Achieving Clinical Response and Remission in Moderate-to-Severe Ulcerative Colitis With Golimumab

Sandborn WJ, Feagan BG, Marano C, et al; PURSUIT-SC Study Group. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146(1):85-95.

Anti–tumor necrosis factor (TNF) agents have become established in the induction and maintenance of response and remission for patients with ulcerative colitis (UC). Golimumab (Simponi, Janssen) is a subcutaneously administered anti-TNF agent that gained US Food and Drug Administration approval in May 2013 for the treatment of moderate-to-severe UC that is refractory to prior treatment or requires continuous corticosteroid therapy (corticosteroid-dependent). This report is a summary of efficacy and safety data on golimumab among patients with UC who were enrolled in a combined phase 2/3 clinical trial.[1]

Study Description

The PURSUIT-SC (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment–Subcutaneous) induction study was a combined phase 2/3 clinical trial that assessed the safety and efficacy of subcutaneous golimumab as induction therapy for patients with UC. The PURSUIT-SC study was representative of a new type of clinical trial design, as it incorporated a seamless phase 2/3 transition in which what is learned in phase 2 (ie, the optimal drug dosage) can be confirmed in phase 3.[2] This multicenter, randomized, double-blind, placebo-controlled study enrolled patients between July 2007 and November 2010. All patients had a biopsy-confirmed diagnosis of moderate-to-severe UC, which was defined as a Mayo score of 6 to 12 with an endoscopic subscore of 2 or greater.

Eligible patients had failed to achieve an adequate response to, or were unable to tolerate, at least 1 conventional therapy (including oral 5-aminosalicylates, oral corticosteroids, azathioprine, and/or 6-mercaptopurine). Alternatively, patients were corticosteroid-dependent. Concurrent treatment with 5-aminosalicylates or corticosteroids had to be administered at a stable dose at least 2 weeks prior to baseline and was continued at stable doses throughout the study. Concurrent treatment with azathioprine or 6-mercaptopurine had to be administered at a stable dose at least 4 weeks prior to baseline and was continued at stable doses throughout the study.

Ineligibility criteria for PURSUIT-SC included a history of or imminent risk for colectomy, gastrointestinal surgery performed within 2 months prior to screening, a history of colonic mucosal dysplasia or adenomatous colonic polyps that were not removed, the presence of enteric pathogens in the screening stool study, or ulcerative proctitis (in which the patient's colitis was generally limited to 20 cm of the colon with rectal bleeding, so the validity of the Mayo score was more questionable). Other ineligibility criteria included prior exposure (within 1 year) to certain biologic agents (including anti-TNF agents such as infliximab [Remicade, Janssen] and adalimumab [Humira, AbbVie], anti-α4 integrin agents such as natalizumab [Tysabri, Biogen Idec], B-cell–depleting agents such as rituximab [Rituxan, Genentech/Biogen Idec], or T-cell–depleting agents such as alemtuzumab [Campath, Genzyme] or visilizumab); requirement for more than 40 mg daily of prednisone (or its equivalent); or receipt of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks prior to administration of the study drug.

The phase 2 dose-finding portion of this study was designed to evaluate the dose response of subcutaneous golimumab induction regimens. Two cohorts of patients were enrolled into this phase: 1 group of 169 patients followed by a second group of 122 patients. In both cohorts, patients were evenly randomized to receive subcutaneous injections (given at Weeks 0 and 2) of either placebo or 1 of 3 golimumab doses, all given as 2 induction doses: 100/50 mg, 200/100 mg, or 400/200 mg. The data for both cohorts were included in the safety analysis, but only data from the first patient cohort were included in the efficacy analysis.

The phase 3 dose-confirming portion of this study evaluated the safety and efficacy of the subcutaneous golimumab induction regimens selected from phase 2. A total of 774 patients were randomized in a 1:1:1 ratio

to receive subcutaneous induction doses (given at Weeks 0 and 2) of either placebo, 200/100 mg golimumab, or 400/200 mg golimumab.

