Celecoxib was as effective as diclofenac plus omeprazole in reducing recurrent ulcer bleeding in arthritis

Chan FK, Hung LC, Suen BY, et al. **Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis.** N Engl J Med. 2002;347:2104-10.

QUESTION

In patients with arthritis at high risk for ulcer bleeding, is celecoxib noninferior (i.e., similar) to diclofenac plus omeprazole in reducing the risk for recurrent ulcer bleeding?

DESIGN

Randomized {allocation concealed*}†, blinded {clinicians, patients, outcome assessors, data collectors, and data analysts}†,* controlled trial with 6-month follow-up.

SETTING

The Endoscopy Center of the Prince of Wales Hospital in Hong Kong, China.

PATIENTS

290 patients who had rheumatoid arthritis, osteoarthritis, or other forms of arthritis; confirmed ulcer healing; a negative test result for *Helicobacter pylori* or successful eradication of *H. pylori*; and anticipated regular use of nonsteroidal antiinflammatory drugs (NSAIDs) during the trial. Exclusion criteria were concomitant use of anticoagulant agents or corticosteroids, gastric or duodenal surgery other than a patch repair, erosive esophagitis, gastric-outlet obstruction, renal failure, terminal illness, or cancer. 287 patients (99%) (mean age 68 y, 56% women) were included in the analysis.

INTERVENTION

Patients were allocated to celecoxib, 200 mg twice daily, plus omeprazole placebo daily (n = 144) or extended-release diclofenac 75 mg twice daily, plus omeprazole, 20 mg daily (n = 143) for 6 months. Patients were permitted to take antacids, acetaminophen or other non-NSAID analgesics, and disease-modifying antirheumatic drugs.

MAIN OUTCOME MEASURES

Recurrent ulcer bleeding (hematemesis or melena with ulcers [a circumscribed mucosal break ≥ 0.5 cm in diameter with a perceptible depth] or bleeding erosions [a flat mucosal break of any size that occurred in the presence of blood in the stomach] confirmed by endoscopy, or a decrease in the hemoglobin level ≥ 2 g/dL in the presence of endoscopically proven ulcers or bleeding erosions). Secondary endpoints were efficacy (patients' assessment of global disease activity and arthritis pain); recurrent ulcer bleeding if not taking low-dose aspirin (≤ 325 mg/d); and other adverse gastrointestinal, renal, and cardiovascular events.

MAIN RESULTS

Analysis was by intention to treat. The groups did not differ for recurrent ulcer bleeding (Table) or for any of the secondary endpoints.

CONCLUSION

In patients with arthritis at high risk for ulcer bleeding, celecoxib was noninferior to diclofenac plus omeprazole in reducing the risk for recurrent ulcer bleeding.

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*See Glossary.

†Information provided by author.

Celecoxib vs diclofenac plus omeprazole for arthritis at 6 months‡

Outcome	Celecoxib	Diclofenac plus omeprazole	Difference (95% CI)
Recurrent ulcer bleeding	4.9%	6.4%	−1.5% (−6.8 to 3.8)

‡CI defined in Glossary; difference is not statistically significant.

COMMENTARY

Serious upper gastrointestinal (GI) complications, such as bleeding or perforation, occur in about 1% to 1.5% of NSAID users annually. Previous GI events, older age, and steroid or warfarin use can substantially increase this risk. Furthermore, serious lower GI events occur at an annual incidence that approaches 1%.

2 strategies are commonly used to decrease complications, especially in high-risk patients: use of COX-2 specific inhibitors (coxibs) or co-therapy with proton-pump inhibitors (PPIs). Compared with standard NSAIDs, coxibs have been shown to decrease upper and lower GI complications and ulcer development (1, 2). Once-daily PPI co-therapy also decreases endoscopic ulcers. 2 randomized trials have shown that PPIs decrease recurrent ulcer bleeding in patients taking nonselective NSAIDs (3, 4).

The well-executed study by Chan and colleagues is the first to compare these 2 strategies. At first glance, the difference of only 1.5% between the 2 groups suggests that they are similar. However, in a noninferiority or equivalence study, the 95% CI of the difference should be carefully examined. The results are consistent with a relatively wide range of outcomes, from the coxibs being 7% better to PPI co-therapy being 4% better. The authors defined noninferiority as an absolute difference < 6% in rebleeding between therapies, but many clinicians would not consider this difference an indicator of equivalence or noninferiority when the rebleeding rate itself is 5% to 6%.

Other factors to consider when choosing a therapy include cost, whether PPIs are already prescribed (e.g., for reflux), the fact that PPIs decrease upper GI symptoms and coxibs decrease lower GI complications, and that compliance may be better with 1 medication (coxib) rather than 2 (PPIs plus NSAIDs).

In this study, the rebleeding rate at 6 months (5% to 6%) also suggests that neither strategy alone is adequate in very high-risk patients. For these patients, I recommend a coxib plus a PPI, although no data exist on the efficacy of this approach.

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References

1. **Bombardier C, Laine L, Reicin A, et al.** N Engl J Med. 2000;343:1520-8.
2. **Laine L, Connors LG, Reicin A, et al.** Gastroenterology. 2003;124:288-92.
3. **Chan FK, Chung SC, Suen BY, et al.** N Engl J Med. 2001;344:967-73.
4. **Lai KC, Lam SK, Chu KM, et al.** N Engl J Med. 2002;346:2033-8.