ORIGINAL ARTICLE

Vedolizumab for the Treatment of Chronic Pouchitis

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ABSTRACT

BACKGROUND

Approximately half the patients with ulcerative colitis who undergo restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) will subsequently have pouchitis, and among those patients, one fifth will have chronic pouchitis.

METHODS

We conducted a phase 4, double-blind, randomized trial to evaluate vedolizumab in adult patients in whom chronic pouchitis had developed after undergoing IPAA for ulcerative colitis. Patients were assigned (in a 1:1 ratio) to receive vedolizumab intravenously at a dose of 300 mg or placebo on day 1 and at weeks 2, 6, 14, 22, and 30. All the patients received concomitant ciprofloxacin from weeks 1 to 4. The primary end point was modified Pouchitis Disease Activity Index (mPDAI)–defined remission (an mPDAI score of ≤4 and a reduction from baseline of ≥2 points in the mPDAI total score; scores range from 0 to 12, with higher scores indicating more severe pouchitis) at week 14. The mPDAI is based on clinical symptoms and endoscopic findings. Other efficacy end points included mPDAI-defined remission at week 34, mPDAI-defined response (a reduction from baseline of ≥2 points in the mPDAI score) at weeks 14 and 34, and PDAI-defined remission (a PDAI score of ≤6 and a reduction from baseline of ≥3 points; scores range from 0 to 18, with higher scores indicating more severe pouchitis) at weeks 14 and 34. The PDAI is based on clinical symptoms, endoscopic findings, and histologic findings.

RESULTS

Among the 102 patients who underwent randomization, the incidence of mPDAI-defined remission at week 14 was 31% (16 of 51 patients) with vedolizumab and 10% (5 of 51 patients) with placebo (difference, 21 percentage points; 95% confidence interval [CI], 5 to 38; P=0.01). Differences in favor of vedolizumab over placebo were also seen with respect to mPDAI-defined remission at week 34 (difference, 17 percentage points; 95% CI, 0 to 35), mPDAI-defined response at week 14 (difference, 30 percentage points; 95% CI, 8 to 48) and at week 34 (difference, 22 percentage points; 95% CI, 2 to 40), and PDAI-defined remission at week 14 (difference, 25 percentage points; 95% CI, 8 to 41) and at week 34 (difference, 19 percentage points; 95% CI, 2 to 37). Serious adverse events occurred in 3 of 51 patients (6%) in the vedolizumab group and in 4 of 51 patients (8%) in the placebo group.

CONCLUSIONS

Treatment with vedolizumab was more effective than placebo in inducing remission in patients who had chronic pouchitis after undergoing IPAA for ulcerative colitis. (Funded by Takeda; EARNEST ClinicalTrials.gov number, NCT02790138; EudraCT number, 2015-003472-78.)

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N Engl J Med 2023;388:1191-200.
DOI: 10.1056/NEJMoa2208450

A Quick Take is available at NEJM.org

Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is routinely performed in patients with ulcerative colitis who undergo colectomy.[1-4] Idiopathic inflammation of the pouch — referred to as pouchitis — is the most common long-term complication of IPAA[1,5]; it develops in approximately half of patients within 5 years after undergoing IPAA[6] and recurs in more than 50% of affected patients.[1,2,7-10]

Pouchitis is characterized by increased stool frequency, abdominal pain, fecal urgency, and impaired quality of life.[1,3,5,11-15] The diagnostic standard is the presence of relevant symptoms with objective confirmation of inflammation determined by endoscopic or histologic assessment.[1,2,4,16] The Pouchitis Disease Activity Index (PDAI) is an established scoring system for the evaluation of pouchitis that is based on clinical symptoms, endoscopic findings, and histologic findings.[16] The modified PDAI (mPDAI) is a simplified instrument that omits the histologic assessment component yet has sensitivity and specificity that are similar to those of the full scoring system.[17] Although no instruments are formally validated for pouchitis, the PDAI and mPDAI are the most widely accepted measures.[18]

Acute pouchitis is usually treated with short-term courses of antibiotic agents[12]; however, chronic pouchitis, which is defined by a symptom duration of longer than 4 weeks, occurs in approximately one fifth of patients.[1,12,19] Retrospective, uncontrolled studies suggest that tumor necrosis factor antagonists, vedolizumab, or ustekinumab may be effective in the treatment of pouchitis that is refractory to antibiotics,[20-25] although none of these treatments were approved in the United States or Europe at the time of this trial.

