Efficacy of Rofecoxib, Celecoxib, and Acetaminophen in Osteoarthritis of the Knee
A Randomized Trial

Gregory P. Geba, MD
Arthur L. Weaver, MD
Adam B. Polis, MA
Mary E. Dixon, BS
Thomas J. Schnitzer, MD, PhD
for the VACT Group

Osteoarthritis (OA) is the most common joint disorder, accounting for significant disability and large health care expenditures.1,3 Although nonsteroidal anti-inflammatory drugs (NSAIDs) have long been used to treat the pain and stiffness associated with OA, the American College of Rheumatology guidelines published in 1995,4 and updated in 2000,5 recommended acetaminophen as first-line therapy for the systemic treatment of symptomatic OA. This decision was partly due to concerns about gastrointestinal tract and other adverse effects associated with NSAIDs and also due to lack of data confirming their superior efficacy over simple analogues. However, the severity of pain often prompts treatment with NSAIDs, which remain commonly used and preferred medicines by many patients with symptomatic OA.1,6,7

The mechanism of action of NSAIDs involves inhibition of prostaglandin synthesis. In humans, prostaglandin synthesis is catalyzed by at least 2 forms of cyclooxygenase, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). COX-1, constitutively expressed in a variety of tissues, is re-

Context Osteoarthritis (OA) is often treated with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or specific inhibitors of cyclooxygenase 2 (COX-2).

Objective To assess the relative therapeutic efficacy of rofecoxib, celecoxib, and acetaminophen in adults with OA.

Design and Setting Randomized, parallel-group, double-blind trial, conducted from June 1999 to February 2000, in 29 clinical centers in the United States.

Patients Three hundred eighty-two patients aged at least 40 years who had OA of the knee that was previously treated with NSAIDs or acetaminophen.

Interventions Patients were randomly assigned to receive rofecoxib, 12.5 mg/d (n = 96); rofecoxib, 25 mg/d (n = 95); celecoxib, 200 mg/d (n = 97); or acetaminophen, 4000 mg/d (n = 94) for 6 weeks.

Main Outcome Measures Assessments over days 1 to 6 and over 6 weeks included pain on walking, night pain, pain at rest, and morning stiffness as measured on a Western Ontario McMaster Universities Osteoarthritis Index (100-mm visual analog scale [VAS]) and global response to therapy compared among 4 treatment groups.

Results 79% of patients completed the study. More patients treated with acetaminophen discontinued early due to lack of efficacy than patients treated with COX-2 inhibitors (31% vs 18%-19%). Efficacy assessed in the first 6 days of therapy showed greatest response to rofecoxib, 25 mg/d, followed by rofecoxib, 12.5 mg/d, celecoxib, and acetaminophen, respectively, in terms of relief of pain on walking (−32.2, −29.0, −26.4, and −20.6 mm change on the VAS; P = .001 vs acetaminophen; P = .05 for 25-mg rofecoxib vs celecoxib), rest pain (−21.8, −18.6, −15.5, and −12.5 mm; P = .02 for either dose of rofecoxib vs acetaminophen and P = .02 for rofecoxib, 25 mg/d, vs celecoxib), night pain (−25.2, −22.0, −18.7, and −18.8 mm; P = .04 for rofecoxib, 25 mg/d, vs both acetaminophen and celecoxib), and morning stiffness (−30.4, −28.4, −25.7, and −20.9 mm; P = .02 for either dose of rofecoxib vs acetaminophen). Over 6 weeks, rofecoxib, 25 mg/d, provided greatest response for night pain (P = .002 vs celecoxib and P = .006 vs acetaminophen and P = .02 vs rofecoxib, 12.5 mg/d), composite pain subscale (P = .03 vs all other treatments), stiffness subscale (P = .04 vs celecoxib and acetaminophen), and physical function subscale (P = .001 vs acetaminophen). Global responses over 6 weeks showed a similar pattern (good or excellent response at week 6: 60%, 56%, 46%, and 39%, respectively; P = .03 for rofecoxib, 25 mg/d, vs celecoxib and acetaminophen; P = .02 for rofecoxib, 12.5 mg/d, vs acetaminophen). All treatments were generally safe and well tolerated.

Conclusion Rofecoxib, 25 mg/d, provided efficacy advantages over acetaminophen, 4000 mg/d, celecoxib, 200 mg/d, and rofecoxib, 12.5 mg, for symptomatic knee OA.

