss to oral analgesics, IA therapies, DMARDs, including the biologicals and surgery.

When we meet an individual who is experiencing pain and loss of function due to arthritis, gastrointestinal (GI) care may not always be at the forefront of our minds. Yet, it is an important element to take into consideration in those patients to whom we prescribe treatment with NSAIDs including both non-selective NSAIDs and Cox-2 selective inhibitors.

As rheumatologists, we are constantly making decisions about which of these options represents the best treatment for an individual with arthritis. We have many factors to consider. To choose the most beneficial management option, we need to take into account comorbid disorders in the patient and constitutional factors such as obesity. The choice of treatment is affected by suitability, availability, practicality, safety and costs.

In this article, the benefit–risk associated with non-selective NSAIDs and Cox-2 selective inhibitors is reviewed and the balance between GI and other risks associated with these treatments is examined.

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Submitted 4 November 2009; revised version accepted 29 January 2010.

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Non-selective NSAIDs and Cox-2 selective inhibitors: their role in the management of arthritis

Both non-selective NSAIDs and the newer Cox-2 selective inhibitors are widely prescribed because of their proven ability to reduce inflammation and control pain, and thus optimize function. They are significantly more effective than acetaminophen in terms of managing pain and thus improving quality of life [1].

The EULAR guidelines of 2003 for OA in the knee recommend that NSAIDs are used if up to 4×1000 mg/day paracetamol (acetaminophen) is ineffective, moving to opioid analgesics (e.g. codeine and tramadol) with or without acetaminophen if NSAIDs prove ineffective [2]. Guidelines for RA similarly recommend the use of non-selective NSAIDs/Cox-2 selective inhibitors [3–5], as do the 2008 guidelines for OA from the National Institute for Health and Clinical Excellence in the UK [6].

Guidelines, of course, remind us that these treatments should be used with caution in individuals who may be at increased cardiovascular, renal and GI risk. This article reviews the evidence that rheumatologists may use in assessing GI risk in the context of the other risks in individuals with arthritis who are taking non-selective NSAID or Cox-2 selective treatments in order to maximize benefit for the patient.

Despite these risks, NSAIDs play a key role in the management of arthritis conditions. That they are more effective than placebo has been shown by several clinical trials. In one randomized control trial, which compared both celecoxib and diclofenac with placebo in 600 patients over a period of 6 weeks, it was shown that both the non-selective NSAID and the Cox-2 selective inhibitor were better than placebo in managing pain [7] (Fig. 1).

Cardiovascular risk: the evidence

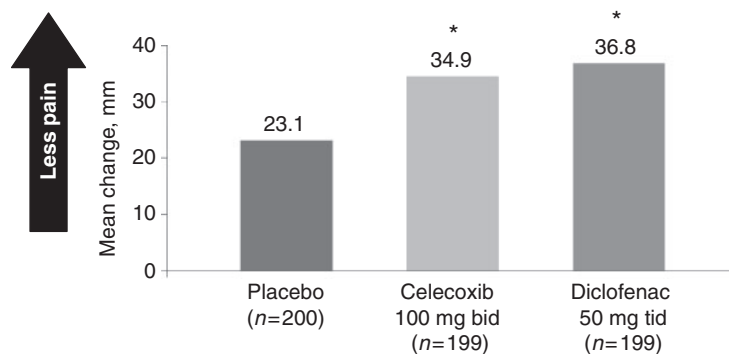
There has been much debate and analysis of cardiovascular risk associated with the use of Cox-2 selective

inhibitors and non-selective NSAIDs in the past decade. The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial [8] and the Adenomatous Polyp Prevention on Vioxx (APPROVE) trial [9] both showed an increase in cardiovascular risk with rofecoxib (50 and 25 mg/day, respectively) compared with naproxen (500 mg/day) or placebo, respectively. Rofecoxib was then voluntarily withdrawn from the market by the company. A whole range of concurrent studies looking at other Cox-2 selective inhibitors and non-selective NSAIDs also found increases in cardiovascular risk.