Vedolizumab is a gut-selective monoclonal antibody[26] that is approved for the treatment of moderately to severely active ulcerative colitis or Crohn's disease in adults. Vedolizumab blocks the interaction of $\alpha_4\beta_7$ integrin with the mucosal addressin cell adhesion molecule 1, thereby inhibiting the migration of gut-homing T lymphocytes across the intestinal vascular endothelium and consequently reducing intestinal inflammation.[26] The mechanism of action of vedolizumab suggests that it may be effective in the treatment of chronic pouchitis, given that lymphocyte infiltration is characteristic of an inflamed pouch.[14,27] Here, we report the results of EARNEST, a randomized, placebo-controlled trial in which vedolizumab was evaluated for the treatment of chronic pouchitis after IPAA for ulcerative colitis.

Methods

Trial Design and Oversight

In this phase 4, multicenter, double-blind, randomized, placebo-controlled trial, the efficacy and safety of vedolizumab were evaluated over a 34-week period in patients with chronic pouchitis. The institutional review boards at each participating trial site approved the protocol, which is available with the full text of this article at NEJM.org. All the patients provided written informed consent. Additional details of the trial design, eligibility criteria, assessments, end points, and statistical analysis are provided in the Supplementary Appendix, available at NEJM.org.

The trial sponsor (Takeda) designed the trial in conjunction with the investigators and provided vedolizumab and placebo. A clinical research organization (Alimentiv), funded by the sponsor, managed the collection of the data and maintained the trial database in a blinded manner; a second clinical research organization (IQVIA) analyzed the data. The trial investigators, participating institutions, clinical research organizations, and sponsor agreed to maintain data confidentiality. The initial draft of the manuscript was written by the first author in collaboration with coauthors who were employees of, or funded by, the sponsor. All the authors interpreted the data, contributed to the writing of subsequent drafts, and approved the final draft for publication. Sponsor-funded medical writing support was provided by Envision Pharma Group. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients were eligible if they were 18 to 80 years of age, had undergone a proctocolectomy and IPAA for ulcerative colitis that had been performed at least 1 year before screening, and had active chronic pouchitis. Active chronic pouchitis was defined by an mPDAI score of at least 5 and a minimum subscore of 2 on the endoscopic domain (on the basis of findings outside the staple or suture line); a description of the mPDAI is provided below. Eligible patients had had at least three recurrent episodes of pouchitis

within 1 year before the screening visit, each of which was treated with an antibiotic or other prescription therapy for at least 2 weeks or with continuous antibiotics for at least 4 weeks immediately before the baseline endoscopy visit. Eligible patients could have received previous treatment with a tumor necrosis factor antagonist or previous conventional treatment but could not have received vedolizumab therapy.

RANDOMIZATION AND TREATMENT-GROUP ASSIGNMENTS

After a 28-day screening period, patients were randomly assigned in a 1:1 ratio to receive intravenous vedolizumab at a dose of 300 mg or placebo on day 1 and at weeks 2, 6, 14, 22, and 30. Randomization was performed on day 1 with the use of an interactive Web-response system and stratified according to continuous antibiotic use at baseline (yes vs. no).

All the patients received concomitant oral ciprofloxacin at a dose of 500 mg twice daily from randomization through week 4. Additional courses of antibiotics were permitted, as needed, for pouchitis flares that occurred after week 14. The use of antibiotics was not permitted between weeks 4 and 14. The use of oral glucocorticoids for the treatment of pouchitis was permitted during the trial if the medication had been taken at a stable dose for at least 4 weeks before randomization; tapering of the dose needed to occur between weeks 4 and 8. Details regarding the coadministration of oral glucocorticoids are provided in the Supplementary Appendix.