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sponsible for the production of prosta-
noids that regulate physiological
functions such as platelet aggregation
and gastric mucosal protection. Al-
though it is constitutively expressed in
the brain, COX-2 is typically only in-
duced in most other tissues by cyto-
kines and other soluble mediators.8,9
COX-2 has been detected in leuko-
cytes and human rheumatoid synovi-
cytes, and it mediates synthesis of pro-
stanooids generated in inflammation and
pain.10-13

Most NSAIDs are dual inhibitors of
COX-1 and COX-2 and therefore can
be associated with gastrointestinal tract
toxicity (such as perforation, ulcer for-
mation, and gastrointestinal tract bleed-
ing) due to COX-1–mediated reduc-
tion in protective prostanoids.14

Selective COX-2 inhibitors may sup-
press pathological responses medi-
ated by prostanoids (eg, pain and in-
flammation) without inducing toxicity
associated with the inhibition of COX-1.
Rofecoxib and celecoxib selectively in-
hbit COX-2. Administration of these
agents has been shown to provide rel-
ief of symptoms of OA15-18 with a re-
duced risk of gastrointestinal toxicity
relative to dual COX inhibitors.19,21

The objective of this study was to es-
timate the efficacy of rofecoxib, cele-
coxib,18 and acetaminophen4,9 in adult
patients with OA of the knee.

METHODS

Patients

The study was conducted at 29 clinical
centers in the United States from June
1999 to February 2000. Men and non-
pregnant women with symptomatic OA
of the knee for at least 6 months were
eligible for study participation if they
were at least 40 years old; fulfilled Ameri-
can College of Rheumatology clinical cri-
teria for OA of the knee;22 and had an
American College of Rheumatology
functional class rating of I, II, or III.23 The
knee designated as the “study joint” was
the primary source of pain or disability
in the lower extremity.

Consistent with patient enrollment in
previous studies,15,16 patients who en-
tered the study were previous users of
either a single, prescription-strength
NSAID or high doses of acetamino-
phen for control of OA symptoms for
at least 30 days prior to entry. Entry
criteria for NSAID users included demonstrat-
ing, while taking the NSAID, a
screening Western Ontario and
McMaster Universities Osteoarthritis
Index (WOMAC24) visual analog scale
(VAS) score of less than 80 mm for the
assessment of walking pain at visit 1
(screening); a minimum VAS score of
40 mm for the assessment of walking
pain after discontinuing the NSAID; an
increase (ie, worsening) from screen-
ing in the walking pain VAS score of at
least 15 mm, and a worsening from
screening in the Investigator Global
Assessment of Disease Status (IGADS)
(performed by the physician investiga-
tor) of at least 1 point on a 5-point Likert scale (range, 0 [very well] to 4
[very poor]) at visit 2.

During the prespecified washout pe-
riod, patients who had discontinued
NSAIDs could take acetaminophen for
intolerable pain, but acetaminophen was
discontinued at least 24 hours before ef-
cicacy assessments. Since previous acet-
aminophen users were not taking
NSAIDs, they were required to have a his-
tory of therapeutic benefit with regular
doses of acetaminophen (1200-4000
mg/d) as exclusive therapy of OA, a score
of 2 (fair), 3 (poor), or 4 (very poor) on
IGADS, and the same minimum VAS
score of 40 mm required of the NSAID
previous users after discontinuing acet-
aminophen therapy for the assessment
of walking pain at visits 1 and 2.

Patients were excluded from the
study if they had a concurrent medi-
cal or arthritic disease or abnormal labo-
atory results (values outside normal
reference range or determined by the
investigator to be of clinical signifi-
cance) that had potential to confound
or interfere with the efficacy evalua-
tion or pose an additional risk to the
patient; history of allergy to study drugs,
hypersensitivity to aspirin, ibuprofen,
or any other NSAID, or sulfonamide-
containing compounds; or received an
investigational drug within 30 days of
screening.

Study Design

Consistent with the typical duration of
other OA studies15,16 and previously
published recommendations,25 we con-
ducted a double-blind, randomized, ac-
tive comparator–controlled trial of 6
weeks’ treatment comparing COX-2 in-
hibitors at indicated once-daily doses
for treatment of knee OA: rofecoxib
(12.5 mg/d and 25 mg/d), celecoxib,
200 mg/d, and the highest recom-
ended dose of acetaminophen—
4000 mg (1000 mg 4 times daily4,9). Pa-
tients who satisfied entry criteria
discontinued their prior NSAID therapy
according to a prespecified schedule
 (>5 plasma half-lives of prior NSAID).
Patients were instructed to return to the
site for visit 2 on significant worsen-
ing of knee pain or related symptoms,
or at the end of their allowed washout
period, whichever came first. For acet-
aminophen users, visit 2 was sched-
uled within 3 to 7 days of screening.

NSAID users were allowed to take
325-mg acetaminophen tablets during
the washout phase as rescue therapy for
OA pain at a daily dose of acetamino-
phen restricted to 2600 mg (8 tab-
lets). No other rescue medication was
allowed during the study. All patients
discontinued use of acetaminophen at
least 12 hours before visit 1 (screen-
ing) and visit 2 (day 1).

