A Phase 2 Study of Tofacitinib, an Oral Janus Kinase Inhibitor, in Patients With Crohn's Disease

William J. Sandborn,[*] Subrata Ghosh,[‡] Julian Panes,[§] Ivana Vranic,[‖] Wenjin Wang,[¶] and Wojciech Niezychowski,[#] on behalf of the Study A3921043 Investigators

*Division of Gastroenterology, University of California San Diego, La Jolla, California; ‡Department of Medicine, University of Calgary, Calgary, Alberta, Canada; §Gastroenterology Department, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red (CIBERehd), Barcelona, Spain; ‖Global Medicine Development, Pfizer Inc, Sandwich, United Kingdom; ¶Global Innovative Pharma Division, and #Global Medicine Development, Pfizer Inc, Collegeville, Pennsylvania

BACKGROUND & AIMS: **Tofacitinib, an orally administered Janus kinase inhibitor, blocks signaling through γ-chain–containing cytokines (interleukins 2, 4, 7, 9, 15, and 21). We performed a phase 2 trial to measure its efficacy in patients with moderate-to-severe active Crohn's disease.**

METHODS: **Patients (N = 139; age, ≥18 y) with moderate-to-severe active Crohn's disease were assigned randomly to groups given 1 mg (n = 36), 5 mg (n = 34), or 15 mg (n = 35) tofacitinib or placebo (n = 34), twice daily for 4 weeks, at 48 centers in 12 countries. The primary end point was the proportion of clinical responders at week 4 (decrease from baseline in the Crohn's Disease Activity Index score of ≥70 points [Response-70]). Secondary end points included clinical remission (Crohn's Disease Activity Index score of <150 points) at week 4.**

RESULTS: **A clinical response was observed in 36% (P = .467), 58% (P = .466), and 46% (P ≥ .999) of patients given the 1-, 5-, and 15-mg doses of tofacitinib, compared with 47% of patients given placebo. Clinical remission was observed in 31% (P = .417), 24% (P = .776), and 14% (P = .540) of patients given the 1-, 5-, and 15-mg doses of tofacitinib, compared with 21% of patients given placebo. The 15-mg dose of tofacitinib reduced levels of C-reactive protein and fecal calprotectin from baseline. Adverse and serious adverse events were similar among groups. Dose-dependent increases in low- and high-density lipoprotein cholesterol were observed in patients given the 5- or 15-mg doses of tofacitinib.**

CONCLUSIONS: **There were no significant differences in the percentage of patients with moderate-to-severe active Crohn's disease who achieved clinical responses (Response-70) or clinical remission after 4 weeks' administration of tofacitinib (1, 5, or 15 mg) or placebo twice daily. However, a large percentage of patients given placebo achieved Response-70 or remission. Reductions in C-reactive protein and fecal calprotectin levels among patients given the 15-mg dose of tofacitinib indicate its biologic activity. ClinicalTrials.gov number: NCT00615199.**

Keywords: Tofacitinib; CP-690,550; Crohn's Disease; Randomized Control Trial.

Crohn's disease is a chronic inflammatory disease of the small intestine and colon characterized by alternating periods of relapse and remission.[1] Proven medications for Crohn's disease include budesonide, corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, and anti–tumor necrosis factor (TNF)α antibodies; not all patients respond to these medications, and serious toxicities are associated with many of them.[2] An unmet need exists for novel therapies with alternative mechanisms of action.

Tofacitinib is a novel, oral, small-molecule Janus kinase (JAK) inhibitor that is being investigated as a targeted immunomodulator for inflammatory bowel disease. It is a highly selective inhibitor of the JAK family of kinases and competes with adenosine triphosphate for binding to the adenosine triphosphate binding site of the kinase domain within JAK enzymes.[3,4] In vitro, tofacitinib

Abbreviations used in this paper: AE, adverse event; ANC, absolute neutrophil count; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; IBDQ, Inflammatory Bowel Disease Questionnaire; JAK, Janus kinase; LDL, low-density lipoprotein; SAE, serious adverse event; TNF, tumor necrosis factor.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.01.029

preferentially inhibits signaling by receptors associated with JAK3 and JAK1, while showing reduced inhibition for JAK2- and TYK2-associated signaling.[4] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common γ-chain–containing receptors for several cytokines, including interleukins 2, 4, 7, 9, 15, and 21, which are integral to lymphocyte activation, proliferation, and function; inhibition of their signaling thus may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional proinflammatory cytokines, such as interleukin 6 and interferon-γ.[4] At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling. Many of these pathways have been implicated in the pathogenesis of Crohn's disease and ulcerative colitis.

