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Efficacy and Safety of Celecoxib in Chinese Patients with Ankylosing Spondylitis: A 6-Week Randomized, Double-Blinded Study with 6-Week Open-Label Extension Treatment

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs are the first-line option for treating ankylosing spondylitis (AS) in China. However, no large-scale controlled trials have been conducted in this ethnic population.
Objective: To evaluate the efficacy and safety of 6 weeks' treatment with celecoxib in patients with AS in China.
Methods: This Phase 3, double-blind, parallel-group study randomized patients with AS aged ≥ 18 to 65 years 1:1 to receive celecoxib 200 mg once daily or diclofenac sustained release 75 mg once daily. After 6 weeks, patients could use celecoxib 400 mg once daily or maintain blinded therapy. The primary efficacy end point was mean change from baseline at Week 6 for Patient's Global Assessment of Pain Intensity score (100-mm visual analog scale). Noninferiority was established if the upper bound of the CI was < 10 mm. Secondary objectives included patients' and physicians' assessments of disease activity, change from baseline in C-reactive protein level, and safety.
Results: In the per-protocol analysis set the least squares mean change from baseline in the Patient's Global Assessment of Pain Intensity score at Week 6 was –23.8 mm and –27.1 mm in patients receiving celecoxib (n = 111) and diclofenac (n = 108), respectively. The 2-sided 95% CI for the treatment difference (celecoxib – diclofenac) was –2.2 to 8.8. Overall, 4.2% and 6.7% of patients in the celecoxib and diclofenac groups, respectively, reported treatment-related adverse events. All were mild to moderate in severity.
Conclusions: Celecoxib 200 mg once daily is noninferior to diclofenac sustained release 75 mg once daily for pain treatment in Chinese patients with AS. ClinicalTrials.gov identifier: NCT00762463.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton manifested by inflammatory back pain, progressive stiffness of the spine, arthritis, enthesitis, and acute anterior uveitis.[1,2] Symptoms of AS traditionally appear during late adolescence and early adulthood, and the condition is a significant health burden in young male adults.[3] If the disease is undiagnosed or inadequately treated, patients with AS may experience continuous pain, stiffness, fatigue, and a progressive loss of spinal mobility and function, which ultimately leads to a reduction in quality of life.[4] The 1984 modified New York criteria describe the classification criteria for AS.[5] Patients may be diagnosed with AS if characteristic radiologic changes of the sacroiliac joint are present, together with defined clinical symptoms and physical findings.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently the mainstay of treatment for AS.[6] In China, where the prevalence of AS is 0.3%,[7] nonselective (ns) NSAIDs and tumor necrosis factor-α (TNFα) antagonists are approved AS treatments. In addition, a number of other medications, including disease-modifying antirheumatic drugs, opioids, and muscle relaxants are prescribed for the treatment of patients with AS.[7] However, evidence suggests that, particularly over the longer term, the use of nsNSAIDs and injectable TNFα antagonists may be limited by the concern for adverse events (AEs) and other undesirable effects.[8,9] The use of nsNSAIDs has been associated with AEs affecting the gastrointestinal (GI) tract[8] and cardiovascular system,[10–13] with diclofenac being associated with a particularly high risk of cardiovascular adverse events.[11] In addition, nsNSAIDs are also believed to exacerbate inflammatory bowel disease that often accompanies spondyloarthropathies.[14–18] Although injectable TNFα antagonists have been shown to be effective treatments for the signs and symptoms of AS,[19,20] the cost of use, inconvenience of administration, and possible safety concerns[9] may limit their use to refractory or severe cases.

Compared with nsNSAIDs, which inhibit both cyclooxygenase (COX)-1 and COX-2, the COX-2 selective NSAIDs are thought to have a superior GI safety profile[21] because they selectively inhibit COX-2–mediated production of inflammatory mediators while preserving the integrity of the gastroduodenal mucosa (through COX-1 mediated synthesis of prostanoids).[22] Furthermore, the rate of cardiovascular AEs has been demonstrated to be comparable to that of nsNSAIDs in a meta-analysis.[23]

Outside of China, the COX-2 selective NSAID celecoxib has been evaluated in 2 double-blind, randomized, controlled, active-comparator trials in patients with AS.[24,25] However, to date, no large-scale randomized controlled trials have been conducted in China, where there is a paucity of efficacy and safety data for this treatment. Therefore the primary objective of our study was to demonstrate noninferiority of celecoxib 200 mg once daily compared with diclofenac sustained release (SR) 75 mg once daily in the treatment of Chinese patients with AS in terms of pain assessment after 6 weeks of treatment.