At visit 2, enrolled patients were ran-
domly assigned (via computer-
generated assignment) to treatment with
either: rofecoxib 12.5 mg/d, rofe-
coxib 25 mg/d, celecoxib 200 mg/d, or
acetaminophen 1000 mg 4 times per
day for 6 weeks. Patients and investi-
gators were blinded to treatment; exact-
matching placebo tablets were used to
blind the study. Patients took rofe-
coxib 12.5 or 25 mg or celecoxib 200
mg or 1000 mg of acetaminophen or
matching placebo each morning from
between 7 and 10 AM, and subse-
quently took matching placebo or acet-
aminophen 1000 mg 3 additional times
to complete 4-per-day dosing.

Early efficacy data were collected on
days 1 through 6 using patient take-
home diaries. Preplanned analysis in-
ccluded determination of efficacy using

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the entire WOMAC Osteoarthritis Index Version VA 3.0 (a VAS ranging from 0 [best] to 100 mm [worst]; assessed by composite subscales and specified questions outlined) and patient global assessment of response to therapy (PGART) on a 5-point categorical scale (range, 0 [none, no response] to 4 [excellent response]). It was prespecified that responses to WOMAC pain walking on a flat surface, night pain, pain at rest and morning stiffness, and PGART would be recorded on take-home forms for days 1 through 6 and analyzed to determine efficacy over the first 6 days. Patients completed questions about night pain and morning stiffness prior to their first dose on days 2 through 6; questions about walking pain and pain at rest were completed at bedtime on days 1 through 6. Clinical efficacy (WOMAC and PGART) and safety measures (physical examination, and patient interview) were administered at scheduled office visits at weeks 2, 4, and 6. Patients completed the entire 24-item WOMAC and PGART at each study visit. Safety evaluation was based on physical examination, laboratory testing, and reporting of adverse events. Cardiovascular and adverse gastrointestinal tract events were adjudicated by a previously reported mechanism involving an external committee blinded to treatment.20

Statistical Analysis

The trial was designed to enroll approximately 200 patients who had used NSAIDs and a target of 100 to 200 patients who had used acetaminophen to ensure that each treatment group would have a minimum of 50 patients who had used NSAIDs and a target of 25 who had used acetaminophen. The analysis plan was first to evaluate the treatments within each subgroup to determine whether the treatment effects were consistent for each prior-use subgroup. Then, if consistent, the plan was to combine the prior-use subgroups to obtain overall estimates of treatment effect. As stated in the protocol, a between-group difference of 10 mm on the WOMAC VAS scale was the anticipated effect size between rofecoxib and acetaminophen. With 50 evaluable patients per treatment and subgroup, the half-width of a 95% confidence interval (CI) for a treatment mean would be 8.3 mm, assuming a within-group SD of 30 mm. With 75 (100) patients per group, the power to detect a treatment difference of 10 mm on the WOMAC scale was 52% (65%).

All analyses in this efficacy trial were conducted using a modified intent-to-treat approach, whereby all patients who took at least 1 dose of study medication were included for analysis. For the analysis of WOMAC data, a patient had to have a baseline value, which was the value obtained after washout from prior therapy and at least 1 on-treatment value to be included in the analysis. For PGART, only 1 on-treatment value was required. Missing values were imputed by carrying forward the most recent, previous, non-missing value. Missing WOMAC data were not imputed nor carried forward. Only 1 patient, in the celecoxib group, did not receive treatment and could not provide on-treatment data.

For the efficacy analyses, all tests were 2-sided and P values ≤.050 were considered statistically significant. For each efficacy parameter, secondary analyses were conducted by previous user subgroup (NSAIDs or acetaminophen). Similar trends were observed in each user subgroup and therefore all results were summarized for the total patient population.

For the 4 WOMAC question scores and the 3 WOMAC composite subscales (ie, pain, stiffness, and physical function), analysis of covariance was used to assess statistical significance of treatment differences in 6-day and 6-week mean changes from baseline to determine 95% CIs and corresponding P values. The model included terms for baseline covariate and treatment group. Changes from baseline in the individual WOMAC question scores were analyzed for early efficacy assessments on days 1 through 6 (early efficacy) as well as for the entire 6-week treatment period. Six-week data were analyzed for changes from baseline in the 3 WOMAC subscales. A 6-day and 6-week average was calculated for each patient. The 6-week average for a patient was the mean of the change from baseline to weeks 2, 4, and 6. The 6-day average was calculated for each patient in the same way.