The Adenoma Prevention with Celecoxib (APC) trial showed a dose-related increase in the composite end-point of cardiovascular death, myocardial infarction (MI) or stroke with celecoxib compared with placebo over 3 years of treatment [10]. The objective of this trial was to test the efficacy and safety of celecoxib compared with placebo in reducing colorectal adenoma recurrence after polypectomy. The participants received either 200 mg celecoxib twice daily (bid) ($n=685$), 400 mg bid ($n=671$) or placebo ($n=679$). In this long-term trial, a safety committee adjudicated and categorized serious cardiovascular events. Of the participants, 77% were followed up for 37 months for adjudicated cardiovascular events. The hazard ratio (HR) for the composite end-point was 2.3 (95% CI 0.9, 5.5) in patients taking 200 mg bid and 3.4 (95% CI 1.5, 7.9) in patients taking 400 mg bid. There were also significant rises in systolic blood pressure levels in both dose groups at 1 and 3 years. These were as follows: 200 mg bid: 1 year, 2.0 mmHg; 3 years, 2.6 mmHg; 400 mg bid: 1 year, 2.9 mmHg; 3 years, 5.2 mmHg.

However, there are conflicting data reported in the literature: in a national case-control study from Finland, Helin-Salmivaara *et al.* [11] set out to evaluate the risk of first MI associated with the use of NSAIDs in the general population. Over 33 000 patients with first-time MI were identified and the authors found an increased risk of first-time MI with rofecoxib and etoricoxib but not celecoxib. They also found an increased risk with diclofenac, indomethacin, ibuprofen and naproxen.

Fig. 1 Mean change in patients' assessment of pain (measured on visual analogue scale) following treatment for 6 weeks with celecoxib 100 mg bid, diclofenac 50 mg tid or placebo [6]. *change significantly better than placebo ($P < 0.001$). Adapted from McKenna *et al.* [7].



In 2006, an analysis of non-selective NSAIDs showed that they too may be associated with cardiovascular (CV) risk. McGettigan and Henry [12] conducted a systematic review of observational studies in which they examined cardiovascular (primarily MI) risk of Cox-2 selective inhibitors and non-selective NSAIDs. They looked at 17 patient-control and six cohort studies in a total of nearly 1 million patients, and found that CV risk was increased with rofecoxib as well as with diclofenac, indomethacin and probably meloxicam. Rofecoxib risk was increased at low and high doses, and was evident during the first 30 days of use as well as with long-term treatment. Their analysis showed that there was neither increased nor decreased risk with naproxen, which had previously been thought to be cardioprotective. Although the relative risk (RR) for ibuprofen was not statistically significantly increased compared with that for naproxen, the lower bound of its 95% CI approached 1 (RR 1.07; 95% CI 0.97, 1.18), which suggests a level of risk (Table 1). In the review, celecoxib showed an increased risk at a dose >200 mg/day, while risk at 200 mg/day was not increased.

At the same time, another meta-analysis looked at differences in cardiovascular outcomes between randomized clinical trials in non-selective NSAIDs and Cox-2 selective inhibitors. This analysis also found similar increased risks in cardiac events between these agents (with the exception of naproxen), though there was some suggestion that Cox-2 selective inhibitors actually had more heterogeneity in cardiovascular risk than the non-selective NSAIDs [13].

Further evidence that both non-selective NSAIDs and Cox-2 selective inhibitors are associated with an increased risk of cardiovascular events comes from a

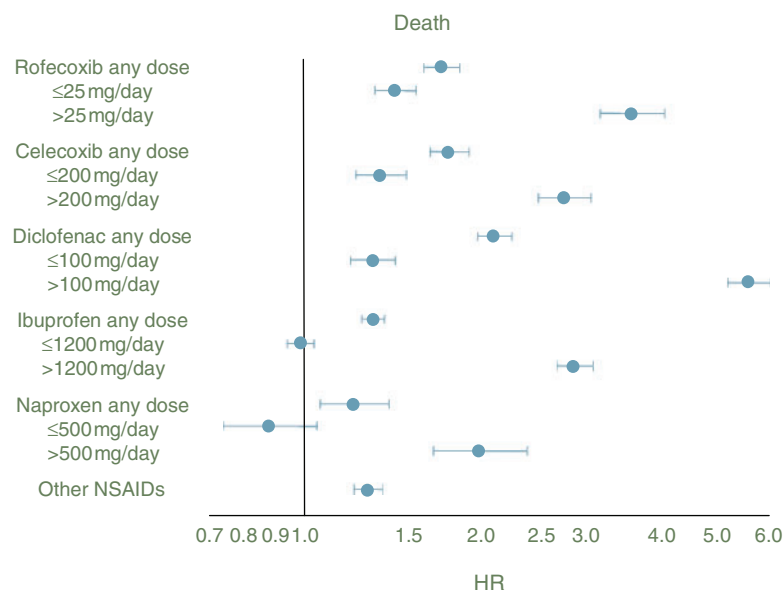
study of 107 092 patients with chronic heart failure, of whom approximately one-third had a history of NSAID use [14]. The HRs for death in patients using specific NSAIDs ranged from 1.22 (95% CI 1.07, 1.39) with naproxen (all doses) to 2.08 (95% CI 1.95, 2.21) with high-dose diclofenac (Fig. 2). With celecoxib (all doses), the HR was 1.75 (95% CI 1.63, 1.88). NSAID use was also associated with dose-dependent increases in the risk of death or hospitalization for MI or heart failure.

