A Randomized, Controlled, Clinical Trial of Etoricoxib in the Treatment of Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the efficacy and tolerability of the highly selective cyclooxygenase-2 (COX-2) inhibitor etoricoxib for the treatment of rheumatoid arthritis (RA).

Methods. A double blind, randomized, placebo and active comparator controlled, 12 week study conducted at 88 US sites. Eligible patients were chronic nonsteroidal antiinflammatory drug (NSAID) users with clinical worsening of RA upon withdrawal of prestudy NSAID. Patients received either placebo, etoricoxib 90 mg once daily, or naproxen 500 mg twice daily (2:2:1 allocation ratio). Primary efficacy measures: patient and investigator global assessments of disease activity and direct assessment of arthritis by counts of tender and swollen joints. Key secondary measures: patient global assessment of pain, the Stanford Health Assessment Questionnaire, and the percentage of patients both completing the study and meeting the ACR20 criteria. Tolerability was assessed by tabulation of adverse events and routine laboratory evaluations.

Results. In all, 816 patients were randomized (placebo = 323, etoricoxib = 323, naproxen = 170), and 448 completed 12 weeks of treatment (placebo = 122, etoricoxib = 230, naproxen = 96). Compared with patients receiving placebo, patients receiving etoricoxib and naproxen showed significant improvements in all efficacy endpoints ($p < 0.01$). Compared with patients receiving naproxen, patients receiving etoricoxib demonstrated significant improvements ($p < 0.05$) on all primary endpoints and most other endpoints including ACR20 criteria. The percentage of patients who achieved an ACR20 response and who completed the study was 21%, 53%, and 39% in the placebo, etoricoxib and naproxen groups, respectively. Etoricoxib and naproxen were both generally well tolerated.

Conclusion. In this study, etoricoxib 90 mg once daily was more effective than either placebo or naproxen 500 mg twice daily for treating patients with RA over 12 weeks. Etoricoxib 90 mg was generally well tolerated in patients with RA. (J Rheumatol 2002:29:1623–30)

Key Indexing Terms:
RHEUMATOID ARTHRITIS | NONSTEROIDAL ANTIINFLAMMATORY DRUGS
NAPROXEN | COX-2 INHIBITORS | ETORICOXIB

Therapy for rheumatoid arthritis (RA) commonly includes nonsteroidal antiinflammatory drugs (NSAID)[1,2]. NSAID are effective in controlling the joint pain and swelling of RA and are often used in conjunction with disease modifying antirheumatic drugs such as methotrexate, or are taken as monotherapy for symptomatic relief[1,2]. Gastrointestinal (GI) bleeding, ulceration, and perforation are the most common serious adverse events associated with NSAID and often lead to discontinuation of NSAID therapy as well as significant morbidity and mortality[3,4]. Continuous exposure to high doses of NSAID, as well as frequent concomitant use of steroids, places RA patients at particular risk for GI associated adverse events[3,5].

NSAID act via inhibition of cyclooxygenase (COX)[6]. COX exists in 2 isoforms that catalyze production of prostaglandins from arachidonic acid. COX-1 is constitutively expressed in platelets and gastric mucosa and is thought to mediate normal physiologic functions, including protection of the gastric mucosa and vascular hemostasis[7,8]. By contrast, COX-2 is upregulated by inflammatory cytokines and is thought to catalyze production of prostaglandins involved in pathologic responses including inflammation, fever, and pain[9]. Unlike COX-1, COX-2 is found in large quantities in the synovia of rheumatoid joints and in the synovia of joints in other inflammatory conditions such as ankylosing spondylitis and psoriatic arthritis[10,11]. Most NSAID nonselectively inhibit both COX-1 and COX-2, resulting in therapeutic antiinflammatory and analgesic effects (via the anti-COX-2 mechanism), but also unwanted GI effects (via the anti-COX-1 mechanism).

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Antiinflammatory therapy that preferentially inhibits COX-2 while sparing COX-1 is therefore expected to provide a safer treatment option, with less GI toxicity, for many patients with RA and other inflammatory disorders.