All trial site personnel were unaware of the treatment assignments during the trial with the exception of the pharmacist or pharmacy designee. To maintain blinding, each infusion bag containing the prepared dose of vedolizumab or placebo was covered with a blinding bag before dispensing.

ASSESSMENTS

Assessments of clinical symptoms, endoscopic inflammation, and histologic inflammation were performed at screening (baseline), week 14, and week 34 or early termination of the trial. Efficacy assessments were based on the PDAI and mPDAI scores (Table S1 in the Supplementary Appendix).[16,17] The PDAI score, which ranges from 0 to 18, evaluates three separate six-point scales for clinical symptoms, endoscopic findings, and histologic findings. The mPDAI uses only two of the three PDAI domains (clinical symptoms and endoscopic findings), and mPDAI scores range from 0 to 12.[17] For both indexes, higher scores indicate more severe pouchitis. Patient-reported data with respect to clinical symptoms (stool frequency, rectal bleeding, fecal urgency or abdominal cramps, and fever) were collected in a diary for 3 days immediately before endoscopy visits. The number of ulcers (>5 mm in greatest dimension) and erosions (≤5 mm in greatest dimension), as well as the Simple Endoscopic Score for Crohn's Disease (SES-CD), were evaluated by means of blinded central reviews of the endoscopic videos obtained at baseline, week 14, and week 34. The SES-CD was adapted to score the pouch as a single intestinal segment, with a score ranging from 0 to 12; higher scores indicate more severe endoscopic disease.[28] Details of the SES-CD are provided in Table S2. Histologic inflammation was also assessed by central histopathologists with the use of the Robarts Histopathology Index (RHI); the RHI total score ranges from 0 to 33, with higher scores indicating more severe histologic disease activity.[29] Details of the RHI are provided in Table S3. Health-related quality of life was evaluated with the use of the Inflammatory Bowel Disease Questionnaire (IBDQ)[30] and the Cleveland Global Quality of Life (CGQL) instrument[31] at weeks 14, 22, and 34. The IBDQ consists of 32 questions, with graded response scores ranging from 1 to 7; higher IBDQ total scores (which range from 32 to 224) indicate better quality of life. The CGQL instrument consists of three items, each of which is scored on a scale ranging from 0 (worst) to 10 (best). The CGQL total score is obtained by adding the scores of the three items together and dividing by 30.

END POINTS

The primary end point was mPDAI-defined remission (an mPDAI score of ≤4 and a reduction from baseline of ≥2 points in the mPDAI total score) at week 14. Secondary end points were mPDAI-defined remission at week 34; PDAI-defined remission (a PDAI score of ≤6 and a reduction from baseline of ≥3 points) at weeks 14 and 34; time to PDAI-defined remission; mPDAI-defined response (described in the protocol as a partial mPDAI-defined response and defined as a reduction from baseline of ≥2 points in the mPDAI total score) at weeks 14 and 34; mean changes from baseline in the PDAI total

Table 1. Demographic and Clinical Characteristics at Baseline (Full Analysis Set).*

Characteristic	Vedolizumab (N = 51)	Placebo (N = 51)
Median age (range) — yr	42.0 (19–67)	45.0 (19–68)
Male sex — no. (%)	32 (63)	38 (74)
Race — no. (%)†		
Asian	3 (6)	6 (12)
Black	1 (2)	1 (2)
White	44 (86)	42 (82)
Multiracial	1 (2)	0
Data missing	2 (4)	2 (4)
Continuous use of antibiotics immediately before baseline — no. (%)	29 (57)	25 (49)
Time since IPAA — no. (%)		
<7 yr	16 (31)	21 (41)
≥7 yr	35 (69)	30 (59)
mPDAI score‡	8.1±1.6	8.0±1.8
mPDAI score category — no. (%)‡		
<5, indicating quiescent pouchitis§	1 (2)	1 (2)
5 to 8, indicating moderately active pouchitis	32 (63)	31 (61)
9 to 12, indicating severely active pouchitis	18 (35)	19 (37)
PDAI score‡	10.5±2.2	10.5±2.5
Previous use of a TNF antagonist after colectomy — no. (%)		
TNF antagonist not used	36 (71)	38 (74)
Treatment failure with a TNF antagonist	15 (29)	12 (24)
No treatment failure with a TNF antagonist	0	1 (2)
Polymorphonuclear leukocyte infiltration — no./total no. (%)		
None or mild	11/50 (22)	11/51 (22)
Moderate or severe	39/50 (78)	40/51 (78)
Category of fecal calprotectin level — no. (%)		
≤250 μg/g	15 (29)	17 (33)
>250 μg/g	36 (71)	34 (67)