Although studies such as these have consistently demonstrated an increased cardiovascular risk associated with NSAID use, the issue remains complex. One recent study suggests that in certain situations, NSAIDs are not associated with an increased risk, and could even be cardioprotective. In this small study of 923

Table 1 RR of cardiovascular events with Cox-2 selective inhibitors and non-selective NSAIDs in a systematic review of 17 patient-control and six cohort studies [11]

	RR (95% CI)
Cox-2	
Celecoxib	1.06 (0.91, 1.23)
Meloxicam	1.25 (1.00, 1.55)
Rofecoxib	1.35 (1.15, 1.59)
NSAID	
Naproxen	0.97 (0.87, 1.07)
Piroxicam	1.06 (0.70, 1.59)
Ibuprofen	1.07 (0.97, 1.18)
Indometacin	1.30 (1.07, 1.60)
Diclofenac	1.40 (1.16, 1.70)

Fig. 2 HRs and 95% CIs for the risk of death associated with NSAID use in patients with chronic heart failure. Adapted with permission from *Gislason et al.* [14]. Copyright © 2009 American Medical Association. All rights reserved.



patients with inflammatory polyarthritis, NSAID use was associated with a reduced risk of cardiovascular mortality [adjusted odds ratio (OR) 0.54; 95% CI 0.34, 0.86] [15]. However, these findings in a general practitioner population might be subject to confounding, e.g. by a tendency to avoid NSAID use in frail patients with existing cardiovascular disease [15].

In summary, emerging evidence shows that both non-selective NSAIDs and Cox-2 selective inhibitors are associated with varying degrees of cardiovascular risk. This risk appears to be dose dependent, and this may have important implications for patients who require long-term treatment with high doses of NSAIDs for OA or RA.

Renal risk

Both non-selective NSAIDs and Cox-2 selective inhibitors are associated with nephrotoxicity [16], which can range from fluid and electrolyte disturbances to overt renal dysfunction, renal papillary necrosis or nephrotic syndrome [17]. As a result, current guidelines recommend that NSAIDs should not be used in patients with severe renal insufficiency, and that caution is necessary in patients with hypertension, congestive heart failure, mild-to-moderate renal insufficiency or other conditions associated with decreased intravascular volume oedema [3, 16].

Although the renal adverse effects of non-selective NSAIDs have been well characterized, the risk associated with Cox-2 selective inhibitors is less well documented. Zhang *et al.* [18] investigated the RRs of renal adverse events associated with rofecoxib or celecoxib in a meta-analysis of 114 clinical trials, involving 116 094 patients, of whom 6394 (5.5%) had peripheral oedema, hypertension or renal dysfunction. The RRs for renal dysfunction or peripheral oedema in patients treated with rofecoxib were 2.31 (95% CI 1.05, 5.07) and 1.43 (95% CI 1.23, 1.66), respectively; in contrast, celecoxib was associated with a lower risk of renal adverse events, with RRs for renal dysfunction and peripheral oedema of 0.61 (95% CI 0.40, 0.94) and 1.09 (95% CI 0.91, 1.31), respectively [18]. The risk of renal adverse events associated with rofecoxib increased with both dose and duration of treatment. These findings suggest that there does not appear to be a class effect in terms of renal adverse events with Cox-2 selective inhibitors [18]. The same caution is needed for all non-selective NSAIDs as well as for all Cox-2 selective inhibitors.

