Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists

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BACKGROUND & AIMS: **The efficacy and safety of vedolizumab, a humanized immunoglobulin G1 monoclonal antibody against the integrin $\alpha4\beta7$, were demonstrated in multicenter, phase 3, randomized, placebo-controlled trials in patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease. We analyzed data from 1 of these trials to determine the effects of vedolizumab therapy in patients with UC, based on past exposure to anti–tumor necrosis factor-α (TNF) antagonists.**

METHODS: **We performed a post hoc analysis of data from the GEMINI 1 study, collected from 464 patients who received vedolizumab or placebo but had not received a previous TNF antagonist (naive to TNF antagonists) and 367 patients with an inadequate response, loss of response, or intolerance to TNF antagonists (failure of TNF antagonists). Predefined outcomes of GEMINI 1 were evaluated in these subpopulations.**

RESULTS: **At Week 6, there were greater absolute differences in efficacy between vedolizumab and placebo in patients naive to TNF antagonists than patients with failure of TNF antagonists, although the risk ratios (RRs) for efficacy were similar for each group. Week 6 rates of response to vedolizumab and placebo were 53.1% and 26.3%, respectively, among patients naive to TNF antagonists (absolute difference, 26.4%; 95% confidence interval [CI], 12.4–40.4; RR, 2.0; 95% CI, 1.3–3.0); these rates were 39.0% and 20.6%, respectively, in patients with failure of TNF antagonists (absolute difference, 18.1%; 95% CI, 2.8–33.5; RR, 1.9; 95% CI, 1.1–3.2). During maintenance therapy, the absolute differences were similar but the RR for efficacy was higher for patients with failure of TNF antagonists than for patients naive to TNF antagonists, for most outcomes. Week 52 rates of remission with vedolizumab and placebo were 46.9% and 19.0%, respectively, in patients naive to TNF antagonists (absolute difference, 28.0%; 95% CI, 14.9–41.1; RR, 2.5; 95% CI, 1.5–4.0) and 36.1% and 5.3%, respectively, in patients with failure of TNF antagonists (absolute difference, 29.5%; 95% CI, 12.8–46.1; RR, 6.6; 95% CI, 1.7–26.5). No differences in adverse events were observed among groups.**

CONCLUSIONS: **Vedolizumab demonstrated significantly greater efficacy as induction and maintenance therapy for UC than placebo in patients naive to TNF antagonists and patients with TNF antagonist failure. There were numerically greater treatment differences at Week 6 among patients receiving vedolizumab who were naive to TNF antagonists than patients with TNF antagonist failure. ClinicalTrials.gov no: NCT00783718.**

Keywords: GEMINI; Inflammatory Bowel Disease; Treatment Failure; Biologic-Naive.

Abbreviations used in this paper: AD, absolute difference; ADA, antidrug antibodies; CI, confidence interval; ITT, intent-to-treat; MCS, Mayo Clinic score; PY, person-year; RR, risk ratios; TNF, tumor necrosis factor-α; TNF-failure, patients with prior TNF antagonist failure; TNF-naive, patients without prior TNF antagonist therapy; UC, ulcerative colitis.

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Ulcerative colitis (UC) is a chronic disease that results from uncontrolled inflammation of the colon. Patients experience bloody diarrhea, abdominal cramps, fatigue, and impaired health-related quality of life.[1] Although no cure exists, tumor necrosis factor-α (TNF) antagonist therapy has greatly improved medical management. However, the most effective treatments currently available fail to adequately control disease activity in many patients. Approximately 50% of patients with UC do not respond to induction therapy with TNF antagonists[2–4] or lose response over time such that after 1 year of treatment, clinical remission is observed in only 17% to 34% of patients.[2,3,5] Furthermore, the risk of serious infection (with immunosuppressants in general, and TNF antagonists specifically) is an important concern.[6,7] Thus, alternative approaches to treatment are needed.

