Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

THERAPEUTICS

Rofecoxib caused fewer endoscopic gastroduodenal ulcers than ibuprofen in osteoarthritis

Laine L, Harper S, Simon T, et al., for the Rofecoxib Osteoarthritis Endoscopy Study Group. **A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis.** Gastroenterology. 1999 Oct;117:776-83.

QUESTION

In patients with osteoarthritis (OA), does rofecoxib at doses of 25 and 50 mg/d cause fewer endoscopic gastroduodenal ulcers than ibuprofen?

DESIGN

Randomized (allocation concealed*), blinded (patients, clinicians, and outcome assessors),* placebo-controlled trial with 24-week follow-up.

SETTING

33 clinical centers in the United States.

PATIENTS

742 patients (mean age 62 y, 68% women, 83% white) ≥ 50 years of age with OA that had required nonsteroidal anti-inflammatory drugs (NSAIDs) for ≥ 6 months. Exclusion criteria were active ulcers; inflammatory bowel disease; previous upper gastrointestinal (GI) surgery; pyloric obstruction; erosive esophagitis; abnormal serum creatinine levels or clearance; fecal occult blood; unstable medical conditions; history of cancer or cerebrovascular events; bleeding diathesis; or need for anticoagulants, ticlopidine, corticosteroids, or aspirin. The intention-to-treat analysis included 93% of the patients.

INTERVENTION

Patients were allocated to 16 to 24 weeks of rofecoxib, 25 mg/d (n = 195); rofecoxib, 50 mg/d (n = 186); ibuprofen, 2400 mg/d (n = 184); or placebo (n = 177). Some other drugs were allowed (acetaminophen, non-NSAIDs, and an antacid [Gelusil]).

MAIN OUTCOME MEASURES

Endoscopic gastroduodenal ulcers ≥ 3 mm at 12 weeks (primary outcome) and 24 weeks (secondary outcome). A similar analysis was done with ulcers ≥ 5 mm at 12 and 24 weeks.

MAIN RESULTS

Patients in the rofecoxib groups and the placebo group had lower rates of endoscopic ulcers of both sizes than did patients in the ibuprofen group at 12 weeks (Table); patients in both rofecoxib groups also had lower rates of endoscopic ulcers of both sizes at 24 weeks ($P < 0.001$ for comparisons with ibuprofen). The rofecoxib and placebo groups did not differ for any outcome. Rofecoxib and ibuprofen had similar efficacy.

CONCLUSION

Rofecoxib, 25 or 50 mg/d, and placebo had lower rates of endoscopic gastroduodenal ulcers than did ibuprofen in patients with osteoarthritis.

Source of funding: Merck & Co., Inc.

For correspondence: Dr. L. Laine, GI Liver Division, Department of Medicine (LAC 12-137), University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033, USA. FAX 323-226-7573. ■

Endoscopic gastroduodenal ulcers ≥ 3 mm with rofecoxib and placebo vs ibuprofen for osteoarthritis†

Comparison at 12 wk	Event rates	RRR (95% CI)	NNT (CI)
Rofecoxib, 25 mg/d, vs ibuprofen	4% vs 25%	85% (68 to 93)	5 (3 to 7)
Rofecoxib, 50 mg/d, vs ibuprofen	7% vs 25%	73% 52 to 85)	5 (4 to 9)
Placebo vs ibuprofen	7% vs 25%	72% (49 to 85)	5 (4 to 10)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated using simple proportions with data provided by author.

COMMENTARY

Most clinicians are aware of the discovery of 2 forms of cyclooxygenase (COX): COX-1, the constitutional form, produces prostaglandins involved in physiologic functions; COX-2, an inducible form, produces inflammatory prostaglandins. The distinction between the 2 forms led to a search for drugs that inhibit COX-2, sparing COX-1, in the expectation that such agents would be free of the serious GI toxicity caused by conventional (nonselective) NSAIDs. The first 2 COX inhibitors, celecoxib and rofecoxib, enjoyed successful launches in North America before any publications were available to assess their effectiveness and toxicity. In late 1999, 4 full reports, including these studies by Laine and Simon and their colleagues and 2 others by Langman and Emery (1, 2), were published; accompanying editorials raised doubts about the true value of these agents (3, 4). Overall, the 4 reports describe the experience of > 7000 patients with RA or OA treated for 6 to 52 weeks (Table, next page).