GI risks

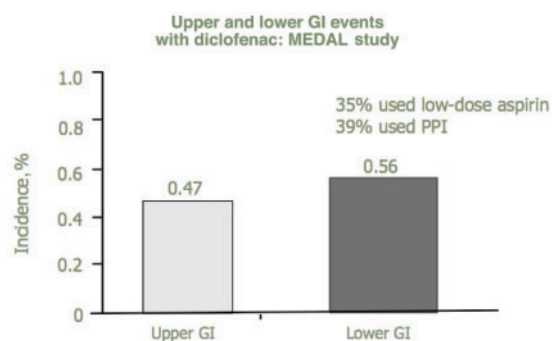
GI damage associated with NSAIDs has been extensively documented. Upper GI problems such as asymptomatic mucosal damage, abdominal pain or dyspepsia, and serious complications such as ulcers or bleeding are common findings in patients treated with NSAIDs [19]; endoscopic lesions have been reported to be present in 24% of patients [20], and up to 4% of patients each year experience complications [21]. Risk factors for NSAID-related

upper GI bleeding include high-dose NSAID treatment, longer duration of treatment, increasing age and a previous history of peptic ulcer [22].

Studies have consistently shown that Cox-2 selective inhibitors offer a more favourable GI toxicity profile than non-selective NSAIDs. For example, in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) study [23], which involved over 34 000 patients with OA or RA who were treated for up to 3.5 years, the incidence of upper GI adverse events was significantly lower with etoricoxib (60 or 90 mg/day) than with diclofenac (150 mg/day) (HR 0.69; 95% CI 0.57, 0.83; $P=0.0001$). Overall in the study, there were more lower GI events than upper GI events (Fig. 3). Similarly, in the Celecoxib Long-term Arthritis Safety Study (CLASS), a randomized controlled trial involving 8059 patients with OA or RA, the combined annualized incidence of upper GI ulcer complications was significantly lower in patients receiving celecoxib than in those receiving diclofenac or ibuprofen (0.44 vs 1.27%, $P=0.04$) in patients not taking aspirin [24]. This risk reduction was also seen in the SUccessive Celecoxib Efficacy and Safety Study-1 (SUCCESS-1), which compared celecoxib with diclofenac or naproxen in a double-blind controlled trial involving 13 274 patients (OR 7.02; 95% CI 1.46, 33.80; $P=0.008$) [25]. The reduction in risk with celecoxib in both CLASS and SUCCESS-1 was confounded by the inclusion of patients taking concomitant ASA; this is consistent with the finding that even low doses of ASA used for prophylaxis of vascular events are associated with an increased risk of peptic ulcer bleeding [26].

The findings of individual studies such as these are reinforced by a systematic review of randomized controlled trials comparing Cox-2 selective inhibitors with either non-selective NSAIDs or placebo [27]. This analysis showed that Cox-2 selective inhibitors were associated with significantly lower risks of gastroduodenal ulcer (RR 0.26; 95% CI 0.23, 0.30) and clinically important ulcer complications (RR 0.39; 95% CI 0.31, 0.50) than non-selective NSAIDs.

Fig. 3 Cumulative incidence of upper and lower GI events in 34 701 OA and RA patients treated with diclofenac or etoricoxib in the MEDAL Study [2]. Adapted from Laine *et al.* [23].



However, the GI toxicity of NSAIDs is not confined to the upper GI tract. Potential adverse effects of these agents in the lower bowel include mucosal inflammation and increased mucosal permeability, ulcerations, strictures, perforation and bleeding [28]. In some cases, the presenting sign may be anaemia due to occult bleeding.

Although such problems have been poorly characterized, accumulating evidence shows that they may account for a significant proportion of GI events in NSAID users. In the MUCOSA trial, which evaluated the impact of misoprostol treatment on upper GI events, lower bowel events were actually more common than gastroduodenal events, being present in 147 and 95 patients, respectively [29]. In a further study, ~40% of all serious GI adverse events were serious lower bowel complications such as obstruction, perforation or major bleeding [30]. More recently, a systematic review has reported that up to 71% of NSAID users have small mucosal breaks or small intestine injury, and that up to 88% of patients with lower GI bleeding were NSAID users [31]. Cox-2 selective inhibitors are associated with a smaller risk of lower GI complications than non-selective NSAIDs [31].

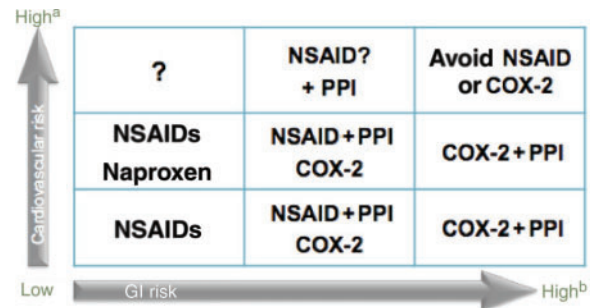
The importance of NSAID-related adverse events in the lower GI tract is highlighted by recent data showing that such events are associated with higher mortality, more prolonged hospitalizations and greater demands on health care resources than upper GI events [32]. The impact of NSAID-related lower GI events is likely to become an increasing clinical concern because the available evidence indicates that these adverse events are becoming more common as the incidence of upper GI events diminishes [32].