The percentage of patients with a good or excellent response to therapy (PGART) was calculated for each treatment group at weeks 2, 4, and 6 with week 6 prespecified to be primary. A logistic regression model was used for analysis of the PGART data, with estimates of odds ratios (ORs), corresponding P values, and 95% CIs. The model included terms for the IGADS at baseline and treatment group. A time-to-event analysis was conducted for the first report of a good or excellent response for first 6-day diary data; the cumulative incidence was calculated by the Kaplan-Meier estimate and compared by Wilcoxon test for ranked survival data.

Numbers and rates of adverse events, gastrointestinal tract symptoms (ie, acid reflux, dyspepsia, epigastric discomfort, heartburn, nausea, and vomiting), and events of special interest (ie, edema, hypertension and gastrointestinal tract bleeding, perforation, and ulceration) were tabulated for each treatment group.

Each patient provided written informed consent prior to enrollment. Institutional review board approval of the study protocol was obtained for each investigational site. Statistical analyses were conducted with SAS version 6.12 (SAS Inc, Cary, NC).

RESULTS

Patient Characteristics

A total of 515 patients were screened; 133 did not meet entry criteria and 382 patients were enrolled (FIGURE 1). Treatment groups were comparable in age, race, sex, prior medication use, OA duration, and baseline IGADS and WOMAC scores (TABLE I). Overall, 68.3% of patients were women, and 85.3% were white. Mean age was 62.6 years (range, 39-91 years). Seventy-seven percent of the patients used...
NSAIDs prior to study entry; 88 patients (23%) were previous acetaminophen users.

Overall, 79% of patients completed the study. Thirty-one percent in the celecoxib group withdrew compared with 18% to 19% taking COX-2 inhibitors. Overall, lack of efficacy was the most commonly cited reason for withdrawal. For this reason, 17% of patients were withdrawn from the acetaminophen group vs 8% taking rofecoxib 25 mg and 12.5 mg and 9% taking celecoxib 200 mg in the other groups. A total of 23 patients (6%) discontinued due to a clinically adverse event (4%-7% per group).

**Efficacy Results**

**Pain Walking on a Flat Surface.** At baseline, mean scores for all efficacy end points were similar among treatment groups. Over 6 days, mean decreases from baseline in the score for walking pain were greatest for rofecoxib 25 mg/d (32.2 mm) and smallest for acetaminophen (20.6 mm) (Table 2). Compared with acetaminophen, improvement in this score was statistically significantly greater in patients treated with rofecoxib 25 mg/d (P<.001); rofecoxib, 12.5 mg/d (P = .004); or celecoxib (P = .04). The difference between the rofecoxib 25 mg/d and celecoxib groups was statistically significant (P = .05). Over 6 weeks, the mean decreases from baseline for walking pain were 30.3 mm for the acetaminophen group and 42.0 mm for the rofecoxib 25 mg/d group (P = .001). There were no other statistically significant differences among groups.

**Night Pain.** Over 6 days, mean decreases from baseline in the average night pain score ranged from 25.2 mm for rofecoxib 25 mg/d to 18.7 mm for celecoxib (Table 2). Improvement in this score was statistically significantly greater in patients treated with rofecoxib 25 mg/d vs those treated with celecoxib (P = .04) or acetaminophen (P = .04).

Over 6 weeks, the mean decreases in the average night pain score ranged from 22.6 mm in the celecoxib group to 32.7 mm in the rofecoxib 25 mg/d.

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**Table 1. Patient Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acetaminophen 4000 mg (n = 94)</th>
<th>Celecoxib 200 mg (n = 97)</th>
<th>Rofecoxib 12.5 mg (n = 96)</th>
<th>Rofecoxib 25 mg (n = 95)</th>
<th>Total (N = 382)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>66 (70.2)</td>
<td>63 (64.9)</td>
<td>63 (65.6)</td>
<td>69 (72.6)</td>
<td>261 (68.3)</td>
</tr>
<tr>
<td>Men</td>
<td>28 (29.8)</td>
<td>34 (35.1)</td>
<td>33 (34.4)</td>
<td>26 (27.4)</td>
<td>121 (31.7)</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.1 (10.90)</td>
<td>62.6 (11.03)</td>
<td>63.4 (10.40)</td>
<td>61.3 (10.93)</td>
<td>62.6 (10.81)</td>
</tr>
<tr>
<td>Median</td>
<td>62.0</td>
<td>63.0</td>
<td>63.5</td>
<td>61.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Range</td>
<td>40-86</td>
<td>39-84</td>
<td>44-86</td>
<td>41-91</td>
<td>39-91</td>
</tr>
<tr>
<td><strong>Race or ethnicity</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79 (84.0)</td>
<td>85 (87.6)</td>
<td>84 (87.5)</td>
<td>78 (82.1)</td>
<td>326 (85.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (7.4)</td>
<td>7 (7.2)</td>
<td>5 (5.2)</td>
<td>8 (8.4)</td>
<td>27 (7.1)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (6.4)</td>
<td>5 (5.2)</td>
<td>7 (7.3)</td>
<td>7 (7.4)</td>
<td>25 (6.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (2.1)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td><strong>Prior drug type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>72 (76.6)</td>
<td>77 (79.4)</td>
<td>72 (75.0)</td>
<td>73 (76.8)</td>
<td>294 (77.0)</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>22 (23.4)</td>
<td>20 (20.6)</td>
<td>24 (25.0)</td>
<td>22 (23.2)</td>
<td>88 (23.0)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) unless otherwise indicated. NSAID indicates nonsteroidal anti-inflammatory drug.*