Previous studies have shown that the selective COX-2 inhibitors rofecoxib and celecoxib are effective and well tolerated treatments for RA[12,13]. We report results of a clinical trial on the efficacy and tolerability of a new highly selective COX-2 inhibitor, etoricoxib, for the treatment of RA. Etoricoxib has > 100-fold selectivity for COX-2 in whole blood assay, a half-life of approximately 22 h, and a rapid time-to-maximum-plasma-concentration of about 1 h[14,15]. In a direct comparison of selective and nonselective NSAID using the whole blood assay, etoricoxib had a higher COX-2/COX-1 selectivity ratio than any other agent tested including celecoxib, rofecoxib, and valdecoxib[14]. A previous dose finding study suggested that etoricoxib was effective in the treatment of RA; 90 mg was the optimal dose[16]. We further investigated the efficacy and safety of etoricoxib 90 mg and the nonselective NSAID naproxen (1000 mg) in a large clinical trial of patients with active RA.

MATERIALS AND METHODS

This randomized, double blind, parallel group 12 week study was conducted at 88 US sites. Each site received the approval of its institutional review board to perform the study. Written informed consent was obtained for every patient evaluated. Patients who completed the 12 week trial or who discontinued due to lack of efficacy were offered the opportunity to enter a blinded active comparator controlled 52 week extension. The data from the 52 week extension will be reported separately.

Patients. Eligible patients were age ≥ 18 years and fulfilled diagnostic criteria for RA as specified by the 1987 revised criteria of the American Rheumatism Association[17]. In addition, patients were required to have an established diagnosis of RA for at least 6 months prior to entering the study, a history of a clinical response to NSAID therapy, and to have been taking NSAID therapy on a regular basis (at least 25 of the past 30 days). Patients with a history of angina or congestive heart failure, with symptoms that occurred at rest or minimal activity, and/or who had a history of myocardial infarction, coronary angioplasty, or coronary bypass within the past year were excluded, as were those with a history of stroke, transient ischemic attack, or hepatitis in the previous 2 years. Patients with uncontrolled hypertension at screening were also excluded. Patients with any medical condition that, in the opinion of the investigator, could have confounded study results or caused undue risk to the patient (e.g., comorbid conditions for which NSAID are contraindicated) were also excluded. Three hemoccult screens were performed prior to allocation and patients with any evidence of active GI bleeding were excluded. At randomization, patients could not be taking concomitant warfarin, ticlopidine, clopidrogel, or digoxin. Patients taking stable doses of disease modifying therapy (except tumor necrosis factor inhibitors) and low doses of corticosteroids (prednisone < 10 mg daily) were allowed to continue therapy. Patients were permitted to take low dose aspirin (up to 100 mg/day).

Procedure. Patients were assessed for disease activity and those who met entry criteria were asked to discontinue their current NSAID use and return for evaluation when symptoms worsened (disease flare). At reevaluation for study inclusion, patients were required to have ≥ 6 tender joints, ≥ 3 swollen joints, and at least a 20% increase in the number of tender and swollen joints compared with initial assessments. In addition, investigators must have rated patients as fair, poor, or very poor on the investigator global assessment of disease activity, and noted either of the following: (1) morning stiffness for ≥ 45 min plus increased duration of morning stiffness by at least 15 min since initial evaluation, or (2) a score of > 40 mm on patient global assessment of pain [100 mm visual analog scale (VAS)] and at least a 10 mm increase in patient assessment of pain over that reported at initial evaluation.

Patients meeting the above flare criteria were randomized to placebo, etoricoxib 90 mg once daily, or naproxen 500 mg twice daily in a 2:2:1 allocation ratio; randomization was stratified by low dose corticosteroid use or not. Efficacy evaluations were performed at baseline and at weeks 2, 4, 8, and 12. Efficacy assessments included all components of the American College of Rheumatology (ACR) core set of outcome measures: patient global assessment of disease activity, investigator global assessment of disease activity, tender joint count, swollen joint count, Stanford Health Assessment Questionnaire (HAQ) of disability (an assessment of the patient's mobility and ability to carry out activities of daily living)[18], patient global assessment of pain, and C-reactive protein (CRP) level[2,17]. Four endpoints were specified as primary: patient global assessment of disease activity (100 mm VAS; 0 = very well, 100 = very poor), investigator global assessment of disease activity (0 to 4 Likert scale; 0 = very well, 1 = well, 2 = fair, 3 = poor, 4 = very poor), tender joint count (total 68 joints), and swollen joint count (total 66 joints). Key secondary measures included patient global assessment of pain (100 mm VAS; 0 = no pain, 100 = extreme pain), HAQ disability score (the average score of 9 disability questions, each graded on a 0 to 3 Likert scale: 0 = without any difficulty; 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do), and the proportion of patients who met the ACR20 criteria for a clinically relevant response (a composite criteria requiring 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR core measures)[16] and who completed the study (ACR20 completers). ACR20 completers was a prespecified endpoint. The percentage of patients meeting ACR20 criteria (based on time weighted average response), regardless of whether or not they completed the study, was also analyzed, although this was not prespecified. CRP concentrations and the percentage of patients who discontinued due to lack of efficacy were also measured.