* Plus–minus values are means ±SD. The full analysis set includes all the patients who underwent randomization and received at least one dose of vedolizumab or placebo. Percentages may not total 100 because of rounding. IPAA denotes ileal pouch–anal anastomosis, and TNF tumor necrosis factor.

† Race was reported by the patient.

‡ Pouchitis Disease Activity Index (PDAI) scores range from 0 to 18, with a cutoff of 7 for the differentiation between "pouchitis" (≥7 points) and "no pouchitis" (<7 points); PDAI scores evaluate three separate six-point scales for clinical symptoms, endoscopic findings, and histologic findings. The modified PDAI (mPDAI) is based on only clinical symptoms and endoscopic findings; scores range from 0 to 12. For both indexes, higher scores indicate more severe pouchitis.

§ Endoscopic images were read by two central readers, with blinded adjudication by a third central reader when necessary (to help determine whether ulcers were erosions [≤5 mm] or large ulcers [>5 mm]). Two patients were enrolled with an mPDAI score of 5 (on the basis of a single central reading only); in these two patients, the mPDAI was scored as 4 after a blinded adjudication deemed the ulcers to be erosions.

score and in the PDAI endoscopic and histologic domain subscores at weeks 14 and 34; mean changes from baseline in the IBDQ and CGQL scores at weeks 14, 22, and 34; IBDQ-defined remission (an IBDQ total score of 170 or higher); and IBDQ-defined response (a change from baseline of ≥16 points in the IBDQ total score).

Prespecified exploratory end points included the change from baseline in the level of fecal calprotectin and in the blood level of C-reactive protein at weeks 14 and 34, the change from baseline in stool frequency at weeks 14 and 34, the percentage of patients with sustained mPDAI-defined and PDAI-defined remission (remission at both weeks 14 and 34), the change from baseline in the PDAI components at weeks 14 and 34, the change from baseline in the total number of erosions and ulcers at weeks 14 and 34, and the change from baseline in the SES-CD total score (for assessment of endoscopic remission, which

was defined as a SES-CD total score of ≤2) and in the RHI total score (for assessment of histologic inflammation) at weeks 14 and 34. Adverse events were reported throughout the trial and were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 23.0.

STATISTICAL ANALYSIS

A sample of 110 patients (55 per group) was planned, but the trial was stopped after 102 patients were enrolled owing to the effect of coronavirus disease 2019 (Covid-19) on recruitment; details are provided in the Supplementary Appendix. The prespecified full analysis set for the efficacy and safety analyses comprised all the patients who underwent randomization and received at least one dose of vedolizumab or placebo.

For dichotomous response-type end points (e.g., remission and response), percentages of patients and between-group differences were calculated. Patients with missing data at a visit were counted as not having had a response or remission at that visit (nonresponse imputation).

For the main analysis of the primary end point, mPDAI-defined remission at week 14, the incidence of remission in the two groups was compared with the use of Fisher's exact test (two-sided); in addition, we performed an analysis that was stratified according to continuous antibiotic use at baseline using the Cochran–Mantel–Haenszel test (two-sided). Unadjusted and adjusted between-group differences in the percentages of patients with a response (calculated with the Cochran–Mantel–Haenszel test for the adjusted analysis) and corresponding 95% confidence intervals are reported. For other response-type end points, the unadjusted between-group differences in the percentages of patients with a response and associated 95% confidence intervals are reported. Confidence intervals have not been adjusted for multiplicity and cannot be used in place of a hypothesis test. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