Accepting that the COX-2 inhibitors are of similar efficacy to nonselective NSAIDs, the main clinical interest is in avoiding clinically important GI damage. During endoscopy, small and superficial ulcers that do not usually cause symptoms are frequently seen in the stomach and duodenum of patients taking conventional NSAIDs. The rates of these mainly nonclinical events with COX-2 inhibitors are approximately 25% of that with conventional NSAIDs. Physicians and patients are, however, more concerned with GI symptoms. Dyspepsia was reduced by only 2% to 3% with a COX-2 inhibitor. Although many patients have been studied in trials of COX-2 inhibitors, few instances of serious GI complications, such as bleeding or perforation, have occurred. The frequency of these potentially serious outcomes is approximately 1% with conventional NSAIDs; COX-2 inhibitors appear to provide a reduction of 0.5% to 1%. This means that 100 to 200 "typical" patients will have to be treated (NNT) with a COX-2 NSAID instead of a conventional NSAID to avoid 1 additional serious complication. In low-risk groups, the NNT for serious complications may be around 500 (4).

Many patients who are unable to tolerate several conventional NSAIDs will probably be switched to the newer agents, and some will benefit. Although not yet the topic of a published study, patients who are at high risk for serious GI complications (e.g., a history of ulcers or GI bleeding) and who need to take an NSAID will probably be the group for whom COX-2 inhibitors will be the most cost-effective. Considering the high cost of these new drugs and the widespread use of NSAIDs in most communities, the routine prescription of COX-2 inhibitors cannot be supported.

(continued on page 97)

Celecoxib was similar to naproxen for rheumatoid arthritis with fewer endoscopic ulcers

Simon LS, Weaver AL, Graham DY, et al. **Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis. A randomized controlled trial.** JAMA. 1999 Nov 24;282: 1921-8.

QUESTION

In patients with rheumatoid arthritis (RA), is celecoxib as efficacious (in anti-inflammatory and analgesic effects) and safe (in avoiding endoscopic upper gastrointestinal [GI] ulcers) as naproxen?

DESIGN

Randomized (allocation concealed*), blinded (patients, clinicians, and outcome assessors),* placebo-controlled, 12-week trial.

SETTING

79 U.S. and Canadian clinical sites.

PATIENTS

1149 patients (mean age 54 y, 73% women) who had RA (American College of Rheumatology criteria) for > 3 months. Inclusion criteria were age ≥ 18 years and receipt of stable medications; oral steroids and disease-modifying antirheumatic drugs were allowed. Exclusion criteria were active GI tract, renal, hepatic, or coagulation disorders; history of cancer or gastric or duodenal surgery; or recent or current esophageal or gastroduodenal ulcers or ≥ 10 erosions. 60% of patients completed the study; follow-up was > 99%.

INTERVENTION

Symptomatic RA was confirmed after nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics were stopped for 2 to 7 days. Patients were then allocated to celecoxib, 100 mg twice/d (n = 240), 200 mg twice/d (n = 235), or 400 mg twice/d (n = 218); naproxen, 500 mg twice/d (n = 225); or placebo (n = 231). NSAIDs, injectable corticosteroids, anticoagulants, and antiulcer drugs were prohibited.

MAIN OUTCOME MEASURES

Improvement in signs and symptoms of RA (8 measures), proportion of patients with endoscopic GI ulcers at 12 weeks, and adverse effects.