Patients who discontinued due to lack of efficacy were eligible to enter an extension study. In the extension, all patients received active therapy, either etoricoxib or naproxen.

Laboratory assessments (serum chemistry, complete blood count, urinalysis) were performed at baseline and at weeks 2, 4, 8, and 12. Clinical and laboratory adverse events were recorded throughout the study. Investigators rated the intensity, relation to study drug (possibly, probably, or definitely drug related; probably not or definitely not drug related), and seriousness (includes events that are life threatening, result in hospitalization, or cause permanent incapacity, or other significant event) of adverse events. Any upper GI perforations, ulcers and bleeds (PUB) or cardiovascular thrombotic events (including cardiac, peripheral vascular, and cerebrovascular events) were reviewed by independent blinded adjudication committees, who determined if they were confirmed events according to prespecified case definitions (confirmed adjudicated events)[19].

Statistical analysis. The primary analytic method for evaluating efficacy was to compare treatment groups using the time weighted average change from baseline across 12 weeks for the 7 ACR core measures. The rates at 12 weeks for ACR20 completers, and the cumulative rates over 12 weeks for discontinuations due to lack of efficacy were also compared between treatment groups. Pair-wise comparisons were based on the difference between mean responses, except for CRP level, where the mean ratio was analyzed via log transformation. A modified intent-to-treat approach was employed — all patients with baseline and at least one post-baseline measurement were included in the analysis. Analysis of covariance [including terms for baseline covariate, stratum (corticosteroid use), and treatment] was used for all efficacy variables except ACR20 completers, and discontinuation rates due to lack of efficacy. The percentages of patients meeting ACR20 completers criteria were compared between treatment groups using the Cochran-Mantel-Haenszel test, with corticosteroid use as a stratification factor; Fisher's exact test was used to make between-treatment comparisons of the discontinuation rates due to lack of efficacy. The analysis of serum CRP was based on the log

of on-treatment value over baseline value. Plots of mean changes from baseline at each time point for the 4 primary endpoints were made to assess the maintenance of therapeutic effect for etoricoxib and naproxen. A last-observation-carried-forward method was used for these longitudinal graphs, but not for the time weighted average changes shown in the table of results. The study was powered to detect significant differences between etoricoxib and placebo on at least 3 of the 4 primary endpoints (95% overall power with sample sizes of 300 per treatment group, $\alpha = 0.05$, 2 tailed).

Tolerability was evaluated by tabulation of all clinical and laboratory safety variables, including adverse events. Active treatments were compared with placebo using Fisher's exact test for the percentages of patients with any drug related clinical adverse event, with any serious clinical adverse event, or who discontinued due to a clinical adverse event. Exposure-adjusted rates were also calculated and analyzed to take account of differential discontinuation rates between the treatment groups. The rates per 100 patient-months were calculated according to the formula:

rate = (number of adverse events/patient months of exposure)*100

where patient months of exposure = (number of patients) * (mean days on treatment/365.25) * 12.

RESULTS

Patients. Of the 1147 patients screened, 816 met eligibility criteria and were randomized. Of 331 patients not randomized, 247 were excluded at the initial screening visit, mainly because they failed to meet inclusion criteria. An additional 84 patients were excluded at the randomization visit, mostly because they failed to meet disease flare criteria. Baseline characteristics of the 816 randomized patients in the 3 treatment groups were similar and are shown in Table 1. A total of 448 of the 816 patients (37.8% of the placebo group, 71.2% of the etoricoxib group, and 55.2% of the naproxen group) completed the 12 week study (Figure 1). The most common reason for discontinuation was lack of efficacy. Significantly more patients discontinued due to lack of efficacy in the placebo and naproxen groups than in the etoricoxib group (54.5%, 36.5%, 21.7%, respectively; $p < 0.01$ for etoricoxib vs placebo and naproxen). The mean number of days that patients received treatment was 48.4 for placebo, 70.3 for etoricoxib, and 62.0 for naproxen. The results of all patients who had at least one post-randomization efficacy measurement [i.e., continued therapy for at least 2 weeks (± 3 days)] were included in the primary analysis of efficacy (97% in the placebo group, 98% in the etoricoxib group, and 98% in the naproxen group).