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group. The decrease in pain scores for those taking 25 mg/d of rofecoxib was statistically significantly greater than for those taking acetaminophen (P = .006), as well as for those taking rofecoxib 12.5 mg/d (P < .02) and celecoxib (P = .002).

Rest Pain. Over 6 days, mean decreases from baseline in rest pain score ranged from 21.8 mm for rofecoxib 25 mg/d to 12.5 mm for acetaminophen (Table 2). Relief of rest pain was statistically significantly greater in patients treated with rofecoxib 25 mg/d (P = .003) and 12.5 mg/d (P = .02) compared with acetaminophen but there were no significant differences in scores between the celecoxib and acetaminophen groups or among the celecoxib and rofecoxib groups.

Over 6 weeks, mean changes from baseline in morning stiffness score ranged from 22.3 mm in the acetaminophen group to 36.2 mm in the rofecoxib 25-mg/d group (P < .001). The difference between effects provided by rofecoxib 12.5 mg/d and rofecoxib 25 mg/d was also statistically significant (P = .05). Differences between celecoxib and acetaminophen as well as differences among celecoxib and rofecoxib were not significant.

### WOMAC Composite Subscales

Improvements in the WOMAC pain, stiffness, and functional disability subscales in each treatment group during the 6-week treatment period are described in Table 2.

#### Pain

Across treatments, mean decreases from baseline in the 6-week domain score for pain ranged from 24.9 mm in the acetaminophen group to 35.4 mm in the 25-mg/d rofecoxib group. Improvement in this score was statistically significantly greater in patients treated with rofecoxib 25 mg/d vs those taking rofecoxib 12.5 mg/d (P = .02), celecoxib (P = .03), or acetaminophen (P = .001).

#### Stiffness

Mean decreases from baseline in the 6-week domain score for stiffness ranged from 21.6 mm in the acetaminophen group to 35.0 mm in the rofecoxib 25-mg/d group. Improvement in this score was statistically significantly greater in patients treated with rofecoxib 25 mg/d vs celecoxib (P = .04) or acetaminophen (P < .001); the difference between rofecoxib groups was not statistically significant (P = .051).

#### Physical Function

Improvement in the average 6-week functional disability score was statistically significantly greater in the rofecoxib 25-mg/d group (29.7 mm) than in the acetaminophen group (19.5 mm; P = .001); there were no other statistically significant differences among treatment groups.

### Patient Global Assessment of Response to Therapy

By day 6, cumulative incidences of first report of a good or excellent response

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### Table 2. Change From Baseline in Individual and Composite Western Ontario and McMaster Universities Osteoarthritis Index Visual Analog Scale

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acetaminophen 4000 mg</th>
<th>Rofecoxib 12.5 mg</th>
<th>Rofecoxib 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First 6 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain walking</td>
<td>–18.8 (–23.2 to –14.4)</td>
<td>–22.0 (–26.4 to –17.6)</td>
<td>–25.2 (–29.8 to –20.6)</td>
</tr>
<tr>
<td>Rest pain</td>
<td>–12.5 (–16.3 to –8.7)</td>
<td>–15.5 (–19.3 to –11.7)</td>
<td>–18.6 (–22.4 to –14.8)</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>–20.9 (–25.3 to –16.5)</td>
<td>–25.7 (–30.1 to –21.3)</td>
<td>–28.4 (–32.8 to –24.0)</td>
</tr>
<tr>
<td><strong>6 Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking pain</td>
<td>–30.3 (–35.5 to –25.1)</td>
<td>–36.2 (–41.2 to –31.2)</td>
<td>–35.1 (–40.1 to –30.1)</td>
</tr>
<tr>
<td>Rest pain</td>
<td>–21.7 (–26.3 to –17.1)</td>
<td>–23.4 (–28.0 to –18.8)</td>
<td>–24.8 (–29.4 to –20.2)</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>–22.3 (–27.5 to –17.1)</td>
<td>–29.1 (–34.3 to –23.9)</td>
<td>–29.0 (–34.2 to –23.8)</td>
</tr>
<tr>
<td>Night pain</td>
<td>–23.6 (–28.4 to –18.8)</td>
<td>–22.6 (–27.2 to –18.0)</td>
<td>–25.2 (–29.8 to –20.6)</td>
</tr>
<tr>
<td>Pain subscale</td>
<td>–24.9 (–29.5 to –20.3)</td>
<td>–28.6 (–33.2 to –24.0)</td>
<td>–28.0 (–32.6 to –23.4)</td>
</tr>
<tr>
<td>Stiffness subscale</td>
<td>–21.6 (–26.6 to –16.6)</td>
<td>–27.9 (–32.9 to –22.9)</td>
<td>–28.2 (–33.2 to –23.2)</td>
</tr>
<tr>
<td>Function subscale</td>
<td>–19.5 (–24.1 to –14.9)</td>
<td>–24.9 (–29.3 to –20.5)</td>
<td>–24.3 (–28.7 to –19.9)</td>
</tr>
</tbody>
</table>