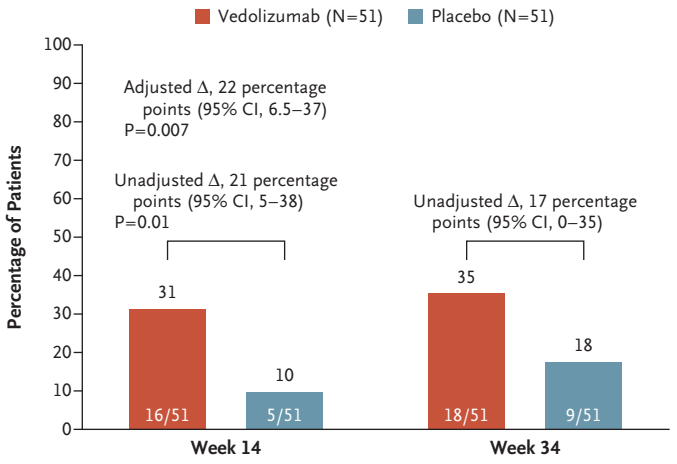

Figure 1. mPDAI-Defined Remission (Full Analysis Set).

Modified Pouchitis Disease Activity Index (mPDAI)–defined remission (which was based on clinical symptoms and endoscopic findings) was defined as an mPDAI score of 4 or lower and a reduction from baseline of 2 or more points in the mPDAI total score. Scores range from 0 to 12, with higher scores indicating more severe pouchitis. The risk difference, 95% confidence interval, and P value for the adjusted analysis were calculated with the use of the Cochran–Mantel–Haenszel test (two-sided) and stratified according to the use of continuous antibiotics at baseline (yes vs. no). The P value for the unadjusted analysis was calculated with the use of Fisher's exact test (two-sided). Confidence intervals have not been corrected for multiplicity and cannot be used in place of a hypothesis test. Patients with missing mPDAI and Pouchitis Disease Activity Index (PDAI) assessments for the determination of response status at a given time point were counted as not having had a response (nonresponse imputation). The full analysis set includes all the patients who underwent randomization and received at least one dose of vedolizumab or placebo. The Δ symbol refers to the difference between the vedolizumab and placebo groups (with the exact 95% confidence interval).

RESULTS

PATIENTS

From October 2016 through March 2020, a total of 165 patients were assessed for eligibility at 13 sites in North America and 18 sites in Europe. Of these patients, 102 underwent randomization: 51 were assigned to the vedolizumab group and 51 to the placebo group. All the patients received at least one dose of vedolizumab or placebo. Overall, 36 patients (71%) in the vedolizumab group and 32 patients (63%) in the placebo group completed treatment (i.e., received all infusions through week 30). Eight patients in each group discontinued vedolizumab or placebo owing to a lack of efficacy (Fig. S1). Demographic and clinical characteristics were similar in the two groups; most (84%) of the patients were White (Table 1). The representativeness of the trial population is presented in Table S15.

The percentage of patients who had been taking glucocorticoids before randomization and were continuing to receive them at baseline was 10% (5 of 51 patients) in the vedolizumab group and 16% (8 of 51 patients) in the placebo group. The percentage of patients who were receiving concomitant glucocorticoids at week 14 was 4%