Table 1. Baseline patient characteristics.

Characteristic	Placebo, N = 323	Etoricoxib 90 mg, N = 323	Naproxen 1000 mg, N =170
Women, %	81	73	77
Mean age, yrs	56	55	56
Mean duration of RA, yrs	9	9	10
RF positive, %	76	76	80
ARA functional class, %			
I	22	21	21
II	59	66	62
III	19	13	17
Taking RA medications, %			
Corticosteroids	32	29	34
DMARD	68	68	69
Methotrexate	47	50	45
Mean patient global assessment of disease activity, 100 mm VAS†	66	65	63
Mean investigator global assessment of disease activity, 0 to 4 scale†	3	3	3
Mean number of tender joints, of 68†	29	29	28
Mean number of swollen joints, of 66†	21	23	23

† Higher score corresponds to more impairment.

Efficacy. Table 2 summarizes the results of the treatment comparisons for the primary and secondary efficacy endpoints. On all 4 primary endpoints, etoricoxib was statistically superior to both placebo ($p < 0.01$) and naproxen ($p < 0.05$), and naproxen was significantly superior to placebo ($p < 0.01$). Treatment effects of etoricoxib occurred at the earliest time point measured (week 2), and were maintained over the entire 12 week study period (Figures 2 and 3). Treatment effects of etoricoxib were consistent independent of corticosteroid use for all the primary endpoints. For all secondary endpoints, both etoricoxib and naproxen were superior to placebo. Additionally, etoricoxib was significantly superior to naproxen ($p < 0.05$) on the following secondary measures: patient global assessment of pain (least squares mean change on a 100 mm VAS: etoricoxib = –27.2 mm, naproxen = –20.5 mm, placebo = –11.4 mm), HAQ disability score (least squares mean change on a 4 point scale: etoricoxib = –0.4, naproxen = –0.3, placebo = –0.2), ACR20 completers (etoricoxib = 52.6%, naproxen = 39.1%, placebo = 20.8%; similar results were found in an analysis of all patients who met ACR20 criteria regardless of whether or not they completed the study: etoricoxib = 57.9%, naproxen = 46.8%, placebo = 27.4%), and discontinuations due to lack of efficacy. There was no significant difference between etoricoxib and naproxen for serum CRP (Table 2).

Tolerability. The adverse event rates for the 3 treatment groups are summarized in Table 3. Because there were differential dropout rates between treatment groups (primarily due to lack of efficacy in the placebo, and to a lesser extent, naproxen groups), exposure-adjusted adverse event rates were also calculated to correct for differences in mean exposure periods between groups (Table 3). Since the 2 measures showed similar patterns of results, the presentation in this section focuses on the simpler non-adjusted count data. However, it should be borne in mind that the non-adjusted data may overestimate adverse events for etoricoxib and naproxen relative to placebo. The active treatments were not significantly different ($p > 0.05$) from placebo with regard to the percentages of patients with any drug related clinical adverse events (15.2% for placebo, 16.1% for etoricoxib, 21.2% for naproxen), discontinuations due to clinical adverse events (3.4% for placebo, 4.0% for etoricoxib, 4.7% for naproxen), or serious