All patients treated in the PURSUIT-SC study were eligible for participation in a 54-week maintenance study of subcutaneous golimumab (PURSUIT-Maintenance). If they did not enter PURSUIT-Maintenance, patients were followed for safety through 16 weeks after the last administration of study drug in PURSUIT-SC.

Patient Assessment

Disease activity was assessed using the Mayo score, which ranges from 0 to 12 and is the sum of 4 subscores—stool frequency, rectal bleeding, endoscopic findings, and Physician Global Assessment—that each range from 0 to 3.[3] Higher Mayo scores are indicative of greater disease activity. Total Mayo scores were calculated at baseline (Week 0) and Week 6, while partial Mayo scores (which excluded the endoscopic subscore) were calculated at screening and Weeks 2 and 4.

The primary study endpoint for the phase 3 portion of the PURSUIT-SC trial was clinical response; major secondary endpoints included clinical remission, mucosal healing, and health-related quality of life. Clinical response was defined as a decrease in the Mayo score from baseline of 30% or more and 3 or more points, along with either a rectal bleeding subscore of 0 or 1 or a decrease in the rectal bleeding subscore of 1 point or more. Clinical remission was defined as a Mayo score of 2 or fewer points, along with not having more than 1 point in any individual subscore. Mucosal healing was separately defined as a Mayo endoscopy subscore of either 0 or 1. The Inflammatory Bowel Disease Questionnaire (IBDQ) was used at both baseline (Week 0) and Week 6 to evaluate health-related quality of life.[4] Comprised of 32 questions, each with responses scored from 1 to 7, the total IBDQ score ranges from 32 to 224. Higher IBDQ scores are indicative of a better quality of life.

Serum trough golimumab concentrations were measured using blood samples collected from the patients at baseline (Week 0) and Weeks 2, 4, and 6. Blood samples were assessed using a validated electrochemiluminescent assay, which has a reported lower limit of detection of 0.039 mg/mL.[5] Antigolimumab antibodies were assessed at Weeks 0 and 6 using a validated antigen-bridging immunoassay.[6]

Patient Characteristics

A total of 1065 patients were randomized from 217 multinational sites, including Eastern Europe, North America, Asia Pacific, South Africa, Western Europe, and Israel. Relatively few patients (n=35) discontinued study treatment, leaving 96.7% of patients completing study participation through Week 6.

Overall, patient demographics and disease characteristics at baseline were similar across treatment groups. Just over half of the patients (56%) were male, and the median age of the study population was 38.0 years (interquartile range [IQR], 29.0-50.0). The median length of UC disease duration was 4.2 years (IQR, 2.0-8.5), and 57.8% of patients had their UC disease limited to the left side of the colon while 42.2% had extensive disease at baseline. At baseline, the median Mayo score was 8.0 (IQR, 7.0-9.0).

The vast majority of patients (93.0%) were receiving concomitant UC medications at baseline, including 5-aminosalicylates (81.9%), nonbudesonide corticosteroids (42.8%), immunomodulatory drugs (32.4%), 6-mercaptopurine/azathioprine (31.2%), budesonide (2.3%), or methotrexate (1.2%). Among the patients receiving corticosteroids, 61.6% were given 20 mg daily or greater of prednisone (or an equivalent dose), and 38.4% were given a dose of less than 20 mg daily (or an equivalent dose).

Efficacy Results

During the phase 2 portion of the PURSUIT-SC study, there was a trend toward a dose-response relationship with golimumab compared with placebo, as determined based on the change in Mayo score from baseline to Week 6. The median change from baseline in the Mayo score was -1.0 for patients randomized to placebo compared with -3.0, -2.0, and -3.0 for patients randomized to the 100/50 mg, 200/100 mg, and 400/200 mg golimumab arms, respectively. By Week 6, more patients in the 400/200 mg golimumab arm had achieved either a clinical response or remission, mucosal healing, or superior IBDQ scores compared with the placebo arm.