Vedolizumab is a novel, gut-selective humanized immunoglobulin G_1 monoclonal antibody to the $\alpha_4\beta_7$ integrin that inhibits adhesion of a gut-homing subset of T lymphocytes to mucosal addressin cell adhesion molecule 1. This mechanism selectively downregulates gut inflammation while preserving systemic immune responses.[8–14] The efficacy and safety of vedolizumab induction and maintenance treatment were demonstrated in the phase 3 GEMINI 1 and GEMINI 2 studies of patients with moderately to severely active UC or Crohn's disease, respectively.[15] Here in the prespecified exploratory and post hoc analyses of GEMINI 1 data, we report the efficacy and safety of vedolizumab in patient subgroups based on their TNF antagonist treatment history.

Methods

Study Design

These results are based on subgroup analyses of data from the multicenter, phase 3, randomized, placebo-controlled GEMINI 1 trial of vedolizumab in patients with moderately to severely active UC (ClinicalTrials.gov, NCT00783718). Details of the study design are reported elsewhere.[15] Briefly, 374 patients were randomized, in a 3:2 ratio, to receive intravenous vedolizumab or placebo induction therapy on Days 1 and 15 (Cohort 1; induction intent-to-treat [ITT] population) (Supplementary Figure 1B). To fulfill sample size requirements for the subsequent maintenance trial, 521 additional patients were enrolled in an open-label group (Cohort 2) and received the same vedolizumab induction regimen as administered in the blinded study. Disease activity was defined using the Mayo Clinic score (MCS), which includes assessment of stool frequency, rectal bleeding, endoscopy, and physician's global assessment. The complete MCS ranges from 0 to 12, with higher scores indicating more active disease. Eligible patients had UC for $\geq$6 months before enrollment, MCS from 6 to 12, and endoscopic subscores of $\geq$2 within 7 days before the first dose of study drug, and evidence of disease extending $\geq$15 cm proximal to the rectum.

Vedolizumab-treated patients from both cohorts with a clinical response at Week 6 were rerandomized (1:1:1) to receive vedolizumab every 8 weeks or every 4 weeks or placebo beginning at Week 6 for up to 46 weeks (maintenance ITT population) (Supplementary Figure 1). Clinical response was defined as a reduction in the MCS of $\geq$3 points and $\geq$30% from baseline (Week 0), with an accompanying decrease of $\geq$1 point in the rectal bleeding subscore or absolute rectal bleeding subscore of 0 or 1. Patients who failed to respond to vedolizumab at Week 6 continued vedolizumab therapy every 4 weeks during maintenance. Patients who had received placebo during induction continued to receive placebo during maintenance or discontinued (Supplementary Figure 1). Patients were evaluated at Weeks 2, 4, and 6 during induction therapy and every 4 weeks thereafter until Week 52.[15]

As part of the eligibility criteria for GEMINI 1, patients had demonstrated, within the previous 5-year period, an inadequate response to, loss of response to, or intolerance of $\geq$1 of the following therapies: corticosteroids (outside the United States only), immunosuppressives (azathioprine or mercaptopurine), and/or infliximab, because this was the only TNF antagonist approved for the treatment of UC at the time of enrollment. An inadequate response to infliximab was defined as signs and symptoms of active disease despite at least one 4-week induction regimen of 2 doses of infliximab at 5 mg/kg intravenously, $\geq$2 weeks apart. Loss of response was defined as the recurrence of symptoms in a patient who had previously benefited from infliximab, and patients with intolerance had experienced treatment-related toxicity (eg, an infusion-related reaction, psoriasiform skin lesion, demyelination, congestive heart failure, infection, or other clinically meaningful adverse events). In the present analyses, the TNF-failure population comprised an aggregate of patients with inadequate response, loss of response, or intolerance to prior TNF antagonist treatment as predefined according to data captured on the case report form at baseline (Week 0) (Supplementary Figure 1B). For classification purposes, we arbitrarily declared in a hierarchical fashion that an inadequate response was considered worse than loss of response and loss of response was considered worse than intolerance. However, patients could have more than one type of failure and were evaluated by each type of failure in the present analyses. Finally, the TNF-naive population comprised patients who had never received a TNF antagonist as defined according to data captured on the interactive voice response system during screening and enrollment (Supplementary Figure 1B). Patients with prior exposure to a TNF antagonist without prior failure were excluded from the analyses; patients without prior exposure on the interactive voice response system, but who had prior