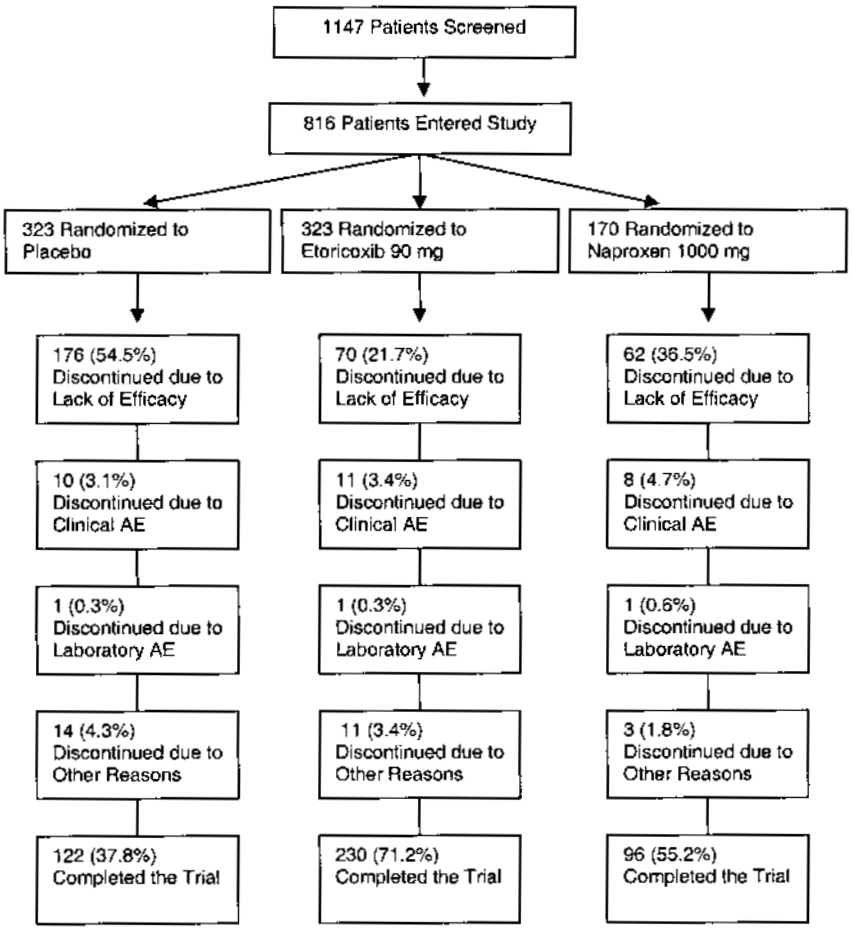

Figure 1. Study flowchart. AE: adverse event; Discontinued due to other reasons: patient lost to followup, moved, withdrew consent, protocol deviation, or study site terminated.

clinical adverse events (0.6% for placebo, 1.9% for etoricoxib, 0.6% for naproxen). Only one serious adverse event was considered drug related by the investigator (atrial fibrillation in the naproxen group). No clinically relevant trends were noted in the overall incidence of laboratory adverse events.

Drug related adverse events occurred most frequently in

Table 2. Efficacy differences between treatments over 12 weeks. Values are mean (95% confidence interval).

	Etoricoxib vs Placebo	Naproxen vs Placebo	Etoricoxib vs Naproxen
Primary endpoints			
PGA of disease activity, 100 mm VAS[§]	–17.0* (–20.3, –13.7)	–11.5* (–15.4, –7.5)	–5.5[†] (–9.5, –1.6)
Investigator global assessment of disease activity, 0–4 scale[§]	–0.63* (–0.78, –0.49)	–0.35* (–0.52, –0.18)	–0.28[†] (–0.45, –0.11)
Tender joint count, total 68 joints[§]	–6.3* (–8.0, –4.6)	–2.9* (–4.9, –0.9)	–3.4[†] (–5.4, –1.4)
Swollen joint count, total 66 joints[§]	–3.3* (–4.4, –2.2)	–1.8* (–3.2, –0.5)	–1.5[‡] (–2.8, –0.1)
Secondary endpoints			
PGA of pain, 100 mm VAS[§]	–15.8* (–19.1, –12.6)	–9.1* (–13.0, –5.3)	–6.7[†] (–10.6, –2.8)
HAQ disability, 0–3 scale[§]	–0.26* (–0.32, –0.19)	–0.14* (–0.22, –0.07)	–0.12[†] (–0.19, –0.04)
Serum CRP, ratio between treatments	0.8* (0.7, 0.9)	0.8* (0.7, 1.0)	1.0 (0.8, 1.1)
ACR20 completers, %	31.8* (24.8, 38.9)	18.2* (9.6, 26.8)	13.6[†] (4.4, 22.7)
Discontinuation due to lack of efficacy, %	–32.3* (–39.9, –25.8)	–18.0* (–27.1, –9.0)	–14.8[†] (–23.3, –6.3)

Negative values = improvement except for ACR20 completers and serum CRP. PGA: patient global assessment. HAQ: Stanford Health Assessment Questionnaire.

* The difference vs placebo was significant ($p < 0.01$). [†] The difference vs naproxen was significant ($p < 0.01$). [‡] The difference vs naproxen was significant ($p < 0.05$). [§] For these measures, the difference shown is for the least squares mean of the time weighted average change from baseline over 12 weeks.

