Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials

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Authors' objectives
To determine the efficacy, gastrointestinal safety, and tolerability of celecoxib (a cyclo-oxygenase 2 inhibitor) used in the treatment of osteoarthritis and rheumatoid arthritis.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from 1998 to 2001 using the search terms 'celecoxib', 'Celebrex' and 'SC-58635'. The authors also obtained the manufacturer reports for all industry-sponsored RCTs completed by 25 May 2000, which met their inclusion criteria. There were no publication restrictions.

Study selection
Study designs of evaluations included in the review
Double-blind RCTs were included.

Specific interventions included in the review
Only studies looking at celecoxib used at a licensed therapeutic dose for at least 12 weeks, compared with either placebo or another non-steroidal anti-inflammatory drug (NSAID) at a standard dose, were included. For the analysis of safety, data on doses of celecoxib above those recommended for treatment were also considered. The dosage levels of celecoxib used by the included studies were 200, 400 and 800 mg/day (which is above the recommended dose). The NSAIDs used as controls in the included studies were diclofenac (150 mg/day), naproxen (1,000 mg/day) or ibuprofen (2,400 mg/day). All of the included trials used a NSAID as the comparator, and five randomised controlled trials (RCTs) also had a placebo group.

Participants included in the review
Patients with active osteoarthritis or rheumatoid arthritis. The proportion of patients in the included trials who had a previous gastrointestinal ulcer ranged from 8 to 21%. The mean age of the included patients ranged from 54 to 63 years.

Outcomes assessed in the review
To be considered for inclusion, studies had to have reported efficacy, tolerability or safety data. The outcome measures reported in the review for efficacy were the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index (for pain, stiffness and physical function), the American College of Rheumatology (ACR-20) responder index, and joint scores (number of painful or tender swollen joints) for rheumatoid arthritis. For tolerability, the withdrawal rates for adverse effects (at 12 weeks) were reported. For gastrointestinal safety, the incidence of ulcers detected by routine endoscopy (at 12 and 24 weeks) and the incidence of symptomatic ulcers, bleeds, perforations and obstructions (up to 24 weeks) were reported.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Studies were assessed according to the following criteria: method of randomisation, concealment of allocation, blinding of trial investigators and patients, completeness of follow-up, and analysis according to intention-to-treat. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.
Data extraction
Summary outcome data were extracted from the original company trial reports. The data were extracted by one of the authors and checked by another. The authors combined multiple celecoxib treatment arms within trials that randomised to more than one dose. The following information was presented in a summary table: details of participants (disease, age, percentage with gastrointestinal ulcer), intervention and control (drug, dose and number randomised), duration, outcome measures for efficacy, and outcome measures used to measure upper gastrointestinal safety.

Methods of synthesis
How were the studies combined?
Separate meta-analyses were undertaken for each comparison and outcome. The efficacy data were analysed separately for osteoarthritis and rheumatoid arthritis, but the two diseases were combined for the analysis of tolerability and safety. Dichotomous data were summarised as a relative risk (RR) and pooled using the Mantel-Haenszel method. Continuous data were summarised as differences in means (MD) and pooled using the inverse variance method. If significant heterogeneity (p<0.1) was present, the data were also pooled using a random-effects model (DerSimonian and Laird). The results were presented with 95% confidence intervals (CIs). The impact of including unpublished studies was evaluated by a sensitivity analysis.

How were differences between studies investigated?
The authors investigated statistical heterogeneity and reported Q values.

Results of the review
Nine RCTs with 15,187 patients were included in the review.

All nine trials were considered to be of a high quality.

Efficacy.
Three trials were excluded from the analysis of efficacy as the results were not available separately for osteoarthritis and rheumatoid arthritis.

Rheumatoid arthritis (results of >1 favour celecoxib): the results here are for celecoxib versus placebo (2 trials, n=1,373) and celecoxib versus NSAID (3 trials, n=2,019), respectively. The RRs were 1.49 (95% CI: 1.25, 1.78; Q=0.06, p=0.81) and 1.04 (95% CI: 0.80, 1.36; Q=6.94, p=0.03) for ARC-20 improvement; 1.39 (95% CI: 1.21, 1.61; Q=0.37, p=0.54) and 1.09 (95% CI: 0.90, 1.32; Q=6.67, p=0.04) for improvement in the number of painful or tender joints; and 1.34 (95% CI: 1.14, 1.56; Q=0.35, p=0.25) and 1.02 (95% CI: 0.85, 1.22; Q=4.96, p=0.08) for improvement in the number of swollen joints.

