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A randomized placebo-controlled trial comparing the efficacy of etoricoxib 30 mg and ibuprofen 2400 mg for the treatment of patients with osteoarthritis[1,2]

A. Puopolo M.D.†, J. A. Boice Ph.D.‡*, J. L. Fidelholtz M.D.§, T. W. Littlejohn M.D.‖, P. Miranda M.D.#, A. Berrocal M.D.¶, A. Ko M.P.H.‡, N. Cichanowitz M.S.J.‡ and A. S. Reicin M.D.‡

† *Milford Emergency Associates, Milford, MA, United States*
‡ *Merck Research Laboratories, Rahway, NJ, United States*
§ *Hilltop Physicians, Inc., Hightop Medical Research Center, Cincinnati, OH, United States*
‖ *Piedmont Medical Research Associates, Winston-Salem, NC, United States*
¶ *Clinica Stella Maris, Lima, Peru*
# *Hospital San Juan De Dios, Santiago, Chile*

Summary

Objective: We compared the efficacy of etoricoxib 30 mg to placebo and ibuprofen 2400 mg for the treatment of osteoarthritis (OA) of the hip and knee.

Design: In this 12-week, randomized, double-blind, placebo- and active-comparator-controlled trial, 548 patients (median age 63 years) with OA of the hip or knee were randomized to receive placebo, etoricoxib 30 mg q.d., or ibuprofen 800 mg t.i.d. Demonstration of etoricoxib's efficacy vs placebo and comparison of its efficacy to ibuprofen were assessed using three co-primary endpoints: Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) Pain Subscale (WOMAC-PS); WOMAC Physical Function Subscale (WOMAC-PFS); and Patient Global Assessment of Disease Status (PGADS). Each primary endpoint utilizes a 0–100 mm visual analog scale. To demonstrate comparable efficacy of etoricoxib vs ibuprofen, the 95% confidence intervals (CIs) for the difference in the least squares (LS) mean change over 12 weeks for all three co-primary endpoints had to fall within ±10 mm. Safety and tolerability data were collected throughout the study.

Results: Mean baseline values for the three co-primary endpoints ranged from 62.52 to 70.14 mm. Both etoricoxib and ibuprofen demonstrated superior ($P \leq 0.002$) efficacy for all primary endpoints. The LS mean (mm) changes (95% CI) over 12 weeks for etoricoxib and ibuprofen, respectively, compared to placebo were given as follows: WOMAC-PS: −11.66 (−16.31, −7.01) and −7.62 (−12.30, −2.94); WOMAC-PFS: −10.15 (−14.74, −5.57) and −7.23 (−11.85, −2.61); PGADS: −11.65 (−16.81, −6.50) and −8.11 (−13.30, −2.92). The efficacy of etoricoxib 30 mg was comparable to ibuprofen 2400 mg. All treatments were similarly well tolerated.

Conclusion: Treatment with etoricoxib 30 mg q.d. provides superior efficacy vs placebo and comparable clinical efficacy vs ibuprofen 2400 mg (800 mg t.i.d.) for the treatment of OA of the hip and knee.

Key words: Osteoarthritis, Etoricoxib, COX-2, Ibuprofen, Selective NSAID.

Abbreviations: AE adverse experience, ANOVA analysis of variance, ANCOVA analysis of covariance, ARA American Rheumatism Association, CHF congestive heart failure, CI confidence interval, COX cyclooxygenase, CV cardiovascular, CVA cerebrovascular accident, DVT deep vein thrombosis, GPAs gastroprotective agents, IGADS Investigator Global Assessment of Disease Status, IGART Investigator Global Assessment of Response to Therapy, LS least squares, MEDAL Multinational Etoricoxib and Diclofenac Arthritis Long-term, MITT modified intention-to-treat, Traditional NSAIDs Traditional nonsteroidal anti-inflammatory drugs, OA osteoarthritis, PGADS Patient Global Assessment of Disease Status, PGART Patient Global Assessment of Response to Therapy, q.d. once daily, t.i.d. three times daily, VA visual analog, VAS visual analog scale, WOMAC Western Ontario and McMaster's University Osteoarthritis Index, WOMAC-PS WOMAC Pain Subscale, WOMAC-PFS WOMAC Physical Function Subscale.

Introduction

Osteoarthritis (OA), generally considered a disease of aging, is the most common form of arthritis in older adults. In its severe form, the chronic pain of OA can lead to a significant reduction in the overall quality of life in patients of any age[1–4]. OA of the knee and hip can be quite disabling since these are major weight-bearing joints[5]. Given current projections indicating that OA could be the fourth leading cause of disability on a world-wide basis by the year 2020, the need for multiple treatment options exists[6].

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[2] Clinical study protocol registered at http://www.clinicaltrials.gov/ct/show/NCT00092755.

*Address correspondence and reprint requests to: Dr Judith A. Boice, Ph.D., Merck Research Laboratories, Clinical Immunology and Analgesia, P.O. Box 2000, Rahway, NJ 07065, United States. Tel: 1-732-594-6297; Fax: 1-732-594-7435; E-mail: judith_boice@merck.com

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Acetaminophen and non-pharmacologic approaches, such as exercise and improvement of joint biomechanics, are considered first-line treatment options for patients with OA[7,8]. However, traditional nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the pain and symptoms associated with this disease[7,9,10]. Nevertheless, there is a greatly elevated risk of gastrointestinal (GI) toxicity associated with traditional NSAIDs due to their additional inhibition of the cyclooxygenase-1 (COX-1) isoenzyme. This risk of NSAID-induced GI toxicity increases in a linear fashion with age[11].