Median serum trough golimumab concentrations were highest at the Week 2 measurement (2.3 mg/mL, 6.2 mg/mL, and 11.7 mg/mL for the 100/50 mg, 200/100 mg, and 400/200 mg golimumab arms, respectively). These levels dropped by Week 6 but still showed a dose-response relationship (0.8 mg/mL, 1.9 mg/mL, and 3.9 mg/mL for the 100/50 mg, 200/100 mg, and 400/200 mg golimumab arms, respectively).

Golimumab exposure (assessed by serum trough concentrations at Week 6) was associated with efficacy. The median Mayo score in the highest quartile improved from baseline by approximately 4 points (P=.013), compared with an increase of approximately 3 in the second and third quartiles and approximately 1 in the lowest quartile. Patients with the highest golimumab exposure also showed the highest rates of clinical response (P=.024) and remission (P=.036) at Week 6. Based on these phase 2 data, the 400/200 mg and

200/100 mg subcutaneous doses of golimumab were chosen for continued development in the phase 3 portion of the PURSUIT-SC study.

In this phase 3 portion, significantly more patients treated in the golimumab arms achieved a clinical response at Week 6 (51.0% for the 200/100 mg arm and 54.9% for the 400/200 mg arm) compared with patients in the placebo arm (30.3%; $P<.0001$ for both comparisons). All other Week 6 secondary endpoints also showed significant improvement among golimumab-treated patients. For example, a greater proportion of golimumab-treated patients achieved clinical remission by Week 6 compared with placebo-treated patients (17.8% and 17.9% for the 200/100 mg and 400/200 mg golimumab arms, respectively, vs 6.4% for the placebo arm; $P<.0001$ for both comparisons). The same significant improvement was also noted for mucosal healing (42.3% and 45.1% for the 200/100 mg and 400/200 mg golimumab arms, respectively, vs 28.7% for the placebo arm; $P=.0014$ and $P<.0001$ for each comparison). Golimumab-treated patients experienced an approximately 2-fold greater change from baseline in their median IBDQ score (22.5 and 21.0 for the 200/100 mg and 400/200 mg golimumab arms, respectively, vs 11.0 for the placebo arm; $P<.0001$).

Golimumab-treated patients exhibited significant and rapid (by Week 2) decreases in median C-reactive protein concentration (-6.57 mg/L and -6.73 mg/L for the 200/100 mg and 400/200 mg golimumab arms, respectively), whereas placebo-treated patients actually experienced an increase in levels (0.35 mg/L). A similar trend was also noted at Week 6 (decreases of -3.35 mg/L and -2.78 mg/L for the 200/100 mg and 400/200 mg golimumab arms, respectively, vs an increase of 1.59 mg/L for the placebo arm).

No major efficacy differences were observed among golimumab-treated patient subgroups, including those related to demographics, UC disease characteristics, history of UC-related medication, or concomitant UC medication. Additionally, there were no significant differences in clinical efficacy between the 200/100 mg and 400/200 mg golimumab treatment groups.

Safety Results

Adverse events were reported at a similar frequency across the 2 golimumab arms and the placebo arm (37.5%, 38.9%, and 38.2% for the 200/100 mg golimumab, 400/200 mg golimumab, and placebo arms, respectively). The most common of these included headache, nasopharyngitis, pyrexia, nausea, anemia, and UC. The incidence of serious adverse events was also relatively similar between golimumab-treated (3.0%) and placebo-treated (6.1%) patients, including serious infections (0.5% and 1.8% in the golimumab and placebo arms, respectively).

There was 1 mortality reported; the patient died of peritonitis and sepsis following surgical complications stemming from an ischiorectal abscess and related bowel perforation.

Injection site reactions were relatively infrequent, occurring in 3.4% of golimumab-treated patients and 1.5% of placebo-treated patients. There were no reports of delayed hypersensitivity or anaphylactic reactions through Week 6.

Antigolimumab antibodies were identified in 3 patients (out of a total of 721 golimumab-treated patients assessed; 0.4%). Two of these patients were receiving concomitant immunomodulatory therapy while in the study.

Conclusions

The primary study endpoint of clinical response was met during the phase 3 portion of PURSUIT-SC, as were several secondary study endpoints, including clinical remission, mucosal healing, and health-related quality of life.

References

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