Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). It is not known whether a specific inhibitor of COX-2 will provide efficacy in osteoarthritis (OA) comparable with NSAIDs. Therefore, we compared the efficacy and safety of the rofecoxib, which specifically inhibits COX-2, with those of the NSAID ibuprofen in patients with OA.

Objective: To compare the clinical efficacy and tolerability of rofecoxib (12.5 and 25 mg once daily) with ibuprofen (800 mg 3 times daily).

Methods: A randomized, double-blind trial of 809 adults with OA was conducted. Patients with OA in whom the knee or hip was the primary source of pain were randomized to 1 of 4 treatment groups on demonstration of disease activity: placebo; rofecoxib, 12.5 or 25 mg once daily; or ibuprofen, 800 mg 3 times daily. Clinical efficacy and safety were monitored during a 6-week treatment period.

Results: Both doses of rofecoxib demonstrated efficacy clinically comparable with ibuprofen as assessed by 3 primary end points (pain walking on a flat surface [Western Ontario and McMaster Universities Osteoarthritis Index], patient global assessment of response to therapy, and investigator global assessment of disease status) according to predefined comparability criteria. Both rofecoxib doses and the ibuprofen dose provided significantly (P<.001) greater efficacy than placebo on all primary end points. Results from secondary end points were consistent with those of the primary end points. All treatments were well tolerated; the overall incidence rates of clinical adverse experiences were not significantly different (P>.05) among the treatment groups.

Conclusion: Rofecoxib was well tolerated and provided clinical efficacy comparable with a high dose of the NSAID ibuprofen.

Arch Intern Med. 2000;160:1781-1787

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the pain and inflammation caused by a variety of clinical disorders, including osteoarthritis (OA). The clinical effects of these drugs result primarily from the inhibition of the enzyme cyclooxygenase (COX), the first step in the conversion of arachidonic acid to prostaglandins.1 Two COX isoforms (COX-1 and COX-2) have been identified and characterized.2,25 Cyclooxygenase-1 is constitutively active throughout the body5,7 and is only slightly upregulated in some cells in response to hormones or growth factors.8,9 In contrast, under basal conditions, COX-2 expression is restricted to the brain,10,11 reproductive tract,12 kidney,13 and pancreatic islet cells,14 but it is markedly upregulated in response to inflammation and other stressors.15-20 These distinct expression patterns have led to the proposal that prostaglandins produced by COX-1 are largely responsible for physiologic functions,21 while COX-2–derived prostaglandins mediate pathophysiologic and inflammatory processes.21

In vitro and ex vivo assays have shown that NSAIDs nonspecifically inhibit both the COX-1 and COX-2 isomers.21-25 As prostaglandins are involved in the maintenance of gastrointestinal (GI) tract mucosal integrity, the well-recognized toxic effects of NSAIDs on the GI tract26 have been proposed to result largely from inhibition of COX-1 activity.21,27 The therapeutic effects of NSAIDs may be attributable to COX-2 inhibition.21,28,29 Therefore, agents that specifically inhibit COX-2 are being evaluated to determine whether they have efficacy equal to NSAIDs with an improved GI tract safety profile.
METHODS

The primary objective of this randomized, placebo-controlled clinical trial was to compare the clinical efficacy of rofecoxib (12.5 and 25 mg once daily) with ibuprofen (800 mg 3 times daily). All subjects gave written informed consent. The study protocol was approved by the institutional review boards or ethical review committees for all 49 investigative sites in 26 countries.

STUDY DESIGN

On confirmation of eligibility, patients were randomized to 1 of 4 treatment groups by a computer-generated allocation schedule: placebo, rofecoxib, 12.5 or 25 mg once daily, or ibuprofen, 800 mg 3 times daily. The primary purpose of this study was to compare the efficacy of rofecoxib with that of ibuprofen; a smaller placebo group was included to confirm that rofecoxib and ibuprofen had efficacy greater than that of the placebo. Thus, the allocation was 1:4:4:4 for placebo, both doses of rofecoxib, and ibuprofen. The masked allocation schedule was generated by an individual not otherwise involved with the study and kept concealed from all study participants. The allocation schedule was unblinded once all data had been entered, reviewed, and certified. Medication was provided in blister packages; study blinding was maintained by using a matching placebo for each study medication. Patients took 3 tablets each morning and 1 tablet at both midday and evening. Patients returned approximately every 2 weeks for 3 visits to assess both efficacy and safety. Patients were provided open-label acetaminophen for osteoarthritic pain not adequately controlled by the study medication; the maximum daily dose of acetaminophen allowed was 2600 mg, and the amount used was recorded. Patients returned 7 to 10 days after their last dose of study medication for posttherapy safety assessment.