*P = .05 compared with acetaminophen 4000 mg.
†P = .01 compared with acetaminophen 4000 mg.
‡P = .05 compared with celecoxib 200 mg.
§P < .001 compared with acetaminophen 4000 mg.
||P < .001 compared with celecoxib 200 mg.
on PGART were 75% in the 25-mg/d and 71% in the 12.5-mg/d rofecoxib groups, 68% for celecoxib, and 54% for acetaminophen groups (rofecoxib 25 mg/d vs acetaminophen, \( P = .05 \); differences for all other comparisons are not statistically significant). Median time to first report of good or excellent PGART for celecoxib was 1.57 (95% CI, 0.86-2.82; rofecoxib 12.5 mg/d vs celecoxib 200 mg/d, 95% CI, 1.05-3.40; differences for all other comparisons are not statistically significant). Median time to first report of good or excellent PGART for celecoxib was 1.89 (95% CI, 0.72-2.36; rofecoxib vs acetaminophen was 1.30 (95% CI, 0.72-2.36; \( P = .38 \)). The OR of celecoxib vs acetaminophen was 1.30 (95% CI, 0.72-2.36; \( P = .38 \)). The OR of rofecoxib 25 mg/d vs celecoxib was 1.89 (95% CI, 1.05-3.40; \( P = .03 \)) and for rofecoxib 12.5 mg vs acetaminophen was 1.57 (95% CI, 0.86-2.82; \( P = .10 \)).

**Safety Results**

Table 3 and Figure 1 describe the clinical adverse event profile. Incidences of specific gastrointestinal events were generally low and comparable among treatment groups. No patient experienced gastrointestinal tract bleeding, perforation, or ulceration during the trial. A total of 7 patients (2%) had hypertension during the study (1-3 patients per group); none of these resulted in study withdrawal. Lower extremity, pedal, and ankle edema were the most common types of edema reported (0%-3.2% per group). Two patients (1, rofecoxib 25-mg/d; 1, acetaminophen) were withdrawn from the study due to edema (pedal or lower extremity). Two patients (1, rofecoxib 25 mg/d; 1, celecoxib) also experienced fluid retention; none of the patients had congestive heart failure. There were no myocardial infarctions in any group during the trial. One previous celecoxib user had received rofecoxib 25 mg/d in the study and had a stroke diagnosed 1 week after completing the trial and cessation of study therapy.

**COMMENT**

In this study, rofecoxib 25 mg/d provided greater therapeutic benefits than maximal daily doses of acetaminophen in treating patients with OA of the knee for all prespecified end points and benefit over rofecoxib 12.5 mg/d and celecoxib 200 mg/d. Previous studies have failed to demonstrate convincingly therapeutic benefit of full anti-inflammatory doses of dual COX-1 and COX-2 inhibiting NSAIDs compared with acetaminophen in the treatment of OA. A 4-week study by Bradley et al,26 involving 184 patients randomized to 3 treatment arms, con-
cluded that the efficacy of acetaminophen in OA of the knee was similar to that of 2 different dosages of ibuprofen. Ibuprofen given at analgesic (1200 mg/d) and anti-inflammatory (2400 mg/d) dose levels provided improvements in the Health Assessment Questionnaire pain and disability scores that were indistinguishable from those obtained from patients treated with acetaminophen at 4000 mg/d (P > .90). Differences in improvement from baseline in pain walking did not reach statistical significance. However, the mean improvement in rest pain provided by both ibuprofen dose levels was superior to that achieved with acetaminophen.