Tofacitinib has been shown to be beneficial in the treatment of rheumatoid arthritis,[5] psoriasis,[6] and ulcerative colitis,[7] and for the prevention of organ allograft rejection[8]; the efficacy of tofacitinib for the treatment of Crohn's disease is unknown. We conducted a 4-week treatment study of tofacitinib in patients with moderate-to-severe active Crohn's disease.

Methods

The study (A3921043, ClinicalTrials.gov NCT00615199) was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines established by the International Conference on Harmonisation. The protocol was approved by the Institutional Review Board at each center. All patients provided written informed consent. The study investigators were responsible for adhering to the study procedures described in the protocol. The study was patient-, investigator-, and sponsor-blinded. Electronically generated blinded codes could be broken only in emergency situations for reasons of patient safety. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

This 4-week, phase 2, multicenter, randomized, double-blind, placebo-controlled study was conducted at 48 centers in 12 countries (Belgium, Czech Republic, France, Hungary, Italy, The Netherlands, Poland, Slovakia, South Africa, Spain, United Kingdom, and United States) between January 9, 2008, and October 29, 2009. Eligible patients, aged 18 years and older, had Crohn's disease for 3 months or longer, with moderate-to-severe disease at baseline defined by a Crohn's Disease Activity Index (CDAI)[9] score of 220 to 450. Confirmation of the diagnosis and extent of disease must have been obtained by endoscopy and/or cross-sectional imaging within 24 months before screening.

Exclusion criteria included the following: hemoglobin level less than 9.0 g/dL, hematocrit less than 30%, white blood cell count less than 3.0×10^9/L, absolute neutrophil count (ANC) less than 1.2×10^9/L, or platelet count less than 100×10^9/L; estimated glomerular filtration rate less than 50 mL/min; total bilirubin, aspartate aminotransferase, or alanine aminotransferase level greater than 2× the upper limit of normal; a history of symptomatic obstructive strictures or short-bowel syndrome; an ostomy, extensive bowel resection (>100 cm), or bowel surgery within 6 months before baseline; chronic or recurrent infections, including latent or inadequately treated *Mycobacterium tuberculosis* infection; malignancy or history of malignancy, with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ. Patients with a positive stool culture for bacterial pathogens and/or a stool test for *Clostridium difficile* toxin were excluded. Cytomegalovirus disease was not specifically evaluated and excluded because it would require gastrointestinal tissue sample analysis; endoscopy was not part of the baseline procedure.

Study Design and Treatment

The study comprised a screening visit within 3 weeks of baseline, a 4-week double-blind treatment period, and a 4-week follow-up period. Patients completed a daily diary of their symptoms from screening onward, and data from the last week before randomization were used to assess baseline symptoms and calculate the baseline CDAI score.

Outpatients were randomized 1:1:1:1 to receive the following: oral tofacitinib 1 mg twice daily, 5 mg twice daily, 15 mg twice daily, or placebo twice daily. These doses for this phase 2 study were selected based on the efficacy and safety results from studies in patients with renal allograft, psoriasis, or rheumatoid arthritis to identify the lowest effective dose while including the maximum proposed therapeutic dose.[5,6,8] Patients were stratified according to disease activity at baseline (CDAI score, <330 vs ≥330 points) and randomized (concealed allocation) into the study. The cut-off value of 330 was chosen as a midpoint of the CDAI score inclusion criteria. The planned total number of 136 patients was based on the assumptions of a 30% clinical response rate (Response-70) for placebo and a difference from placebo of 25% in clinical response rate in 1 or more active doses over placebo. Under these assumptions, there was a greater than 84% probability to have an observed difference in Response-70 greater than 15% and have the lower bound of the 80% two-sided confidence interval (CI) for the difference greater than 0.

Concomitant Medications

Patients who previously had not received any treatment for Crohn's disease were excluded from this study. The following concomitant therapies were prohibited: azathioprine, 6-mercaptopurine, methotrexate