ENTRY CRITERIA

The study included 2 groups of patients with OA. NSAID users: These patients discontinued their prior NSAID therapy on confirmation of eligibility. Following a washout period (longer than 3 plasma half-lives of prior NSAID use), patients’ pain walking on a flat surface was assessed using question 1 of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC 3.0), a patient-reported 100-mm visual analog scale (VAS). Patients were randomized to the study if they reported a minimum of 40 mm and an increase of 15 mm on the VAS compared with the value at the screening visit (ie, before discontinuation of NSAIDs), and if the investigator’s global assessment of disease status worsened by at least 1 point on a 0-to-4 Likert scale compared with the screening visit.

Rofecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone, inhibits human COX-2 with a greater than 800-fold degree of selectivity relative to COX-1 in an in vitro assay with Chinese hamster ovary cell lines expressing COX-1 or COX-2. Using ex vivo human whole blood assays, rofecoxib showed dose-related inhibition of COX-2 activity but no significant inhibition of COX-1 activity with single oral doses ranging from 5 to 1000 mg. Rofecoxib is, therefore, a specific inhibitor of the COX-2 isomorph in humans.

Clinical evidence to support the hypothesis that rofecoxib has an improved GI tract safety profile compared with NSAIDs would consist of data demonstrating that rofecoxib provides improved GI tract safety compared with an NSAID at doses that provide comparable clinical efficacy. In 2 large multicenter placebo-controlled clinical trials, rofecoxib demonstrated a favorable safety profile compared with other NSAIDs, including aspirin at a dose of 325 mg per day.

EFFICACY ASSESSMENTS

To obtain a comprehensive assessment of the effect of rofecoxib on the multiple clinical manifestations of OA, a variety of efficacy end points were included in the study that were derived from the assessments made by both the patient and the investigator.

At each visit, the patient completed the WOMAC and a global assessment of overall disease status (100-mm VAS, ranging from “very well” to “very poor”). At treatment visits, the patient also rated the overall response of his or her OA to study medication on a 0-to-4 Likert scale (“none” to “excellent”). The physician rated (1) overall assessments of disease status (0-to-4 Likert scale of “very poor” to “very well”), (2) overall response of the patient’s OA to study medication, and (3) study joint tenderness. Examination of study knee or hip joint for tenderness was performed with the patient in the supine position. Tenderness was defined as pain in response to passive motion or pressure; the hip was internally and externally rotated, and the knee was moved through the full available range to detect any end range pain and palpated around the medial and lateral joint lines while the knee was in the neutral position. Pain on palpation (knee only) or during passive range movement of the knee was considered tender. There was no attempt to quantify the amount of tenderness score.

Downloaded From:  by a Non-Human Traffic (NHT) User on 01/17/2019
of motion (hip and knee) was graded according to the following scale: 0, no pain; 1, patient states there is pain; 2, patient states there is pain and winces; and 3, patient states there is pain, winces, and withdraws. Other measurements of efficacy included amount of rescue acetaminophen consumed and discontinuation from the study because of lack of efficacy of the study medication. The primary end points were pain walking on a flat surface, patient response to therapy, and investigator global assessment of disease status. Secondary end points included the WOMAC subscales (pain, stiffness, and disability), patient global assessment of disease status, investigator assessment of response to therapy, patients discontinued from the study because of lack of efficacy, acetaminophen use, and study joint tenderness.

TOLERABILITY ASSESSMENTS

Spontaneously reported adverse experiences and vital signs were monitored at every visit. Laboratory investigations, including hematology (complete blood cell count with differential), chemistry (electrolyte, urea nitrogen, creatinine, total protein, albumin, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin levels), and urinalysis (protein, glucose, pH, red blood cells, and white blood cells, with microscopic examination if there were any abnormal results) were performed at screening, randomization, 4 and 6 weeks of therapy, and the posttherapy visit. For all adverse experiences, the investigator recorded the intensity, the relation to test drug ("definitely not" and "probably not" related were scored as not drug-related adverse experiences; "possibly," "probably," and "definitely" related were scored as drug-related adverse experiences), the outcome, and any action taken.

