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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Commentary

Golimumab in Moderate-to-Severe Ulcerative Colitis

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In May 2013, golimumab (Simponi, Janssen), a new anti–tumor necrosis factor (TNF) agent, was approved by the US Food and Drug Administration (FDA) for treatment of adults with moderately to severely active ulcerative colitis. Historically, there has been a relative paucity of treatment options for ulcerative colitis as compared with Crohn's disease. We have long had a third anti-TNF agent available for treatment of Crohn's disease but not for ulcerative colitis. It even took a long time to formally test the first anti-TNF agent in ulcerative colitis, which finally occurred in the original ACT studies[1] of infliximab (Remicade, Janssen); there had been many naysayers claiming that an anti-TNF agent would not work in ulcerative colitis. We used to think that ulcerative colitis was immunologically different from Crohn's disease, which is why it was thought that a target other than TNF-α was needed to treat ulcerative colitis; we thought that ulcerative colitis and Crohn's disease could not be immunologically identical because how else could it be explained that, at their extremes, the 2 diseases could look so different? However, we now know that these 2 diseases are very similar genetically. In fact, there is almost no genetic difference between ulcerative colitis and Crohn's disease. Therefore, it should not be surprising that many of the treatments that work in one disease work in the other. Thus, I believe that patients should be considered responsive to anti-TNF agents until proven otherwise and that, for many patients, the issue is whether they received sufficient anti-TNF to achieve adequate trough and/or tissue levels.

Infliximab was the first anti-TNF agent to be approved for treatment of ulcerative colitis and was shown to be reasonably effective for this indication. The initial studies of infliximab in ulcerative colitis were conducted in patients who were, by definition, naive to anti-TNF therapy.[1] Then along came adalimumab (Humira, AbbVie), which was also shown to be reasonably effective in ulcerative colitis in clinical trials.[2] The FDA has asked for more dose-finding studies to determine whether adalimumab would be more efficacious by using a higher dose in patients with ulcerative colitis. However, as we saw in many of the earlier anti-TNF studies in Crohn's disease, once a second or third anti-TNF agent was used, the drug's efficacy dropped off. This does not make scientific sense because if patients who had a previous response to a drug have already been preselected and are now being given the same class of drug, the population should be enriched for responders. Something else must be going on. One explanation is that patients who develop antibodies to one biologic agent will promptly develop antibodies to other biologic agents. Could it be that inhibiting TNF-α ultimately results in producing more TNF-α, and, thus, more of the second drug is needed to have a clinical effect? Accordingly, the adalimumab results[3] were not quite as good as the infliximab results[1] because 40% of the patients in the adalimumab clinical trial for ulcerative colitis (ULTRA) had previously been exposed to infliximab, and we know that patients previously exposed to an anti-TNF agent are not going to do as well as patients who are naive to anti-TNF agents.

This is all germane to golimumab because one of the important points that readers need to keep in mind is that patients in the golimumab trial conducted by Sandborn and colleagues[4] have not previously been on an anti-TNF agent. Although we should not compare study results directly between anti-TNF agents, the golimumab remission data at Week 6 and long term at Week 52 are similar to data from the adalimumab trial: golimumab has a remission rate of approximately 18% at Week 6 (compared with 6% in the placebo group),[4] and adalimumab has a remission rate of 16.5% (compared with 9% in the placebo group) at Week 8.[3] This is in spite of the fact that golimumab was evaluated

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only in patients who were naive to anti-TNF therapy (ie, a more favorable patient population).

In addition, as with other anti-TNF agents, there is clearly a relationship between golimumab's trough levels and efficacy: the higher the trough level, the better the improvement in Mayo score and the higher the rate of remission.[4] Golimumab appears to be relatively comparable with adalimumab in terms of efficacy, so, in my mind, it does not matter which agent is used as second-line therapy and which agent is used as third-line therapy; having to choose between these 2 agents is a good problem to have. At present, we do not have a way to measure serum levels of golimumab, but we have learned that measuring levels is helpful in monitoring efficacy of infliximab and adalimumab. We do not yet know how best to dose escalate patients receiving golimumab. In general, we go to weekly adalimumab for patients who lose response or who have a partial response to adalimumab and low serum levels.

Determining the optimal dose is an important area for future research for golimumab and anti-TNF agents in general. Ideally, we should measure drug levels to guide therapy and more effectively achieve the clinical response of mucosal healing. We still do not know the optimal serum level of anti-TNF agents for all patients; some patients appear to need much higher drug levels than others in order to have a beneficial effect. Although golimumab is convenient to use and well tolerated in terms of the actual injection, in certain patients, especially those with more active disease, higher doses are needed. The golimumab study[4] did test 2 different doses of the drug. The lower dose appeared to be as effective as the higher dose, which must mean that there is a lot of individual variation in patients and that it is not just about giving more of the drug; it is about giving more to the right patient. Choosing the right starting dose may involve taking into account endoscopic severity, extent, and surrogate markers such as C-reactive protein and albumin. Determining the ideal dosage of golimumab will help improve treatment of patients with ulcerative colitis.

Dr Abreu has been a consultant for AbbVie Laboratories, Prometheus Labs, Sanofi-Aventis, Takeda, UCB, Pfizer, Janssen, the Mucosal Healing Ad Board, and GSK Holding Americas Inc; has been on the Scientific Advisory Board for AbbVie Laboratories; has provided lecturing/teaching for AbbVie Laboratories; has been on the Board of Directors for the GI Health Foundation; has given lectures and developed educational content for WebMD Health; has developed GI Health Foundation educational material for Focus Medical Communications; and has provided CME lectures and developed content for Prova Education, Inc.

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