Etoricoxib is a member of the COX-2 selective inhibitor class of NSAIDs and exhibits a reduced risk of GI toxicity compared to traditional NSAIDs[12,13]. Recent long-term randomized placebo-controlled trials have demonstrated an increased time-dependent risk of thrombotic cardiovascular (CV) events with other COX-2 selective NSAIDs compared with placebo[14,15]. Meta-analyses and reviews by regulatory authorities in the United States and Europe indicate that this risk likely extends to traditional NSAIDs[16–19].

Etoricoxib's anti-inflammatory and analgesic efficacy for the treatment of acute and chronic pain have been established in multiple studies using a once daily dosing regimen and is reviewed elsewhere[20]. In countries where it is approved, the recommended once daily dose of etoricoxib for the treatment of OA is 60 mg. The purpose of this study, the second of two replicate, randomized, placebo- and active-comparator-controlled trials, was to examine the efficacy as well as the safety and tolerability of etoricoxib 30 mg q.d. compared to placebo and ibuprofen 800 mg t.i.d. in patients with OA of the knee or hip. In the first of these two studies (Sponsor protocol number 071), the efficacy of etoricoxib 30 mg was found to be superior to placebo and comparable to ibuprofen 2400 mg for the treatment of OA of the hip and knee[21]. The identification of lower effective doses of NSAIDs including selective COX-2 inhibitors is important in the context of mechanism-based side effects such as edema and hypertension, which are known to be dose-related.

Patients and methods

The protocol for this study was approved by the Institutional Review Board at each study center. All patients provided written informed consent prior to their participation in the study.

This 12-week, placebo- and active-comparator-controlled trial was conducted in 548 patients in 49 centers (41 in the United States and eight in Latin America) under double-blind (with in-house blinding) conditions to evaluate the efficacy, safety, and tolerability of etoricoxib 30 mg compared to placebo and ibuprofen 800 mg t.i.d. for the treatment of OA of the knee and hip. Otherwise healthy male and female OA patients 40 years or older, were enrolled. Women of child-bearing potential were determined to be in a nongravid state and were instructed to use contraceptive measures during the study. Eligible patients were required to have a clinical and radiographic diagnosis of OA of the knee or hip for at least the previous 6 months or were newly diagnosed patients with clinical symptoms consistent with OA of the study joint for at least the previous 6 months. All patients were required to have pain on motion or weight bearing for the majority of days during the previous month, which was partially relieved by rest. Radiographic criteria included joint space narrowing for hip OA. Patients with knee OA were required to have both tibiofemoral osteophytes and tibiofemoral joint space narrowing. All eligible patients met American Rheumatism Association (ARA) functional class I, II, or III criteria[22] and were required to have been using NSAIDs or acetaminophen to treat their OA. The primary source of pain for each patient was in the lower extremity. In cases where both knees and/or hips were affected, the most painful joint was selected for study evaluation. Patients who were regular users of NSAIDs (at least 25 of the last 30 days preceding enrollment) were required to have a prestudy score of less than 80 mm (based on the 0–100 mm visual analog scale [VAS]) for patient assessment of pain while walking on a flat surface. Following cessation of NSAID therapy (washout period) patients were instructed to return to the clinic upon experiencing a flare of OA pain. Prespecified washout periods for the various prior NSAIDs that were used ranged from 3 to 20 days. A sufficient flare within the washout period was defined as a patient-reported pain score of at least 40 mm while the patient walked on a flat surface, and was at least 15 mm greater than that recorded at the prestudy visit as well as a worsening of at least one point (0- to 5-point Likert scale) for Investigator Global Assessment of Disease Status (IGADS).

Patients who were classified as acetaminophen users (1.2–4 g of acetaminophen daily for at least 25 of the last 30 days preceding enrollment) reported no NSAID use for treatment of their OA and were required to have minimum scores of 40 mm for patient-reported pain while walking on a flat surface and Patient Global Assessment of Disease Status (PGADS), and an IGADS of fair, poor, or very poor. The number of acetaminophen users at each study site was limited to 20%, since this agent acts only as an analgesic, and unlike etoricoxib and ibuprofen, does not have anti-inflammatory activity.

All patients were required to stop taking rescue acetaminophen at least 12 h (24 h if they were using extended-release formulations) prior to all treatment visits and for acetaminophen users only, prior to screening.

EXCLUSION CRITERIA

Patients were excluded if they had medical conditions, such as recent joint injuries or rheumatologic, autoimmune, or musculoskeletal diseases that could confound or interfere with efficacy evaluations.

TREATMENT

Qualified patients were randomized to receive placebo, etoricoxib 30 mg q.d., or ibuprofen 800 mg t.i.d. for 12 weeks. Within each study center, patients were randomly allocated using a computer-generated allocation schedule; allocation was not stratified in this study. All study personnel, including investigators, study site personnel, patients, monitors, central laboratory and other study personnel, remained blinded to treatment allocation throughout the study. Study medication was supplied in two coded study bottles, labeled "bottle A" (containing either etoricoxib 30 mg tablets or matching placebo) and "bottle B" (containing either ibuprofen 800 mg tablets or matching placebo). Patients were instructed to take one tablet in the morning from bottle A and one tablet in the morning, afternoon, and evening from bottle B. Acetaminophen was provided as rescue medication for pain, if needed. Treatment compliance and amount of rescue acetaminophen use were determined by tablet counts.