Patients and Methods

Study design

Our study (ClinicalTrials.gov identifier NCT00762463) was a randomized, active-comparator, double-blind, parallel-group, noninferiority study conducted at 5 centers across China. The protocol was approved by the institutional review board or independent ethics committee at each center, and the study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and local regulatory requirements. The study consisted of a double-blind treatment period lasting 6 weeks, followed by a 6-week extension period. All patients provided written informed consent before any screening procedures were performed.

The study included a total of 6 study visits: screening visit (Visit 1), baseline visit (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 12 (Visit 6 for those enrolled in the extension period) or when the study drug was terminated (end-of-treatment visit) (Figure 1). However, unscheduled visits were possible at any time during the study treatment if required.

The primary objective was to demonstrate noninferiority of celecoxib 200 mg once daily compared with diclofenac SR 75 mg once daily in the treatment of patients with AS in the per-protocol analysis set population, in terms of their pain assessment at Week 6. Diclofenac was chosen as the active comparator in this study because it is commonly used to treat AS.[26] A dose of 75 mg diclofenac SR once daily was chosen to minimize the emergence of AEs that have been associated with the higher dose of 150 mg daily.[27,28]

Patients

Adult male and female patients aged 18 to 65 years were eligible for inclusion if they had AS according to the 1984 modified New York criteria for classification of AS.[5] In addition, all patients must have had a diagnosis of AS with axial involvement but without peripheral joint involvement (synovitis) at the time of study entry. Patients were required to have been receiving daily treatment with NSAIDs 30 days before study entry. Patients were excluded if they had known inflammatory enteropathy, the presence of other extra-articular manifestations, known vertebral compression, or the need to wear a corset during the study. In addition, patients were excluded if they required the use of concomitant muscle relaxants, hypnotics, anxiolytics, sedatives, tranquillizers, or antidepressant drugs, or the concomitant use of anticoagulants, ticlopidine, lithium, aspirin $>$ 150 mg/d, methotrexate $>$ 15 mg/wk, prednisolone $>$ 10 mg/d (or equivalent dose of other corticosteroids), NSAIDs, or COX-2 inhibitors (other than study drug or biologics). Women with childbearing potential were required to have been using adequate contraception.

Treatment

Patients were randomized 1:1 to receive either celecoxib 200 mg once daily or diclofenac SR 75 mg once daily for 6 weeks

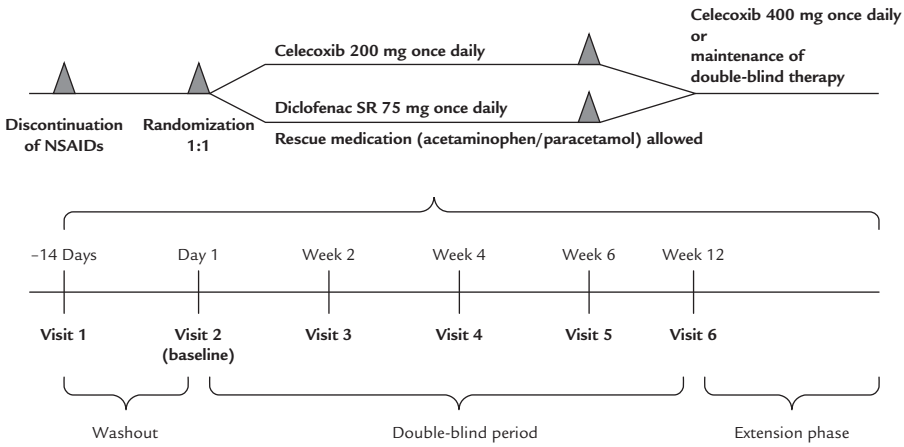

Figure 1. Study design. NSAID = nonsteroidal anti-inflammatory drug; SR = sustained release.