A second study,27 involving 178 patients assigned to receive either 750 mg/d of the dual COX-1 and COX-2 inhibitor naproxen, or 2600 mg/d of acetaminophen, demonstrated greater efficacy of the NSAID for only 1 end point: rest pain. No statistically significant difference was noted in other end points, including pain on motion, 50-foot walk time, and physician assessment of disease activity. Failure to demonstrate superiority of NSAIDs over acetaminophen in these previous trials, in part, may have been because earlier studies examined a more limited profile of less responsive end points, and in part because of inadequate power to detect differences in these studies.

Recently, Pincus et al28 reported the results of a 6-week OA trial, similar in size to our study, comparing acetaminophen with diclofenac plus misoprostol that are consistent with the results we report herein. For WOMAC end points, diclofenac provided statistically significantly greater responses compared with acetaminophen. Previous studies comparing rofecoxib and celecoxib to dual-inhibiting NSAIDs have shown comparable efficacy of the COX-2-specific agents compared with either high-dose ibuprofen16 or naproxen.17,18

Ours is the first study, to our knowledge, that assesses the effects of COX-2 inhibitors and maximal daily dosages of acetaminophen in the treatment of symptomatic OA across this broad range of patient-reported end points. Across multiple clinical end points, rofecoxib 25 mg/d provided greater benefit in adult patients with OA of the knee than did maximal doses of acetaminophen. Differences in response to these 2 treatments were observed within 6 days of initiating therapy and were maintained over the 6-week treatment period. Compared with acetaminophen, 12.5 mg/d of rofecoxib also resulted in significantly greater proportion of positive PGART responses over 6 weeks, and both rofecoxib 12.5 mg/d and celecoxib 200 mg/d provided more rapid relief of pain walking in the first 6 days of therapy than did acetaminophen. By the end of 6 weeks of therapy, approximately 39% of patients treated with acetaminophen assessed their response to be good or excellent, and, therefore, had also responded to therapy.

Since OA is a symptomatic disease, with poor correlation of objective measures of disease with symptoms,25 most clinical studies focus on patient-reported symptomatic outcome measures (ie, WOMAC and PGART), which are generally assessed over several weeks. Such a study design was previously recommended by an expert panel25 and is similar to the one we used. Since there is no current consensus on the magnitude of effects that are clinically important, this study focused on statistically significant differences in treatment effects.

In this study, the renal and vascular safety profile of rofecoxib and celecoxib was similar to that of acetaminophen. Incidences of edema-related events were low in each treatment group, with lower extremity, ankle, and pedal edema being the most common types reported. Hypertension and cardiovascular events rarely occurred in this trial. In a recent report based on selected gastrointestinal tract safety and efficacy trials on COX-2 inhibitors, the annualized rates of myocardial infarction for rofecoxib were 0.74%; for celecoxib, 0.80%; and for placebo, 0.52%.29 The placebo estimate was obtained from a meta-analysis of 4 randomized trials of aspirin for cardioprotection.29 A more recent meta-analysis that included placebo-controlled trials using the cardiovascular event end point, defined by the Anti-Platelet Trialists’ Collaboration,30 showed no significant difference in rates of these events between rofecoxib and placebo. In our study, no significant differences were found comparing COX-2 inhibitors with acetaminophen although the trial was of relatively short duration.

Our study had several potential limitations. We prespecified 5 key efficacy end points instead of a single primary end point, raising potential concerns for interpretation of statistical differences due to multiplicity of analyses. However, the findings were consistent across all end points, which in aggregate indicates a rank order of efficacy as follows: rofecoxib 25 mg/d > rofecoxib 12.5 mg/d = celecoxib 200 mg/d > acetaminophen. The consistency of the data across all 5 key end points provides support for selective COX-2 inhibitors, especially rofecoxib 25 mg/d, having greater efficacy than acetaminophen 4000 mg/d in the treatment of symptomatic OA of the knee. It is possible that a higher dose of celecoxib would have resulted in greater efficacy although previous studies have demonstrated that 200 mg/d is the dose level that provides maximal efficacy in OA.17,18 perhaps because of lack of proportional increase in plasma levels beyond this dose.29 Further statistical power also may have been provided by larger group sizes. Additional studies to evaluate the relative efficacy of these agents in OA may be helpful.

The efficacy and safety profiles of selective COX-2 inhibitors and acetaminophen need to be considered especially when treating patients with OA who tend to be older, regularly require analgesics, and are especially at risk for NSAID-related adverse events.28 Selective COX-2 inhibitors are more expensive than acetaminophen and some NSAIDs; thus, individualized decisions need to be made regarding optimal medical management and modification of treatment based on patient response, published efficacy and safety data, and overall cost considerations.5,14,17,28
COX INHIBITORS FOR KNEE OSTEOARTHRITIS

Pritchard KA, O
378-385.

