When should COX-2 selective NSAIDs be used for osteoarthritis and rheumatoid arthritis?

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EVIDENCE-BASED ANSWER

Cyclo-oxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs) are as effective as acetaminophen and nonselective NSAIDs in treating of osteoarthritis, and are equally effective in reducing pain and inflammation and improving of joint function for patients with rheumatoid arthritis, when compared with nonselective NSAIDs. The COX-2 selective NSAIDs also have a better gastrointestinal safety profile in short-term (6–12 month) treatment (strength of recommendation [SOR]: **A**, based on meta-analysis of randomized controlled trials with patient-oriented outcomes).

However, with recent growing concern of the cardiovascular safety of COX-2 selective NSAIDs, it is imperative to select appropriate patients by considering benefit vs risks, which include serious gastrointestinal bleeding (**TABLE 1**), history of intolerance to nonselective NSAID, cardiovascular disease or associated risks, renal disease, patient's preference, and cost.

CLINICAL COMMENTARY

Nonselective NSAIDs with misoprostol or a PPI instead of COX-2 inhibitor is a reasonable strategy

Although celecoxib is an effective NSAID, rofecoxib and lumericoxib are the only COX-2 selective inhibitors that definitively reduce gastrointestinal (GI) ulcerations/complications compared with nonselective NSAID therapy.[1,2] However, neither of these are on the market. Data from the CLASS study showed no reduced risk of GI ulcerations/complications with celecoxib vs ibuprofen or diclofenac among patients receiving low-dose aspirin.[3] Low-dose aspirin reduces cardiovascular events for patients with moderate or high cardiovascular risk (Framingham scores ≥10%). Therefore, using nonselective NSAID therapy in combination with either misoprostol or a proton pump inhibitor (eg, omeprazole) instead of celecoxib, is a reasonable and proven strategy to provide NSAID therapy for patients on low-dose aspirin who are at high risk for NSAID-associated gastropathy.

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Evidence summary

A Cochrane review[4] (6 randomized controlled trials, N=1689, mean duration 5.8 weeks) assessed the efficacy and safety of acetaminophen in the management of osteoarthritis, comparing it with placebo and NSAIDs. Acetaminophen was superior to placebo in pain reduction and global assessment (number needed to treat [NNT]=2) with a similar safety profile. NSAIDs were better than acetaminophen in pain reduction, patient (NNT=6) and physician global assessment (NNT=17), but no better for functional improvement. Compared with nonselective NSAIDs, acetaminophen led to fewer withdrawals (number needed to harm [NNH]=20) and fewer GI adverse events (NNH=9), but

there was no statistical difference when compared with COX-2 selective NSAIDs.

Another Cochrane review[5] (26 randomized controlled trials) found that rofecoxib (Vioxx) was more effective than placebo (NNT=5), and equally effective with other NSAIDs in the management of osteoarthritis. They reported fewer GI adverse events (endoscopically observed gastric erosion and ulcers) with rofecoxib than with other NSAIDs—naproxen (Naprosyn), ibuprofen (Motrin), diclofenac (Cataflam), nabumetone (Relafen), diclofenac/misoprostol (Arthrotec), and nimesulide. However, the withdrawal rate due to adverse events and the increase in blood pressure and edema were significantly greater with rofecoxib than placebo at 6 weeks.

Two Cochrane reviews[6–7] confirmed the efficacy of celecoxib (Celebrex) and rofecoxib in treating of rheumatoid arthritis. One review included 2 RCTs (N=8734) with a placebo arm (8 weeks) and naproxen arm (9 months).[7] The rofecoxib groups (25 mg, 50 mg) had more responders than the placebo group (NNT=8 and 6 respectively). Compared with naproxen (1 g), no difference was seen in efficacy in the OMERACT outcomes (Outcome Measures for Rheumatoid Arthritis Clinical Trials), but all combined GI adverse events (perforation, ulcer, obstruction, bleeding, and all episodes of GI bleeding) were significantly reduced at 9 months (NNH=20). The withdrawals were the same in the 3 groups. Compared with placebo, the rofecoxib groups had similar incidence of elevated blood pressure and edema (NNH=50 and 100, respectively). Compared with the naproxen group, no difference was seen in renal adverse events, but total cardiovascular thrombotic events (NNH=200) and nonfatal MI (NNH=300) increased at 9 months in the 50 mg rofecoxib group.

