The Efficacy of Diacerein in Hand Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Study

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ABSTRACT

Background: Diacerein is a drug used in osteoarthritis (OA) that elicits an inhibitory effect on interleukin-1 and metalloproteases. Although diacerein has shown modest efficacy and safety in the treatment of knee and hip OA, there have been no placebo-controlled clinical trials for hand OA.

Objective: The aim of the current study was to investigate the efficacy and tolerability of diacerein in patients with hand OA.

Methods: Patients fulfilling the American College of Rheumatology criteria for hand OA participated in this randomized, double-blind, placebo-controlled study. Eligible patients were >40 years of age, had at least 1 tender joint, and had a joint pain visual analog scale of >30 mm. Patients received diacerein (50 mg) or placebo BID for 12 weeks. The primary end point was the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain score at 4 weeks. Secondary end points were AUSCAN pain score at 12 weeks and AUSCAN physical function and stiffness score, patient and physician global assessment, functional index of hand OA scores, and multidimensional health assessment questionnaire results at 4 weeks and 12 weeks.

Results: Eighty-six Korean patients were enrolled (42 diacerein, 44 placebo). The intention-to-treat and per-protocol analyses revealed no significant differences between the 2 groups in terms of change in AUSCAN pain score at 4 weeks, except for improvement in physician global assessment at 4 weeks (per-protocol analysis, $P = 0.004$). The safety profile of diacerein was comparable to placebo, except for frequent discoloration of the urine (88% vs 20%).

Conclusion: These results suggest that diacerein 50 mg BID may be ineffective in controlling the symptoms of hand OA. ClinicalTrials.gov identifier: NCT00685542.

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Key words: Australian/Canadian Osteoarthritis Hand Index, diacerein, hand, osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) affects >30% of the elderly population (65 years and older) and commonly involves the knees, hips, spine, and hands.[1] The reported prevalence of hand OA in the elderly varies according to which diagnostic criteria are applied; it ranges from 6% to 20% with clinical criteria to 80% with radiologic criteria.[2] OA typically affects the distal and proximal interphalangeal and the first carpometacarpal joints, resulting in a variable degree of pain and stiffness. The impact of hand OA on health-related quality of life is estimated to be almost equivalent to that of rheumatoid arthritis.[3–6]

Evidence-based treatment guidelines for hand OA are incomplete because there is a scarcity of well-designed randomized studies.[7] NSAIDs are effective in controlling symptoms but are associated with serious adverse events such as gastrointestinal hemorrhage. The efficacy of disease-modifying OA drugs in terms of joint symptoms and structures remains unknown. Although 1 report found that chondroitin polysulfate partially prevented radiographic progression in OA, its efficacy in symptom control is unclear.[8]

Diacerein is a drug that was developed specifically for the treatment of OA. It has inhibitory effects on both interleukin (IL)-1β and metalloproteases such as collage-

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nase and stromelysin, while exerting no effects on phospholipase A_2, cyclooxygenase, or lipoxygenase.[9–11] Diacerein has exhibited anti-inflammatory effects and reduced structural changes in various OA animal models.[12–14] In recent meta-analyses, diacerein showed modest efficacy and a good safety profile in the treatment of human knee and hip OA.[15–17] The most common adverse effect was diarrhea, which was reported in ~30% of patients. Despite the proven efficacy of diacerein in lower-extremity OA, the efficacy and safety of diacerein in hand OA remain to be clarified. The aim of the current study was to investigate the clinical efficacy and tolerability of diacerein in hand OA by performing a double-blind, randomized, placebo-controlled study.

PATIENTS AND METHODS

Study Population

Patients fulfilling the American College of Rheumatology criteria for hand OA[18] were enrolled at a rheumatologic clinic in the Seoul National University Hospital between June 2008 and May 2009. Eligible patients were >40 years old, had >1 tender joint, and had joint pain >30 mm according to a visual analog scale (100 mm) after a 2-week washout period. Patients with a history of hand joint surgery or treatment with oral corticosteroids, intra-articular corticosteroids, or hyaluronic acid injection within the previous 3 months were excluded.

All patients were required to provide written informed consent. The study protocol was reviewed and approved by the Seoul National University Hospital institutional review board.

Study Design

This was a double-blind, randomized, placebo-controlled study. After a 2-week washout period, eligible patients were randomized 1:1 to receive diacerein 50 mg or placebo BID for 12 weeks. The study medication and placebo were provided by Myungmoon Pharmaceutical Co, Ltd (Seoul, Korea). The dosage of diacerein was based on the results of a previous study for knee OA, which reported that the efficacy and safety of a 50-mg BID dose was superior to placebo.[19] An independent pharmacist allocated patients to each group by using a predetermined random number table. The efficacy and tolerability of the medication were evaluated at 2, 4, 8, and 12 weeks by a single rheumatologist (E.B.L.) Acetaminophen (650 mg) was used as a rescue drug. Efficacy failure was defined as use of acetaminophen for >7 consecutive days. In such cases, the study medication was replaced with nabumetone 500 mg BID.

The primary study end point was the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain score at 4 weeks after starting the study medication.[20,21] Four weeks was chosen as the time point of measurement for the following reasons. First, severity of pain was the primary end point of the study, and a guideline on hand OA studies suggests measuring pain severity at 4 to 6 weeks for symptom-modifying OA drugs.[22] Second, primary end points are measured at 4 weeks in most hand OA studies in which pain is assessed.[23–26] The secondary end points were AUSCAN pain score at 12 weeks and AUSCAN physical function and stiffness score, functional index of hand OA score, and multidimensional health assessment questionnaire score at 4 and 12 weeks. The reliability, validity, and responsiveness of the Korean version of AUSCAN were evaluated before the initiation of the current study.[27] The study was performed in compliance with the Declaration of Helsinki.

Safety Assessment

Clinical features (abdominal pain, diarrhea, headache, skin rash, and urine discoloration) and laboratory tests (complete blood count, liver function tests, and serum creatinine) were evaluated at 2, 4, 8, and 12 weeks. The following medications, which can all influence the symptoms of hand OA, were prohibited during the 12-week study period: NSAIDs, analgesics, glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, avocado/soybean unsaponifiables, methylsulfonylmethane, SKI306X, lipid extract from *Perna canaliculus*, vitamin C, vitamin E, devil's claw, and *Zingiberaceae*.

Statistical Analysis

The AUSCAN pain score at 4 weeks was the primary end point. Improvement in AUSCAN pain score at 4 weeks was hypothesized to be 20% in the diacerein group and 10% in the placebo group. Assuming an SD of 16 mm, an α level of 0.05, and power of 0.80, the required number of patients in each group was 32 (1-tailed *t*-test). Assuming a dropout rate of 25%, the aim was to enroll 43 patients in each group.

An intention-to-treat analysis (ITT) was performed first, followed by a per-protocol (PP) analysis. The primary end point data were compared by using the Student *t*-test. To account for group and time interaction, a mixed model analysis was used to evaluate the statistical significance of secondary end points. In addition, changes in AUSCAN indices