Implications for the choice of treatment

Clearly, NSAIDs can be associated with cardiovascular, renal and GI risks. How, then, might the benefits of NSAID therapy best be balanced against these risks?

Appropriate treatment strategies for patients at different levels of GI or cardiovascular risk are summarized in Fig. 4 [33]. In patients at risk of GI adverse events, with low or moderate cardiovascular risk, either a combination of a non-selective NSAID and a proton pump inhibitor, or a Cox-2 selective inhibitor is appropriate. The available evidence indicates that these two strategies have equivalent GI safety profiles [35], although there have been relatively few direct comparisons [34]. In patients at highest risk of GI events, but low or moderate cardiovascular risk, a combination of a Cox-2 selective inhibitor and a proton pump inhibitor may be considered. Evidence to support this approach comes from a randomized, double-blind study in which the incidence of recurrent bleeding was significantly lower in (*Helicobacter pylori*-negative) patients receiving celecoxib 200 mg bid. plus esomeprazole 20 mg bid than in those receiving celecoxib alone [35]. In view of the increased risk of cardiovascular events associated with some Cox-2 selective inhibitors and non-selective NSAIDs, these agents should be used

Fig. 4 Strategies to decrease cardiovascular and GI adverse events with NSAIDs or Cox-2 selective inhibitors. ^aAmerican Heart Association Guidelines define patients at risk of CV events as 10-year risk of CV event $\geq 10\%$ [36]. ^bHigh risk indicates patients with previous ulcer bleed at estimated rate of UGI complications of >28.8 cases per 100 patient years [37]. Adapted from *Lanas et al.* [32].



very cautiously in patients at high cardiovascular risk. In patients at high cardiovascular risk who are at moderate risk of GI adverse events, the combination of a non-selective NSAID and a proton pump inhibitor may be appropriate; in patients with both high cardiovascular risk and high GI risk NSAIDs should be avoided completely if possible.

While the use of a proton pump inhibitor may reduce the risks of NSAID-related upper GI adverse events, this strategy is unlikely to have any impact on the risk of lower GI events [31]. In view of the increased recognition of the latter events [32], and the evidence that the risk of such events is lower with Cox-2 selective inhibitors than with non-selective NSAIDs [31], there is a case for the use of Cox-2 selective inhibitors in preference to non-selective NSAIDs in patients at risk of lower GI events. However, this raises the question of how such patients can be identified; as noted above, the presence of anaemia may be a key factor in identifying lower GI bleeding in NSAID-treated patients. The introduction of a novel end-point named Clinically Significant Upper and/or Lower GI Events (CSULGIEs) captures adverse events throughout the entire length of the GI tract, and may provide important information on the NSAID-related risk of lower GI events.

Conclusions

NSAIDs remain an essential option for treating inflammation and pain, but clearly, as clinicians we should aim to minimize NSAID-related risks wherever possible. This may involve the use of a Cox-2 selective inhibitor, alone or with gastroprotective therapy, and the choice of an agent with a low risk of renal or cardiovascular adverse effects. We should be vigilant in identifying our patients' risks of adverse events, and in monitoring such risks, use all available data to improve outcomes for our patients.

Rheumatology key messages

- NSAIDs and Cox-2 selective inhibitors are associated with cardiovascular, GI and renal risk.
- The level of risk varies according to drug and dose.
- Individual patient risk needs to be assessed when prescribing anti-inflammatory treatments.

Acknowledgements

Medical writing assistance was provided by Just: Health PR Ltd, with financial support from Pfizer Inc. The author was fully involved in all stages of the preparation of the manuscript, which was based on a round table conference under the chairmanship of Professor Lanås and the author. A medical writer assisted with searches of the literature and collation of data and supported the author in the drafting of the text.

Supplement: This paper forms part of the supplement entitled 'Balancing gastrointestinal benefit–risk in individuals who are prescribed NSAIDs for arthritis.' This supplement was supported by an unrestricted grant from Pfizer Inc.

Disclosure statement: J.W.J.B. is an advisor to Pfizer and has received honoraria as a speaker from Pfizer and MSD.

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