Table 2. Secondary Efficacy End Points (Full Analysis Set).*

End Point	Vedolizumab (N=51)	Placebo (N=51)	Difference (95% CI)†
mPDAI-defined remission at wk 34 — no. (%)‡	18 (35)	9 (18)	17 (0 to 35)
PDAI-defined remission — no. (%)§			
Wk 14	18 (35)	5 (10)	25 (8 to 41)
Wk 34	19 (37)	9 (18)	19 (2 to 37)
mPDAI-defined response — no. (%)¶			
Wk 14	32 (63)	17 (33)	30 (8 to 48)
Wk 34	26 (51)	15 (29)	22 (2 to 40)
Change from baseline in PDAI total score‖			
Baseline value	10.5±2.2	10.5±2.5	—
Change at wk 14	−3.1±4.0	−1.4±2.7	−1.7 (−3.2 to −0.3)
Change at wk 34	−3.9±4.2	−2.1±3.5	−1.7 (−3.7 to 0.2)
Change from baseline in PDAI endoscopic subscore**			
Baseline value	4.6±1.2	4.5±1.4	—
Change at wk 14	−1.2±1.6	−0.1±1.2	−1.1 (−1.8 to −0.5)
Change at wk 34	−1.7±2.1	−0.9±1.9	−0.8 (−1.8 to 0.2)
Change from baseline in PDAI histologic subscore††			
Baseline value	2.5±1.4	2.6±1.4	—
Change at wk 14	−0.5±2.1	−0.1±1.5	−0.4 (−1.1 to 0.4)
Change at wk 34	−0.4±1.9	−0.1±1.6	−0.3 (−1.2 to 0.6)
Change from baseline in IBDQ total score‡‡			
Baseline value	137.9±33.5	131.5±30.8	—
Change at wk 14	21.1±29.0	16.7±27.0	4.4 (−7.4 to 16.2)
Change at wk 34	33.1±34.4	23.1±21.6	9.9 (−4.8 to 24.6)
IBDQ-defined remission — no. (%)§§			
Wk 14	20 (39)	16 (31)	8 (−11 to 26)
Wk 34	22 (43)	10 (20)	23 (5 to 41)
IBDQ-defined response — no. (%)¶¶			
Wk 14	25 (49)	25 (49)	0 (−20 to 20)
Wk 34	23 (45)	18 (35)	10 (−10 to 29)
Change from baseline in CGQL score‖‖			
Baseline value	0.56±0.16	0.52±0.20	—
Change at wk 14	0.11±0.17	0.07±0.16	0.04 (−0.03 to 0.11)
Change at wk 34	0.14±0.18	0.11±0.14	0.03 (−0.05 to 0.11)

* Patients with missing mPDAI and PDAI assessments for the determination of response status at a given time point were counted as not having had a response (nonresponse imputation).

† Percentage-point differences are shown for binary end points and mean differences for continuous end points. Confidence intervals have not been corrected for multiplicity and cannot be used in place of a hypothesis test.

‡ mPDAI-defined remission (which was based on clinical symptoms and endoscopic findings) was defined as an mPDAI score of 4 or lower and a reduction from baseline of 2 or more points in the mPDAI total score. mPDAI scores range from 0 to 12, with higher scores indicating more severe pouchitis.

§ PDAI-defined remission (which was based on clinical symptoms, endoscopic findings, and histologic findings) was defined as a PDAI score of less than 7 and a reduction from baseline of 3 or more points. PDAI scores range from 0 to 18, with higher scores indicating more severe pouchitis.

¶ mPDAI-defined response was defined as a reduction from baseline of 2 or more points in the mPDAI total score.

‖ In the vedolizumab group, data were missing for 1 patient at baseline, for 7 patients at week 14, and for 20 patients at week 34. In the placebo group, data were missing for 11 patients at week 14 and for 20 patients at week 34.

** The PDAI endoscopic inflammation subscore is based on the evaluation of edema, granularity, friability, loss of vascular pattern, mucus exudates, and ulceration. In the vedolizumab group, data were missing for 6 patients at week 14 and for 18 patients at week 34. In the placebo group, data were missing for 11 patients at week 14 and for 19 patients at week 34.

†† The PDAI acute histologic inflammation subscore is based on the evaluation of two components: polymorphonuclear leukocyte infiltration and the mean percentage of ulceration detected per low-power field (also referred to as ulceration per low-power field [mean]). In the vedolizumab group, data were missing for 6 patients at week 14 and for 18 patients at week 34. In the placebo group, data were missing for 10 patients at week 14 and for 19 patients at week 34.

Table 2. (Continued.)

‡‡ The results of the analyses of the prespecified Inflammatory Bowel Disease Questionnaire (IBDQ) end points at week 22 are provided in Table S4. In the vedolizumab group, data were missing for 5 patients at week 14 and for 16 patients at week 34. In the placebo group, data were missing for 1 patient at baseline, for 8 patients at week 14, and for 12 patients at week 34.

§§ IBDQ-defined remission was defined as an IBDQ total score of 170 or higher. The IBDQ total score, which ranges from 32 to 224, with higher scores indicating better quality of life, was calculated by summing the scores from each of the 32 questions in the questionnaire.