Acquisition of data: Geba, Weaver, Dixon, Schnitzer.
Analysis and interpretation of data: Weaver, Polis, Schnitzer.
Drafting of the manuscript: Geba, Weaver, Schnitzer.
Critical revision of the manuscript for important intellectual content: Geba, Weaver, Polis, Dixon, Schnitzer.
Statistical expertise: Polis, Schnitzer.
Obtained funding: Weaver, Schnitzer.
Administrative, technical, or material support: Geba, Weaver, Dixon.

Study supervision: Weaver, Dixon.

VACT study group included the following investigators:
R. Betts, MD, Edmonds, Wash; A. M. Brabham, MD, Columbia, SC; W. Chase, MD, Austin, Tex; R. Fleischmann, MD, Dallas, Tex; G. Gladstein, MD, Stamford, Conn; N. Gaylis, MD, Miami Beach, Fla; M. Greenwald, MD, Rancho Mirage, Calif; K. Bordenave, MD, Albuquerque, NM; K. Pryhuber, MD, Rochester, NY; A. Kivitz, MD, Duncansville, Pa; T. Littlejohn III, MD, Winston-Salem, NC; R. Model, MD, Sellersville, Pa; D. Norden, MD, Norristown, Pa; A. Chodock, MD, Mamaroneck, NY; G. Myerson, MD, Atlanta, Ga; J. Neall, MD, Lexington, Ky; R. Ettlinger, MD, Tacoma, Wash; J. Forstot, MD, Boca Raton, Fl; J. Jozeuievicius, MD, Kalamazoo, Mich; S. Miller, MD, San Antonio, Tex; A. Razzetti, MD, Deland, Fla; J. Rubin, MD, Raleigh, NC; E. R. Harris, MD, Whittier, Calif; I. Ali, MD, Oklahoma City, Okla; T. Schnitzer, MD, PHD, Chicago, Ill; A. Veale, MD, Lincoln, Neb; L. Gilderman, DO, Pembroke Pines, Fla; W. Storms, MD, Colorado Springs, Colo; and E. Morris, MD, Baltimore, Md.

Role of the Sponsor: Performed literature search and participated with investigators in finalizing study design; responsible for implementation of study, monitoring for adherence to good clinical practice and collection of data under blinded conditions, and analysis of results based on locked database. Fully disclosed data analysis plan and reviewed all statistical analyses and results with coauthors. With all coauthors, prepared manuscript and made revisions. Final version based on external coauthors’ instruction and final approval.

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Individual responsibility has a place, but to blame those who suffer most is cruel. Let us not deflect attention from what I believe needs to be done: put justice first and provide health insurance for all citizens.

Robert L. Ferrer, MD, MPH
San Antonio, Tex


CORRECTIONS

Missing References and Errors in Tables: In the Original Contribution entitled “Efficacy of Rofecoxib, Celecoxib, and Acetaminophen in Osteoarthritis of the Knee” published in the January 2, 2002, issue of THE JOURNAL (2002;287:64-71), 2 references were cited incorrectly and 2 were inadvertently omitted. On page 70, in the second column at the bottom, reference 29 should refer to Mukherjee et al and reference 30 should refer to Konstam et al (see below). In the third column on that page, second paragraph, the sentence ”It is possible that a higher dose . . . perhaps because of lack of proportional increase in plasma levels beyond this dose” refers to citation 31, AHFS Drug Information (previous citation 30) and in the next paragraph, the first sentence that reads “The efficacy and safety profiles . . . NSAID-related adverse events.” should be cited as reference 32. The corresponding corrected references are:

In addition, Tables 2 and 3 were printed with errors. In Table 2, the 95% CI for morning stiffness (6 weeks) should read (−34.2 to −23.8). In Table 3 the first reference to “upper respiratory tract infection” should instead read “urinary tract infection.”

Change in Recommendation: In the JAMA Patient Page entitled “Rubella” published in the January 23/30, 2002, issue of THE JOURNAL (2002;287:542), the second sentence under the heading “Rubella Immunization Schedule” should have read, “Women who receive the vaccine should use birth control or abstain from sex for at least 28 days (not ‘3 months’) to avoid becoming pregnant.” The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention shortened its recommended period to avoid pregnancy after receipt of rubella-containing vaccine from 3 months to 28 days in a notice (MMWR Morb Mortal Wkly Rep. December 14, 2001;50:1117) released shortly before publication of this JAMA Patient Page.

Obituary Listings of US physicians are no longer published in JAMA. They are now available online on the Web site of the American Medical Association. The listing is now fully searchable and will be updated monthly. The listing can be accessed on the AMA Homepage at http://www.ama-assn.org by clicking on “Physicians and Medical Students,” then “News and Events,” and then “Obituary Listing,” or accessed directly at http://www.ama-assn.org/ama/pub/category/7255.html.