STATISTICAL ANALYSIS

The primary measure for each efficacy end point (except discontinuation because of lack of efficacy) was the mean response (change from baseline) over all observation times in the 6-week treatment period. All data collected from discontinuation and unscheduled visits were included in this analysis; no missing values were imputed. For each end point, a patient had to have a baseline measurement and at least 1 measurement during the 6-week treatment period for the mean change from baseline to be computed. Only 14 of the 809 randomized patients were excluded from the analysis for one or more of the primary end points because of missing baseline or on-treatment data. Eighty-five percent of the randomized patients had a measurement recorded for all 3 primary end points at all of the planned observation times.

For each end point, analysis of covariance (ANCOVA) was used to model patient mean change from baseline as a function of the categorical predictors treatment, study center, and history of ulcer or upper GI tract bleeding, and a continuous covariate, the baseline measurement. Mean patient change from baseline and SEs resulting from the ANCOVA were used for the comparisons of rofecoxib doses vs placebo and the step-down approach (25 mg first, and if significant, followed by 12.5 mg) was used for the comparisons of rofecoxib doses vs placebo.

This study had greater than 99% power to demonstrate comparable efficacy (according to the criteria cited) between rofecoxib and ibuprofen if their true difference is 0. Power calculations were based on observed treatment effects in other placebo-controlled studies with rofecoxib. Since this study was designed using variability data from a pilot study (data on file, Merck Research Laboratories), provision was made for larger variability. If the underlying SDs were 25% larger than those observed in the pilot study, the power was approximately 94%.

RESULTS

Between April 30 and November 7, 1997, 1023 patients with OA were screened and 809 were enrolled in the study (Figure 1). Patients randomly assigned to the 4 treatments...
ment groups had similar sociodemographic and clinical characteristics, including baseline values for efficacy end points (Table 1, Figure 1, and Figure 2; additional data not shown).

Of the 809 patients, 709 (88%) completed the study; the overall discontinuation rate was comparable among treatment groups (Figure 3; additional data not shown). There was a significantly higher discontinuation rate because of clinical adverse experiences in the ibuprofen group compared with the placebo group (P < .05), whereas both rofecoxib groups were not significantly different from placebo. There were significantly fewer discontinuations because of lack of efficacy (P ≤ .009) in the active therapy groups compared with the placebo group (Figure 3). The number of patients who withdrew for other reasons was similar between all groups (P > .05).

**Efficacy**

Figure 2 presents the mean change from baseline during the 6-week treatment period for the 3 primary end points (pain walking on a flat surface, patient response to therapy, and investigator global assessment of disease status) and the secondary end point of the physical function subscale of the WOMAC; data for all primary and secondary end points are shown in Table 2. For all 4 end points, the treatment effect was similar among all active groups and was superior to the placebo group. Maximum treatment effects were seen (Figure 2) by the first event was not significantly different among the treatment groups (41.9% in the placebo group vs 50.8% [rofecoxib, 12.5 mg], 53.3% [rofecoxib, 25 mg], and 51.8% [ibuprofen] in the active groups). Drug-related clinical adverse events were more common in all active therapy groups compared with placebo (10.8% vs 27.5%, 31.0%, and 30.5%, respectively; P = .003). Clinical adverse events that led to discontinuation from the study were most common in the ibuprofen group (1.4% vs 4.1%, 3.7%, and 8.4%, respectively; P = .03 vs placebo for ibuprofen only); this was mostly accounted for by adverse experiences related to the GI tract. Two symptomatic gastric ulcers were observed in the study; both were in the ibuprofen treatment group. The most common clinical adverse experiences were epigastric discomfort (0% vs 5.7%, 5.8%, and 8.0%, respectively), diarrhea (4.1% vs 4.5%, 5.0%, and 5.2%, respectively), and nausea (1.4% vs 2.9%, 6.6%, and 3.6%, respectively). The incidence of any laboratory adverse event was not significantly different among the treatment groups (4.1% in the placebo group vs 10.7% [rofecoxib, 12.5 mg], 7.6% [rofecoxib, 25 mg], and 13.4% [ibuprofen] in the active groups). The mean changes in body weight and blood pressure were similar in all treatment groups. Adverse experiences of edema or hyper-