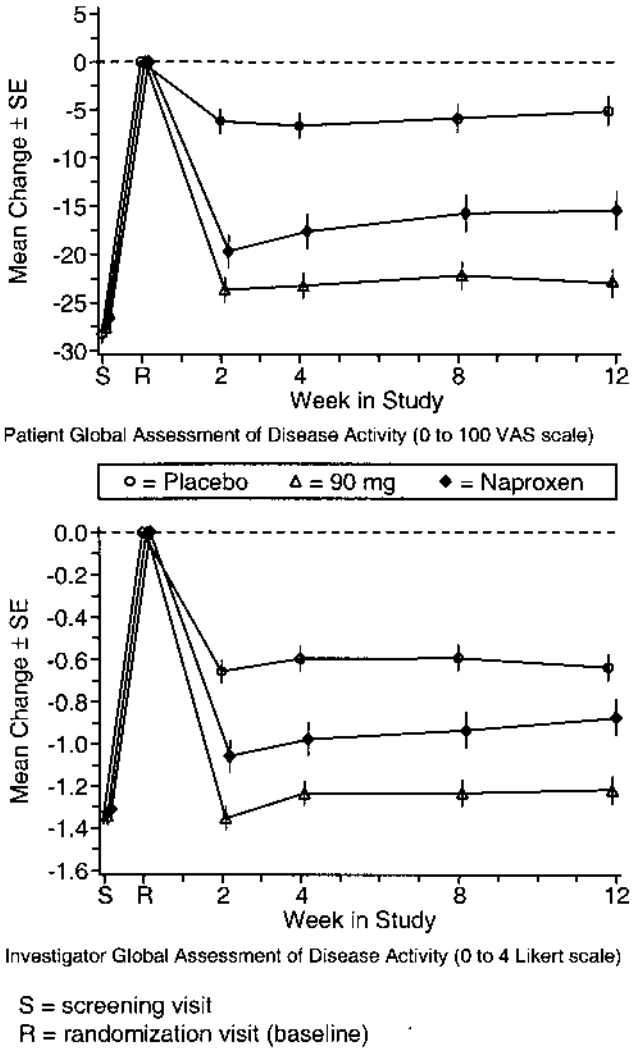

Figure 2. Changes from baseline in patient global assessment (top, 0 to 100 VAS scale) and investigator global assessment (bottom, 0 to 4 Likert scale). A last-observation-carried-forward approach was used for missing values.

the digestive system, with naproxen patients experiencing slightly higher incidences of dyspepsia, heartburn, and nausea than patients in the other treatment groups (Table 3).

Discontinuations due to adverse events in the digestive system in any one treatment group were low (1.2% placebo, 0.9% etoricoxib, and 2.4% naproxen). There was only one confirmed adjudicated PUB in the study: a patient taking naproxen had melena with a concomitant drop in hemoglobin > 2 g/dl. Although there was an increase in hypertension adverse events in patients taking etoricoxib and naproxen versus placebo (Table 3), discontinuations due to hypertension adverse events were rare (1 patient taking etoricoxib and 1 taking naproxen). Taking into account the differential dropout rates between treatment groups, hypertension rates between etoricoxib and naproxen were similar (an event rate of 0.9 per 100 patient-months for each). Over 12 weeks, mean systolic blood pressures decreased slightly from baseline in the placebo and etoricoxib groups, and increased slightly in the naproxen group (the maximum difference between means at any time point was < 2 mm Hg). Mean diastolic blood pressures did not change substantially from baseline values in any treatment group during the study (the maximum difference at any time point was ≤ 1 mm Hg). The incidences of edema adverse events with etoricoxib, naproxen, and placebo were all similar (Table 3). One patient taking etoricoxib discontinued due to edema.

There were 2 confirmed adjudicated cardiovascular adverse events in the study, a transient ischemic attack in a patient with a history of hypertension, hyperlipidemia, and coronary artery disease who was taking low dose aspirin, and a non-Q wave myocardial infarction in a patient with borderline hypercholesterolemia who was not taking low dose aspirin. These occurred while taking etoricoxib and were both considered definitely not drug related by the investigator.

DISCUSSION

Our study demonstrated that a 90 mg daily dose of the highly selective COX-2 inhibitor etoricoxib was more effective than placebo and superior to naproxen 1000 mg daily for treating patients with RA. Superior efficacy was consistently observed over a diverse range of measures, including tender and swollen joint counts and assessments of pain, inflammation, physical function, and global disease activity. More patients taking etoricoxib than patients taking placebo or naproxen met ACR20 criteria for a clinically relevant response. The treatment effects of etoricoxib occurred by the first assessment, at 2 weeks, and were sustained throughout the 12 weeks of study. Significantly fewer patients discontinued due to lack of efficacy in the etoricoxib group than in the placebo or naproxen groups.

