Lumiracoxib reduced ulcer complications compared with ibuprofen and naproxen in osteoarthritis and did not increase cardiovascular outcomes

Schnitzer TJ, Burmester GR, Mysler E, et al. **Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial.** Lancet. 2004;364:665-74.

Farkouh ME, Kirshner H, Harrington RA, et al. **Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial.** Lancet. 2004; 364:675-84.

QUESTION

In patients with osteoarthritis, what is the gastrointestinal and cardiovascular safety of the cyclooxygenase-2 (COX-2) inhibitor lumiracoxib compared with the nonsteroidal antiinflammatory drugs (NSAIDs) ibuprofen and naproxen?

METHODS

Design: Randomized controlled trial (Therapeutic Arthritis Research and Gastrointestinal Event Trial [TARGET]).
Allocation: Concealed.*
Blinding: Blinded (clinicians, patients, {data collectors, outcome assessors, and data analysts}†).*
Follow-up period: 52 weeks.
Setting: {849 centers in 29 countries}‡.
Patients: 18 325 patients ≥ 50 years of age (mean age 63 y, 76% women) who had osteoarthritis of the hip, knee, or hand (American College of Rheumatology preliminary classification criteria) or osteoarthritis of the cervical or lumbar spine (confirmed by radiography); had at least moderate pain; and were expected to need treatment for ≥ 52 weeks. Exclusion criteria were gastroprotective drugs (e.g., proton-pump inhibitors, misoprostol, and full-dose H_2-antagonists); anticoagulation therapy; active upper gastrointestinal ulceration in the past 30 days; upper gastrointestinal bleeding in the past year; history of gastroduodenal perforation or obstruction; history of myocardial infarction (MI), stroke, coronary artery bypass grafting, invasive coronary revascularization, or new-onset angina in the previous 6 months; electrocardiographic evidence of silent myocardial ischemia; severe congestive heart failure; serious hepatic, renal, or blood coagulation disorders; or severe anemia. Use of low-dose aspirin was allowed.
Intervention: Patients were stratified by low-dose aspirin use (75 to 100 mg/d) and nonuse and age (50 to 64, 65 to 74, and ≥ 75 y) and were allocated to lumiracoxib, 400 mg daily (n = 9156); ibuprofen, 800 mg 3 times/d (n = 4415); or naproxen, 500 mg twice daily (n = 4754) for 52 weeks.
Outcomes: Gastrointestinal: definite or probable upper gastrointestinal ulcer complications (clinically significant bleeding, perforation, or obstruction from erosive or ulcer disease). Cardiovascular: composite of confirmed silent MI and confirmed or probable clinical MI, ischemic or hemorrhagic stroke, and cardiovascular death. A combined gastrointestinal and cardiovascular endpoint was also assessed. Outcomes were assessed for comparisons between lumiracoxib and each NSAID and the NSAID data pooled.
Patient follow-up: 99.6% (all patients who received ≥ 1 dose of the study drug and had no outcome events within the first 48 h [modified intention-to-treat analysis]).

MAIN RESULTS

In all patients and in those not taking low-dose aspirin, fewer patients who received lumiracoxib had definite or probable upper gastrointestinal ulcer complications than did those taking ibuprofen or naproxen; no difference was seen among patients taking low-dose aspirin (Table). The rate of the composite cardiovascular endpoint did not differ between the lumiracoxib and NSAID groups (Table). Groups also did not differ when analyzed by aspirin use.

CONCLUSIONS

In patients with osteoarthritis, a greater reduction in ulcer complications was seen with the cyclooxygenase-2 inhibitor lumiracoxib than with the nonsteoridal antiinflammatory drugs ibuprofen and naproxen. Ulcer complication rates did not differ in patients taking low-dose aspirin. Cardiovascular outcomes were not increased with lumiracoxib.

Source of funding: Novartis Pharma AG.

For correspondence: Ulcer complications: Professor C.J. Hawkey, Institute of Clinical Research Trials Unit, University Hospital, Nottingham, England, UK. E-mail cj.hawkey@nottingham.ac.uk. Cardiovascular outcomes: Professor M.E. Farkouh, New York University School of Medicine, New York, NY, USA. E-mail michael.farkouh@med.nyu.edu. ■

*See Glossary.

†Information provided by authors.

‡**Hawkey CJ, Farkouh M, Gitton X, et al.** Aliment Pharmacol Ther. 2004;20:51-63.

Lumiracoxib (Lum) vs ibuprofen (Ibu) or naproxen (Nap) for osteoarthritis at 52 weeks[§]

Outcomes	Patient populations	Comparisons	Event rates	RRR (95% CI)	NNT (CI)
Definite or probable ulcer complications	All patients	Lum vs NSAIDs	0.32% vs 0.91%	65% (47 to 77)	170 (121 to 270)
		Lum vs ibu	0.23% vs 0.75%	70% (39 to 85)	192 (119 to 415)
		Lum vs nap	0.40% vs 1.06%	62% (36 to 77)	153 (98 to 310)
	Nonaspirin users	Lum vs NSAIDs	0.20% vs 0.92%	78% (61 to 88)	140 (102 to 208)
		Lum vs ibu	0.15% vs 0.82%	82% (55 to 93)	150 (96 to 275)
		Lum vs nap	0.25% vs 1.02%	75% (49 to 88)	131 (86 to 243)
	Low-dose aspirin users	Lum vs NSAIDs	0.69% vs 0.88%	21% (–52 to 59)	Not significant
		Lum vs ibu	0.51% vs 0.52%	0.9% (–219 to 69)	Not significant
		Lum vs nap	0.84% vs 1.17%	29% (–57 to 67)	Not significant
				RRI (CI)	NNH
Composite cardiovascular endpoint	All patients	Lum vs NSAIDs	0.65% vs 0.55%	18% (–19 to 72)	Not significant
				RRR (CI)	NNT
		Lum vs ibu	0.43% vs 0.52%	17% (–51 to 54)	Not significant
				RRI (CI)	NNH
		Lum vs nap	0.84% vs 0.57%	48% (–8.7 to 139)	Not significant