**Tolerability**

The incidence of any clinical adverse event was not significantly different among the treatment groups (41.9% in the placebo group vs 50.8% [rofecoxib, 12.5 mg], 53.3% [rofecoxib, 25 mg], and 51.8% [ibuprofen] in the active groups). Drug-related clinical adverse events were more common in all active therapy groups compared with placebo (10.8% vs 27.5%, 31.0%, and 30.5%, respectively; P = .003). Clinical adverse events that led to discontinuation from the study were most common in the ibuprofen group (1.4% vs 4.1%, 3.7%, and 8.4%, respectively; P = .03 vs placebo for ibuprofen only); this was mostly accounted for by adverse experiences related to the GI tract. Two symptomatic gastric ulcers were observed in the study; both were in the ibuprofen treatment group. The most common clinical adverse experiences were epigastric discomfort (0% vs 5.7%, 5.8%, and 8.0%, respectively), diarrhea (4.1% vs 4.5%, 5.0%, and 5.2%, respectively), and nausea (1.4% vs 2.9%, 6.6%, and 3.6%, respectively). The incidence of any laboratory adverse event was not significantly different among the treatment groups (4.1% in the placebo group vs 10.7% [rofecoxib, 12.5 mg], 7.6% [rofecoxib, 25 mg], and 13.4% [ibuprofen] in the active groups). The mean changes in body weight and blood pressure were similar in all treatment groups. Adverse experiences of edema or hyper-

---

**Table 1. Patient Characteristics by Treatment Assignment**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (n = 244)</th>
<th>Rofecoxib, 12.5 mg (n = 244)</th>
<th>Rofecoxib, 25 mg (n = 242)</th>
<th>Ibuprofen, 2400 mg (n = 249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>63.1 ± 9.7</td>
<td>64.9 ± 9.4</td>
<td>62.8 ± 9.3</td>
<td>64.1 ± 8.3</td>
</tr>
<tr>
<td>Female, %</td>
<td>85.1</td>
<td>81.1</td>
<td>78.9</td>
<td>78.3</td>
</tr>
<tr>
<td>Duration of osteoarthritis, y, mean ± SD</td>
<td>9.3 ± 8.4</td>
<td>8.3 ± 6.4</td>
<td>8.5 ± 7.1</td>
<td>9.0 ± 7.5</td>
</tr>
<tr>
<td>ARA functional class II or III, %</td>
<td>88</td>
<td>88</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>Knee/hip as study joint, %</td>
<td>77/23</td>
<td>78/22</td>
<td>80/20</td>
<td>75/25</td>
</tr>
<tr>
<td>Prior use of NSAIDs, %</td>
<td>91</td>
<td>91</td>
<td>87</td>
<td>92</td>
</tr>
</tbody>
</table>

*ARA indicates American Rheumatism Association; NSAIDs, nonsteroidal anti-inflammatory drugs.*
COMMENT

The discovery of 2 isoforms of COX, the target enzyme inhibited by NSAIDs, has led to a number of questions concerning the role of inhibiting COX-1 vs COX-2 in terms of the efficacy and safety of this widely prescribed class of drugs. Previous work has demonstrated that specific inhibitors of COX-2 are efficacious in the treatment of OA, but left open the question of how that efficacy compares with NSAIDs, which inhibit both COX-1 and COX-2. In this report, we demonstrated that the efficacy of rofecoxib, which specifically inhibits COX-2, was comparable with that of a high dose of the NSAID ibuprofen. Importantly, we characterized the effect of rofecoxib on a variety of the clinical manifestations of OA, and in all cases, we found the efficacy of rofecoxib to be comparable with ibuprofen. These results were obtained in a large, diverse population of patients from 26 different countries, and the results were consistent across race, age, sex, study joint, and prior OA medication use (NSAID vs acetaminophen). Our data also demonstrated that rofecoxib, 12.5 and 25 mg, provided comparable clinical efficacy. Based upon these and other data, it is recommended that 12.5 mg be used as the initial dose of rofecoxib for the treatment of OA.