MAIN RESULTS

Patients in the celecoxib and naproxen groups had similar outcomes, with more improvements at 12 weeks in signs and symptoms of RA than with placebo (5 of 8 measures for the celecoxib, 100-mg group; 7 of 8 measures for the celecoxib, 200-mg and 400-mg groups; and 4 of 8 measures for the naproxen group). Similar patterns were shown at 2 and 6 weeks. Patients in the placebo group withdrew from the study more often because of treatment failure than did patients in the celecoxib or naproxen groups (P < 0.001 for all comparisons). The placebo and celecoxib groups did not differ for endoscopic GI ulcers; more patients in the naproxen group had ulcers than did those in the other 4 groups (P < 0.001), although endoscopy was done in only 57% of patients. The rate of total adverse effects was 19% for placebo; 28%, 25%, and 26% for the 100-mg, 200-mg, and 400-mg celecoxib groups, respectively; and 31% for naproxen.

CONCLUSIONS

Celecoxib was as effective as naproxen for improving signs and symptoms of rheumatoid arthritis with similar rates of adverse effects and withdrawals. Celecoxib was associated with fewer endoscopic gastrointestinal ulcers.

Source of funding: G.D. Searle & Co.

For correspondence: Dr. L.S. Simon, Beth Israel Deaconess Medical Center, 110 Francis Street, Suite 5C, Boston, MA 02215, USA. FAX 617-632-7795. ■

*See Glossary.

COMMENTARY *(continued from page 96)*

Summary of data from randomized trials of gastrointestinal (GI) events with cyclooxgenase-2 inhibitors vs conventional nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with rheumatoid arthritis or osteoarthritis*

Outcomes at 6 to 52 wk	Study	Comparison	Event rates	RRR (95% CI)	NNT (CI)
Endoscopic ulcers ≥ 3 mm	Simon†	Celecoxib vs naproxen	5% vs 26%	79% (66 to 87)	5 (4 to 8)
	Emery‡	Celecoxib vs diclofenac	4% vs 16%	73% (44 to 87)	9 (6 to 19)
	Laine§	Rofecoxib vs ibuprofen	5% vs 25%	79% (66 to 87)	6 (4 to 8)
Dyspepsia	Simon†	Celecoxib vs naproxen	4% vs 5%	21% (–5 to 59)	Not significant
	Emery‡	Celecoxib vs diclofenac	10% vs 13%	23%(–18 to 50)	Not significant
	Langman‖	Rofecoxib vs 3 NSAIDs	23.5% vs 25.5%	Data not available	Data not available
GI events leading to discontinuation of treatment	Simon†	Celecoxib vs naproxen	1% vs 2%	54% (–35 to 85)	Not significant
	Emery‡	Celecoxib vs diclofenac	6% vs 16%	64% (41 to 79)	11 (7 to 19)
	Laine§	Rofecoxib vs ibuprofen	8% vs 29%	73% (60 to 82)	5 (4 to 7)
	Langman‖	Rofecoxib vs 3 NSAIDs	5.7% vs 7.8%	Data not available	Data not available
Major GI event or major bleeding	Simon†	Celecoxib vs naproxen	0% vs 0.4%	100% (–25 to 100)	Not significant
	Emery‡	Celecoxib vs diclofenac	0% vs 1%	100% (37 to 100)	82 (33 to 2360
	Laine§	Rofecoxib vs ibuprofen	0.2% vs 1%	76% (–84 to 97)	Not significant
	Langman‖	Rofecoxib vs 3 NSAIDs	1.3% vs 1.8%	Data not available	Data not available

*RRR, NNT, and CI calculated from data in article or provided by author (Laine).
†Simon = Simon LA, Weaver AS, Graham DY, et al. JAMA. 1999;282:1921-8. (3 doses of celecoxib combined, 12-wk trial).
‡Emery = Emery P, Zeidler H, Kvien TK, et al. Lancet. 1999;354:2106-11. (24-wk trial).
§Laine = Laine L, Harper S, Simon T, et al. Gastroenterology. 1999;117:776-83. (24-wk trial with main analysis based on 12-wk data provided by author).
‖Langman = Langman MJ, Jensen DM, Watson DJ, et al. JAMA. 1999;282:1929-33. (systematic review of 8 studies of 6-wk to 1-y of duration, drug company–funded review. NSAIDs were ibuprofen, diclofenac, and nabumetone).

David Henry, MB, ChB
Patricia McGettigan, MD
University of Newcastle
Newcastle, New South Wales, Australia

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