Because the superiority of etoricoxib over naproxen was an unexpected finding in this study (it was not one of the prespecified objectives), additional sensitivity analyses to confirm the validity of these results were performed. For the 4 primary endpoints, an analysis of last-observed values showed a statistically significant improvement ($p < 0.05$) in patients treated with either etoricoxib or naproxen over placebo and in patients treated with etoricoxib over naproxen (data not shown). For the ACR20 analysis, in addition to the prespecified analysis of ACR20 responders and completers, further analyses of all patients achieving an ACR20 (based on a time weighted average of individual response measures), and regardless of completion status, were performed; the results were consistent with those of the prespecified primary and key secondary endpoints, in that patients treated with etoricoxib showed statistically significant improvements compared to those taking either naproxen or placebo.

These findings confirm results from previous studies showing that selective COX-2 inhibitors are effective in the treatment of RA[12,13]. A unique finding in our study was that

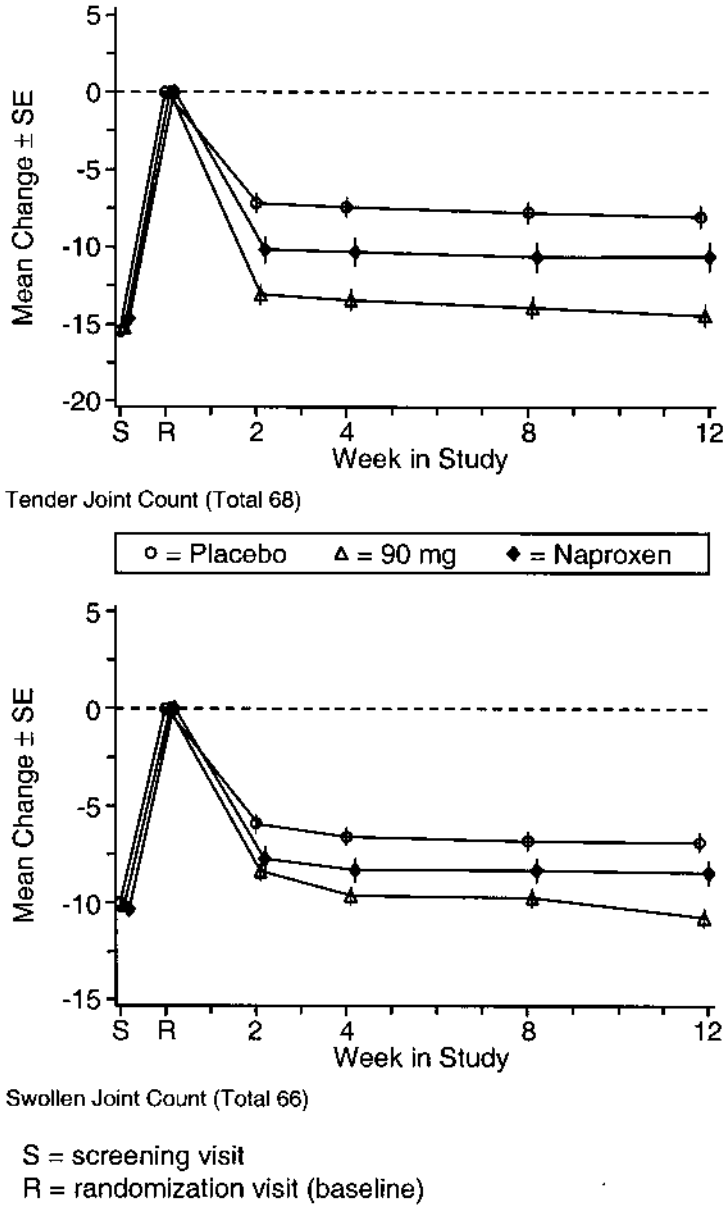

Figure 3. Changes from baseline in number of tender joint count (top) and swollen joint count (bottom). A last-observation-carried-forward approach was used for missing values.