The NSAIDs are associated with a number of toxic effects, the most important of which are related to the GI tract and the kidney. To firmly establish an improved safety profile of rofecoxib in contrast to NSAIDs, it is important that the safety profiles be compared using doses that provide equivalent efficacy. This study rigorously demonstrated that both once-daily doses (12.5 mg and 25 mg) of rofecoxib...
(which specifically inhibits COX-2) provided comparable clinical efficacy with ibuprofen, 800 mg 3 times daily (a dual COX-1 and COX-2 inhibitor). Therefore, it is appropriate to compare the safety and tolerability of rofecoxib, 12.5 and 25 mg, with those of ibuprofen, 2400 mg.

It is important to note that no adverse events unique to the specific inhibition of COX-2 were apparent in the rofecoxib treatment groups as assessed in this 6-week controlled clinical trial. All active treatments were generally well tolerated. Adverse experiences potentially attributable to renal effects of COX inhibition, such as edema, hypertension, weight gain, and changes in blood pressure, were comparable in all treatment groups, including the placebo group.

An important clinical adverse effect of NSAIDs is their propensity to lead to serious upper GI tract events, such as perforations, gastric and duodenal ulcerations, and upper GI tract bleeding. In other clinical studies, as assessed by endoscopy, the incidence of abnormalities of the GI mucosae associated with rofecoxib, 25 and 50 mg, was substantially less than that associated with ibuprofen, 800 mg 3 times daily. Our study was not intended to assess endoscopically diagnosed ulcerations and was not large enough or long enough to compare the incidence of serious upper GI tract events. However, in an overview analysis of all clinical trials performed with rofecoxib, including our study, the incidence of serious upper GI tract events was found to be significantly less with rofecoxib compared with NSAIDs.

In summary, we have demonstrated that specific inhibition of COX-2 provides efficacy in the treatment of OA that is comparable with that of high doses of the NSAID ibuprofen. The safety of rofecoxib, 12.5 and 25 mg once daily, was not significantly different from placebo and ibuprofen, 800 mg 3 times daily.

Accepted for publication December 8, 1999.

This work was funded by grants from Merck & Co Inc, West Point, Pa.

Presented as an abstract at the European League Against Rheumatism 14th Congress in Glasgow, Scotland, June 6-12, 1999.

Other members of the Rofecoxib/Ibuprofen Comparator Study Group are as follows: A. Alves de Matos, MD, Lisbon, Portugal; Andre Beaulier, MD, Sainte-Foy, Quebec; Jamie Beier, MD, Esbjerg, Denmark; William Bensen, MD, Hamilton, Ontario; Marco Broginni, MD, Varese, Italy; Ricardo Castro, MD, Sao Paulo, Brazil; H. Eckhardt, MD, Vogtareuth, Germany; Bernard Combe, MD, Montpellier, France; Peter T. Dawes, MD, Stoke-on-Trent, England; Martin de Arruda-Martins, MD, Stockholm, Sweden; Gabriel Herrero-Beaumont, MD, Madrid, Spain; Marco Broggini, MD, Varese, Italy; Ricardo Castro, MD, Sao Paulo, Brazil; H. Eckhardt, MD, Vogtareuth, Germany; Carlos Fuentealba, MD, Santiago, Chile; D. Geissler, MD, Klagenfurt, Austria; Mel Gomes, MD, Lisbon, Portugal; Nigel Gilchrist, MD, Christchurch, New Zealand; Franciso Gutierrez, MD, Santiago, Chile; Kurt Haas, MD, Stockholm, Sweden; Gabriel Herrero-Beaumont, MD, Madrid, Spain; Boulou Harouati, MD, Montreal, Quebec; Bruce Kirkham, MD, Kogarah, Australia; Peter Koz, MD, Vienna, Austria; Michel