Similar cardiovascular adverse events were reported in the APPROVE trial.[9] In this study, patients taking rofecoxib 25 mg daily for 18 months had increased total thrombotic events (MI, stroke, peripheral arterial and venous thrombosis, and pulmonary embolism) when compared with placebo (NNH=63). A recent study also raised the same concern of increased cardiovascular adverse events with celecoxib.[10] This study demonstrated an increase risk of cardiovascular events (combined death, myocardial infarction, stroke, and heart failure) for patients taking celecoxib 200 mg twice a day (NNH=77) or 400 mg twice a day (NNH=42).

TABLE 1

Prediction of serious gastrointestinal bleeding

RISK FACTORS PRESENT	RISK OF GI BLEEDING
0 factor	0.4 %
Any 1 factor	1.0 %
All 4 factors	9.0 %

Risk factors include age >75 years, history of peptic ulcer disease, history of gastrointestinal bleeding, history of cardiovascular disease

Source: Silverstein et al, *Ann Intern Med* 1995.[8]

Many patients taking low-dose aspirin for cardioprotection also frequently require treatment of pain and inflammation with a NSAID. Even low-dose aspirin (75 mg/d) is known to be associated with increased GI toxicity (ulcers and hemorrhages).[11] A recent double-blind, randomized placebo-controlled trial found that 12 weeks of treatment with a combination of low-dose aspirin and a COX-2 selective NSAID (rofecoxib) had more than twice the incidence of endoscopically confirmed gastric and duodenal ulcers, compared with aspirin alone, and no difference with a nonselective NSAID.[12] This has raised the safety concern of concomitant use of a COX-2 selective NSAID with low-dose aspirin.

Recommendations from others

The American Pain Society recommends that for patients with osteoarthritis, acetaminophen is the drug of choice for mild pain.[13] For moderate to severe pain and or inflammation, a COX-2 selective NSAID is the first choice, unless the patient is at significant risk for hypertension or renal disorder. For patients with active rheumatoid

FAST TRACK

Using a nonselective NSAID and misoprostol or a PPI instead of a COX-2 inhibitor is a reasonable and proven strategy

FAST TRACK

Select patients for COX-2 inhibitors by considering risks:

- CV disease
- GI bleeding
- renal disease
- patient preference
- cost

TABLE 2

Risk factors for upper gastrointestinal adverse events

Age ≥65 years
Comorbid medical conditions
Oral glucocorticoids
History of peptic ulcer disease
History of upper gastrointestinal bleeding
Anticoagulants

Source: American College of Rheumatology, *Arthritis Rheum* 2000.[12]

arthritis and moderate to severe pain with or without inflammation, a COX-2 selective NSAID should be used concomitantly with a disease-modifying antirheumatic drug (DMARD), unless contraindicated by existing uncontrolled hypertension and renal disease. It further recommends that for a person who is at risk for a cardiovascular event, an aspirin (75–160 mg/d), should be given along with a COX-2 selective NSAID.

The American College of Rheumatology recommends that a COX-2 selective NSAID should be considered for a person with osteoarthritis and pain not relieved by an adequate dose of acetaminophen (not to exceed 4 g/d).[14,15] The COX-2 selective NSAID is particularly advantageous for those who have higher risk factors for adverse GI events (**TABLE 2**). For a person with rheumatoid arthritis, in addition to DMARDs, NSAIDs (salicylates, nonselective NSAID, or COX-2 selective NSAID) should be used to reduce joint pain and swelling and improve joint function. Patients with additional risks for cardiovascular events should be cautioned about use of a COX-2 selective NSAID.

A recent AHRQ report on managing osteoarthritis underscores the importance of physician-patient partnership and patient's self management of osteoarthritis, and recommends acetaminophen (up to 4 g/day) as the drug of choice.[16] It further cautions the injudicious use of NSAIDs because of its greater GI toxicity when compared with acetaminophen, and its higher medical costs. ■

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