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Phase 1b Study of the Safety, Pharmacokinetics, and Disease-Related Outcomes of the Matrix Metalloproteinase-9 Inhibitor Andecaliximab in Patients With Rheumatoid Arthritis

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ABSTRACT

Purpose: Andecaliximab (GS-5745) is a highly selective monoclonal antibody against matrix metalloproteinase-9 (MMP9), a proteolytic enzyme implicated in the pathogenesis of rheumatoid arthritis (RA). This study assessed the safety and pharmacokinetic (PK) parameters of andecaliximab in patients with RA and evaluated the effects of andecaliximab treatment on exploratory disease biomarkers.

Methods: In this double-blind, Phase 1b trial, patients with active RA were randomized (4:1) to receive 400-mg andecaliximab or placebo every 2 weeks for a total of 3 intravenous infusions. The primary and secondary end points were safety and the PK parameters of andecaliximab, respectively. Data were summarized by using descriptive statistics.

Findings: A total of 18 patients were randomized; 15 received andecaliximab (participants with confirmed RA diagnosis without current administration of a biologic DMARD a biologic DMARD (disease-modifying antirheumatic drug), aged 18 to 70 years old, weighing >45 to <120 kg). No deaths, serious adverse events, or study discontinuations occurred. All reported adverse events were grade 1 or grade 2 in severity. Mean plasma andecaliximab exposure was 587 d · μg/mL and 878 d · μg/mL at days 1 and 29, respectively, suggesting moderate accumulation. The median terminal $t_{1/2}$ was 5.65 days; mean volume of distribution at steady state was 4560 mL. Mean MMP9 coverage (the percentage of total plasma MMP9 bound by therapeutic antibody) was maintained at ~80% after the first administration of andecaliximab.

Implications: Andecaliximab administered as 3 infusions over 29 days was generally safe and well tolerated in patients with RA. The majority of total plasma MMP9 was bound by andecaliximab after the first administration. Clinical studies of increased treatment duration in larger patient cohorts are warranted. ClinicalTrials.gov identifier: NCT02176876. Registered on 25 June 2014. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: autoimmune diseases, cartilage matrix, matrix metalloproteinase-9, pharmacokinetics, rheumatoid arthritis, therapeutic antibody.

INTRODUCTION

Rheumatoid arthritis (RA), a chronic autoimmune disease causing inflammation of the synovium and subsequent joint and bone damage,[1] affects ~0.24% of the population worldwide.[2] Patients with RA can experience significant disability, decreased quality of life, and increased mortality compared with unaffected individuals.[3–5] Although the underlying cause remains unknown, RA is characterized by production of autoantibodies, increased levels of inflammatory cytokines, and erosion of cartilage and bone in the affected joints.[6] Standard treatment consists of chronic administration of disease-modifying antirheumatic drugs (DMARDs), incorporating conventional synthetic DMARDs and

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4 key classes of biologic agents, including antibodies targeting tumor necrosis factor α, interleukin-6, interleukin-1, and cytotoxic T-lymphocyte associated protein 4 (CTLA-4).[7–10] Patients may also receive need-based treatment with glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) for the control of symptoms and pain.[7–10]

Despite recent advances in RA therapeutics leading to approval of several pro-inflammatory pathway-targeting drugs, a subset of patients respond insufficiently to available treatments, resulting in continuing pain, joint damage, and disability progression. Previous studies suggest that increased proteolytic system activity is important in early articular cartilage and subchondral bone degradation.[11,12] Specifically, the gelatinase matrix metalloproteinase-9 (MMP9) is overproduced in the joints of patients with RA[13,14] and may contribute to cartilage degradation, increased activation and/or recruitment of pro-inflammatory cytokines, and RA synovial fibroblast invasion.[15–17] MMP9 is secreted as a zymogen, pro-MMP9. Activation of pro-MMP9 through sequential processing and cleavage of the prodomain yields active MMP9, which possesses enhanced degradative capabilities.[15,18]

Previous investigative small-molecule nonspecific MMP inhibitors were ineffective in treating patients with osteoarthritis and RA and were associated with side effects (eg, musculoskeletal syndrome).[19,20] In RA, MMP9 is differentially overexpressed in diseased joints,[12,13] suggesting that an MMP9-specific inhibitor may offer an improved safety profile compared with nonspecific MMP inhibitors and a lower potential for systemic immunosuppressive effects compared with many DMARDs. Andecaliximab (GS-5745; Gilead Sciences, Inc, Foster City, California, USA), a monoclonal antibody that exhibits selective and potent allosteric inhibition of MMP9,[21,22] may overcome many of the limitations of nonspecific MMP small-molecule inhibitors previously investigated in the treatment of arthritic diseases.

The present study reports results from a Phase 1b trial examining the safety and tolerability of andecaliximab administered intravenously every 2 weeks for a total of 3 infusions in patients with active RA. The pharmacokinetic (PK) parameters of andecaliximab and effects on select disease biomarkers are also described. To the best of our knowledge, this study is the first reported use of a selective MMP9 inhibitor in patients with RA in a clinical trial setting.

PATIENTS AND METHODS

Study Design

This Phase 1b, randomized, double-blind, placebo-controlled, multicenter study assessed the safety and PK profile of andecaliximab and evaluated exploratory disease-related outcomes in patients with RA. Patients were enrolled from 4 participating centers (1 site in the Czech Republic and 3 sites in Hungary). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. Written informed consent was obtained from all enrolled patients before randomization.

All study protocols were approved by an independent ethics committee and institutional review board. Ethics approval in the Czech Republic was obtained from Ethics Committee of the Institute for Clinical and Experimental Medicine (IKEM) and Thomayer Hospital (TN) (reference number: M-15-05, L-15-09). Ethics approval in Hungary was obtained from Medical Research Council, Ethics Committee for Clinical Pharmacology (reference number: MRC: 22553-0/2014-EKL).

Study Participants

Male and nonpregnant, nonlactating female participants with a confirmed diagnosis of RA based on the 1987 revised American College of Rheumatology guidelines,[23] with active disease (mean high-sensitivity C-reactive protein [hs-CRP] level ≥8 mg/L during screening), aged 18 to 70 years inclusive, and weighing ≥45 to <120 kg at screening were eligible for study inclusion. In addition to standard exclusion criteria, subjects who received antibiotics, biologic DMARDs, any B cell–depleting agent, or any investigational biologic agent or device within a specified time period before randomization were excluded from the study. Patients were allowed concurrent use of conventional synthetic DMARDs, including hydroxychloroquine, leflunomide, methotrexate, minocycline, or sulfasalazine, if the dose was stable for at least 45 days before randomization and maintained throughout the study. In addition, patients were allowed systemic corticosteroids up to a maximal dose of 10 mg/d of prednisone or equivalent and NSAIDs, or other analgesics, if doses were stable for at least 30 days before randomization and maintained throughout the study.