Table 2. Efficacy Results by End Point According to Treatment Assignment*

<table>
<thead>
<tr>
<th>Efficacy End Points</th>
<th>Placebo (n = 74)</th>
<th>Rofecoxib, 12.5 mg (n = 244)</th>
<th>Rofecoxib, 25 mg (n = 242)</th>
<th>Ibuprofen, 2400 mg (n = 249)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain walking on a flat surface †</td>
<td>-18.92 (−23.72 to −14.12)</td>
<td>-34.32 † (−37.03 to −31.60)</td>
<td>-35.07 † (−38.22 to −31.33)</td>
<td>-33.55 † (−36.26 to −30.84)</td>
</tr>
<tr>
<td>Patient global assessment of response to therapy §</td>
<td>-1.56</td>
<td>-2.28 †</td>
<td>-2.44 †</td>
<td>-2.22 †</td>
</tr>
<tr>
<td>Investigator global assessment of disease status §</td>
<td>-1.00</td>
<td>-1.47 †</td>
<td>-1.59 †</td>
<td>-1.40 †</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical function subscale †</td>
<td>-8.76 (−12.72 to −4.79)</td>
<td>-18.73 † (−20.98 to −16.49)</td>
<td>-20.64 † (−22.91 to −18.37)</td>
<td>-18.06 † (−20.30 to −15.82)</td>
</tr>
<tr>
<td>Pain subscale †</td>
<td>-11.89 (−15.98 to −7.80)</td>
<td>-23.37 † (−25.68 to −21.05)</td>
<td>-24.78 † (−27.13 to −22.44)</td>
<td>-22.89 † (−25.21 to −20.58)</td>
</tr>
<tr>
<td>Stiffness subscale †</td>
<td>-8.88 (−13.38 to −4.38)</td>
<td>-21.24 † (−23.77 to −18.70)</td>
<td>-20.79 † (−23.33 to −18.24)</td>
<td>-20.17 † (−22.69 to −17.65)</td>
</tr>
<tr>
<td>Patient global assessment of disease status †</td>
<td>-10.02</td>
<td>-26.93 †</td>
<td>-29.05 †</td>
<td>-25.28 †</td>
</tr>
<tr>
<td>Patients discontinued because of lack of efficacy, No. (%)</td>
<td>9 (12.2)</td>
<td>8 (3.3)</td>
<td>7 (2.9)</td>
<td>9 (3.6)</td>
</tr>
<tr>
<td>Investigator global assessment of response to therapy §</td>
<td>-1.70 (−1.91 to −1.49)</td>
<td>-2.44 † (−2.56 to −2.32)</td>
<td>-2.56 † (−2.68 to −2.44)</td>
<td>-2.40 † (−2.52 to −2.28)</td>
</tr>
<tr>
<td>Tenderness in study joint</td>
<td>-0.56 (−0.70 to −0.42)</td>
<td>-0.84 † (−0.93 to −0.76)</td>
<td>-0.93 † (−1.01 to −0.85)</td>
<td>-0.82 † (−0.90 to −0.74)</td>
</tr>
<tr>
<td>Acetaminophen usage for rescue, tablets/d</td>
<td>1.36</td>
<td>0.88</td>
<td>0.82</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*All values are least squares means (95% confidence intervals) except for the end point “patients discontinued because of lack of efficacy.”
†Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a visual analog scale of 0 to 100 mm.
‡P ≤ .009 compared with placebo.
§Likert scale (0-4).
LaRoche, MD, Toulouse Cedex, France; Hans Ivar Lund, MD, Esbjerg, Denmark; Terry Macedo, MD, Auckland, New Zealand; Christian Marcelli, MD, Caen, France; Roberto Marcolongo, MD, Siena, Italy; Lyn March, MD, St Leonards, Australia; Erich Mur, MD, Innsbruck, Austria; Pasquale Oriente, MD, Naples, Italy; G. Passero, MD, Rome, Italy; Karel Pavelka, MD, Prague, Czech Republic; Jean Pierre Pelletier, MD, Montreal, Quebec; F. Raeman, MD, Merksem, Belgium; Erik Rosal, MD, Guatemala City, Guatemala; Peter Ryan, MD, Victoria, Australia; Manfred Shattenkirchner, MD, Munich, Germany; F. Singer, MD, Laab in Walde, Austria; Malcolm Smith, MD, Daws Park, Australia; Hyman Tannenbaum, MD, Montreal, Quebec; Glen Thomson, MD, Winnipeg, Manitoba; Jesus Tornero, MD, Gualadajara, Spain; Desiree Van der Heijde, MD, Maastricht, Holland; Sol Villegas de Morales, MD, Caracas, Venezuela; and P. Villeger, MD, St Gallen, Switzerland.

We thank Magaly Garcia Woolard, Francis D’Anzi, and Jovanni Gonzalez for their help in conducting this study.


REFERENCES