[§]Composite cardiovascular endpoint = confirmed or probable clinical myocardial infarction (MI), silent MI, stroke, or cardiovascular death; NSAIDs = nonsteroidal antiinflammatory drugs (ibuprofen and naproxen data pooled). Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

Ten key principles guided the design and execution of TARGET (1). First, the primary goal of the study was to robustly investigate the gastrointestinal safety of the new COX-2 inhibitor lumiracoxib using 2 NSAIDs, naproxen and ibuprofen, as the comparators. Second, the planned sample size was substantially greater than that recruited for previous outcome studies on other COX-2 inhibitors (specifically celecoxib and rofecoxib) (2, 3), in part to ensure proper examination of aspirin's influence as a co-prescription. Third, randomization was stratified by aspirin use. Fourth, a fixed-term design was implemented to retain patients through a 12-month, rather than a 6-month, enrollment, thus attempting to maintain power for the full duration of the study. Fifth, the patient retention strategy was reinforced by special symptom control measures to ensure a minimum 12-month protocol adherence of 60% (compared with 57% at 6 mo, and only 43% at 12 mo, in the celecoxib gastrointestinal outcomes study) (1, 2).

The sixth principle was to examine all drug-related effects and side effects with a study of adequate size to detect drug-related differences, particularly in thrombotic cardiovascular events. The seventh principle addressed potential thrombotic complications. By recognizing that all NSAIDs may not exert identical effects on thrombosis and bleeding, the investigators designed TARGET to include comparison drugs that are known to have a potent and a weak effect on platelets (naproxen and ibuprofen, respectively). The eighth principle focused on homogeneity of the target population (with inclusion of only patients with osteoarthritis), thereby providing a stable and predictable base for assessing drug-related and other influences. The ninth principle was to establish individual expert panels and prospective protocols for all of the major anticipated drug-related study outcomes. Finally, the size of TARGET was intended to ensure that even rare adverse events could be evaluated with reasonable confidence.

In adhering to their predetermined design principles, TARGET's investigators seem to have achieved their study objectives. Their sample size calculations were well rationalized and, with 18 325 patients (from 849 centers in 29 countries), the study was thought to have sufficient power to address both its primary and secondary endpoints. Outcome measures, randomization protocols, blinding, stratification (by age and low-dose aspirin use), and follow-up arrangements were reasonable. Categorization of definite, probable, and possible upper gastrointestinal (ulcer) complications was exhaustive (1), and criteria for potential cardiovascular, as well as renal and hepatic, events were appropriately selected.

The major conclusions reported by TARGET were that lumiracoxib showed a 3- to 4-fold reduction in ulcer complications compared with naproxen and ibuprofen, and the positive gastrointestinal outcome was not associated with an increased rate of serious cardiovascular events. It is important to note that the data showed no difference in the incidence of MI between lumiracoxib and either ibuprofen or naproxen, regardless of aspirin use. However, an accompanying editorial (4) expressed concern about "an excess of MIs with lumiracoxib compared with naproxen (18 [0.38%] vs 10 [0.21%]; hazard ratio 1.77 [95% CI 0.82 to 3.84]), although most of these events were nonfatal. In patients who were not taking low-dose aspirin, the hazard ratio climbed even higher." The editorial writers also drew attention to the exclusion in this study of "patients with known and significant pre-existing coronary artery disease" and, in disagreement with the study investigators, they commented that "the statistical power of TARGET is inadequate to detect significant differences in rates of MI."

To all intents and purposes, TARGET was a well-executed, methodologically rigorous study that carefully considered, and tried to avoid, the pitfalls encountered by earlier studies of COX-2 inhibitors (2, 3). And, at least in selected subgroups of patients, the TARGET data seem encouraging. Nonetheless, based on apparently valid criticisms of the study findings (4), clinicians must again be left with a lingering hesitancy about the place of even the newer COX-2 inhibitors in day-to-day practice. So, as before, appropriate drug selection for patients with arthritis depends primarily on clinical judgments that account for both individual patient status and the physician's interpretation of available "best evidence."

Lawrence Hart, MD
McMaster University
Hamilton, Ontario, Canada

References

1. **Hawkey CJ, Farkouh M, Gitton X, et al.** Aliment Pharmacol Ther. 2004; 20:51-63.
2. **Silverstein FE, Faich G, Goldstein JL, et al.** JAMA. 2000;284:1247-55.
3. **Bombardier C, Laine L, Reicin A, et al.** N Engl J Med. 2000;343:1520-8, 2 p following 1528.
4. **Topol EJ, Falk GW.** Lancet. 2004;364:639-40.