Osteoarthritis (results of <0 favour celecoxib): in terms of the WOMAC composite score, the MD was -5.67 (95% CI: -7.45, -3.89; Q=2.26, p=0.32) for celecoxib versus placebo (3 trials, n=1,883) and 0.42 (95% CI: -1.45, 2.30; Q=4.36, p=0.11) for celecoxib versus NSAID (3 trials, n=1,853).

Tolerability (results of <1 favour celecoxib).
For withdrawals due to any adverse effects, the RR was 1.49 (95% CI: 1.15, 1.92; Q=1.08, p=0.90) for celecoxib versus placebo (5 trials, n=3,826) and 0.86 (95% CI: 0.72, 1.04; Q=10.86, p=0.15) for celecoxib versus NSAID (7 trials, n=5,425). For withdrawals due to gastrointestinal adverse effects, the RR was 1.68 (95% CI: 1.07, 2.65; Q=0.32, p=0.99) for celecoxib versus placebo (5 trials, n=3,826) and 0.54 (95% CI: 0.42, 0.71; Q=1.99, p=0.96) for celecoxib versus NSAID (7 trials, n=5,425).

Gastrointestinal safety (results of <1 favour celecoxib).
For ulcers detected by endoscopy, the RR was 1.53 (95% CI: 0.73, 3.21; Q=0.12, p=0.73) for celecoxib versus placebo (2 trials, n=933) and 0.29 (95% CI: 0.21, 0.41; Q=11.33, p=0.05) for celecoxib versus NSAID (5 trials, n=2,742). The trial of celecoxib versus NSAIDs (n=7,968) gave an RR of 0.55 (95% CI: 0.26, 1.14; Q=0.00, p=0.97) for serious upper
gastrointestinal events (bleeds, perforations, obstructions) at 24 weeks, and 0.61 (95% CI: 0.39, 0.96; Q=0.66, p=0.42) for serious upper gastrointestinal events plus ulcers at 24 weeks.

Benefits of celecoxib in patients receiving low-dose aspirin (results of <1 favour celecoxib).

For celecoxib versus NSAID (4 trials, n=2,022), the RR was 0.27 (95% CI: 0.16, 0.48; Q=17.79, p=0.001) for no prophylactic aspirin use and 0.49 (95% CI: 0.28, 0.86; Q=3.12, p=0.54) for prophylactic aspirin use.

Further results are available in the review in relation to WOMAC scores of pain, joint stiffness and physical functioning, as well as withdrawals due to adverse events.

Authors' conclusions
Celecoxib is as effective as other NSAIDs for the relief of symptoms of osteoarthritis and rheumatoid arthritis, and has significantly improved gastrointestinal safety and tolerability.

CRD commentary
The review addressed an appropriate question using clear inclusion/exclusion criteria. The literature search was fairly comprehensive and data were obtained from the manufacturers. Unpublished studies were considered for inclusion. It was not reported how the studies were selected for inclusion, or how many reviewers were involved in the process. The data were extracted by a single author and checked by a second; this would minimise any errors and reduce the likelihood of bias. The validity of the included studies was examined, but it was not stated if this was undertaken at the same time (and in the same way) as the data extraction. Relevant details of the included studies were presented in tabular format. Differences between the included studies were investigated statistically and the studies were pooled appropriately. However, the results of the celecoxib group from one trial (n=1,099) (included in the analysis of tolerability and prophylactic use of aspirin) was used twice in the meta-analysis, as it included two NSAID comparison groups (diclofenac and ibuprofen). The authors' conclusions follow from the results.

The first author has acted as a paid consultant to Pfizer and Pharmacia. The second author is employed on a fellowship funded by Pfizer. The third author is an employee of Pfizer.

Implications of the review for practice and research
The authors did not state any implications for further research and practice.

Funding
Pfizer; Searle.

Bibliographic details

PubMedID
12242171

Original Paper URL
http://bmj.bmjournals.com/cgi/content/full/325/7365/619

Other publications of related interest
These additional published commentaries may also be of interest. Symmons D. Review: celecoxib is as effective as other NSAIDs and leads to fewer gastrointestinal adverse effects. Evid Based Med 2003;8:51. Systematic review of celecoxib for osteoarthritis and rheumatoid arthritis [letters]. BMJ 2003;326:334-6.
Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /adverse effects; Arthritis, Rheumatoid /drug therapy; Aspirin /administration & dosage; Celecoxib; Cyclooxygenase Inhibitors /adverse effects; Gastrointestinal Diseases /chemically induced; Humans; Osteoarthritis /drug therapy; Pyrazoles; Randomized Controlled Trials as Topic /methods /standards; Sulfonamides /adverse effects; Treatment Outcome

AccessionNumber
12002008512

Date bibliographic record published
31/10/2003

Date abstract record published
31/10/2003

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.