etoricoxib was more effective than the comparator NSAID, naproxen, on most endpoints measured, including all primary and key secondary endpoints. This differs from findings in a recent study with etoricoxib and naproxen sodium (a different formulation to that studied here) looking at acute dental pain, in which the 2 treatments were similarly effective[20]. It also differs from results in studies with other selective COX-2 inhibitors in RA, which did not show improved efficacy over nonselective NSAID[12,13]. The reason for the superior efficacy of etoricoxib in this study is unclear. Potential explanations include the high degree of COX-2 inhibition achieved by etoricoxib, sustained drug levels over dosing intervals, or better tissue penetration. It should also be acknowledged that different patients respond to different NSAID with varying efficacy and that the most effective treatment for one patient, or group of patients, may not be the best for another individual patient or group. At this time, it is not clear if the superior efficacy of etoricoxib over naproxen is a unique feature of the population represented in the present study, or whether the findings can be generalized to the RA population as a whole. A reasonable conclusion on the basis of the currently available evidence is that etoricoxib has efficacy that is at least equivalent to high doses of nonselective NSAID, and that under certain circumstances superiority to some NSAID in some patients can be shown.

Etoricoxib was generally well tolerated by the patients in

Table 3. Number (%) and rates of patients with adverse events (AE).

	Placebo		Etoricoxib 90 mg		Naproxen 1000 mg	
	Count (%), N = 323	Rate† PTM‡ = 514	Count (%), N = 323	Rate† PTM‡ = 746	Count (%), N = 170	Rate† PTM‡ = 346
Any drug related clinical AE	49 (15.2)	9.5	52 (16.1)	7.0	36 (21.2)	10.4
Any serious clinical AE	2 (0.6)	0.4	6 (1.9)	0.8	1 (0.6)	0.3
Discontinued due to clinical AE	11 (3.4)	2.1	13 (4.0)	1.7	8 (4.7)	2.3
Deaths	0	0	0	0	0	0
Common drug related AE*						
Digestive						
Diarrhea	13 (4.0)	2.5	4 (1.2)	0.5	0 (0.0)	0.0
Dyspepsia	4 (1.2)	0.8	6 (1.9)	0.8	4 (2.4)	1.2
Heartburn	3 (0.9)	0.6	5 (1.5)	0.7	5 (2.9)	1.4
Nausea	6 (1.9)	1.2	5 (1.5)	0.7	5 (2.9)	1.4
Renovascular						
Lower extremity edema	5 (1.5)	1.0	5 (1.5)	0.7	5 (2.9)	1.4
Hypertension	1 (0.3)	0.2	7 (2.2)	0.9	3 (1.8)	0.9
Laboratory						
Decreased hematocrit	0 (0.0)	0.0	2 (0.6)	0.3	4 (2.4)	1.2
Decreased hemoglobin	0 (0.0)	0.0	2 (0.6)	0.3	5 (3.0)	1.4

PTM: † Rate per 100 patient-months. ‡ Patient-months at risk. * Incidence ≥ 2% in any treatment group.

this study, consistent with results from prior clinical trials for other indications[20, 21]. The overall incidence of adverse events and discontinuations due to adverse events was similar in the 3 treatment groups. The main proposed advantage for selective COX-2 inhibitors is reduced GI toxicity. The findings in our study were consistent with improved GI tolerability. Compared with naproxen, the incidences of "nuisance" GI symptoms such as dyspepsia, heartburn, and nausea were reduced in patients taking etoricoxib, and fewer patients taking etoricoxib discontinued due to GI adverse events than patients taking naproxen. Because of the relatively low incidence of clinically significant GI PUB, very large longterm trials or pooled analyses are required to assess any advantage of selective COX-2 inhibitors over nonselective NSAID in this regard[19,22]. Our study was too small and too brief to address this issue. Only one confirmed adjudicated PUB was reported.

Since COX-2 is known to be constitutively expressed in the human kidney, and data with both selective COX-2 inhibitors and nonselective NSAID have suggested that they have an effect on renal physiology[23,24], particular attention was paid to the typical NSAID related renal effects of edema and hypertension in this study. Etoricoxib and naproxen showed a small increase in hypertension adverse events compared with placebo. Mean changes in blood pressure among the treatment groups were small, and both etoricoxib and placebo treatment groups showed small decreases in mean systolic blood pressure compared to baseline. Most patients who experienced a hypertension adverse event continued in the study. The incidences of edema adverse events for etoricoxib and naproxen were similar to placebo.

In summary, etoricoxib 90 mg once daily provided clinically meaningful improvements of the signs and symptoms of RA that were superior to those of placebo and of naproxen 500 mg twice daily. The treatment effects of etoricoxib were observed early and were maintained over the 12 week study. Etoricoxib 90 mg was generally well tolerated in this population of patients with RA. These data support the addition of etoricoxib to the available therapeutic options in the management of patients with RA.

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