¶¶ IBDQ-defined response was defined as a change from baseline of at least 16 points.

‖‖ The Cleveland Global Quality of Life (CGQL) score was determined by calculating the average CGQL utility score (scores range from 0 to 10, with higher scores indicating better quality of life) from 3 days immediately before endoscopy (or bowel preparation for endoscopy) for each patient. In the vedolizumab group, data were missing for 1 patient at baseline, for 6 patients at week 14, and for 18 patients at week 34. In the placebo group, data were missing for 2 patients at baseline, for 9 patients at week 14, and for 22 patients at week 34. The results of the analysis of the prespecified CGQL end point at week 22 are provided in Table S4.

(2 of 45 patients) in the vedolizumab group and 5% (2 of 40 patients) in the placebo group; the percentages at week 34 were 3% (1 of 33 patients) and 3% (1 of 32 patients), respectively. The percentage of patients who were receiving antibiotics after randomization, in addition to the ciprofloxacin that was administered up to week 4 as specified in the protocol, was 59% (30 of 51 patients) in the vedolizumab group and 37% (19 of 51 patients) in the placebo group (Table S10).

EFFICACY

Primary End Point

At week 14, the percentage of patients who had mPDAI-defined remission was significantly higher with vedolizumab than with placebo (31% [16 of 51 patients] vs. 10% [5 of 51 patients], P=0.01) — a difference of 21 percentage points (95% confidence interval [CI], 5 to 38) (Fig. 1). Sensitivity analyses of the primary end point are provided in Table S4. A post hoc analysis in which the subgroup of patients who received concomitant antibiotics before week 14 and before week 34 (in addition to the initial 4 weeks of treatment with ciprofloxacin) was compared with the subgroup who did not receive concomitant antibiotics showed that a high percentage of patients in the vedolizumab group had mPDAI-defined remission at weeks 14 and 34, irrespective of whether additional concomitant antibiotics were used before week 14 or week 34 (Fig. S10).

Secondary End Points

The percentage of patients who had mPDAI-defined remission at week 34 and the percentage of those who had PDAI-defined remission at weeks 14 and 34 were higher in the vedolizumab group than in the placebo group. The between-group difference in the incidence of mPDAI-defined remission at week 34 was 17 percentage points (95% CI, 0 to 35) (Fig. 1 and Table 2). The between-group difference in the incidence of PDAI-defined remission was 25 percentage points (95% CI, 8 to 41) at week 14 and 19 percentage points (95% CI, 2 to 37) at week 34 (Table 2).

Similarly, the differences between the groups in the incidence of mPDAI-defined response favored vedolizumab over placebo at both week 14 and week 34 (Table 2). Also shown in Table 2 are the mean change from baseline in the PDAI total score and in the PDAI endoscopic and histologic domain subscores. There were no substantial differences between the groups in the mean change from baseline in the IBDQ and CGQL scores (Table 2 and Figs. S7, S8, and S9). The percentage of patients who had IBDQ-defined remission at week 34 was higher with vedolizumab than with placebo (difference, 24 percentage points; 95% CI, 5 to 41). The analysis of the PDAI clinical domain subscores is provided in Table S6, and the analysis of the mPDAI and PDAI total scores and the PDAI clinical, endoscopic, and histologic domain subscores is provided in Figure S3. A subgroup analysis of mPDAI-defined remission at weeks 14 and 34 is provided in Figure S4.

Exploratory End Points

The percentage of patients who had sustained mPDAI-defined remission was higher with vedolizumab than with placebo (difference, 22 percentage points; 95% CI, 6 to 37). The percentage of patients who had sustained PDAI-defined remission also favored vedolizumab over placebo (difference, 23 percentage points; 95% CI, 8 to 39). The analyses of sustained mPDAI-defined and PDAI-defined remission according to continuous antibiotic use at baseline are provided in Table S5.

Table 3. Adverse Events (Safety Analysis Set).*

Event	Vedolizumab (N=51)	Placebo (N=51)
	number of patients (percent)	
Any adverse event	47 (92)	44 (86)
Adverse events reported in ≥5% of patients in either group		
Pouchitis	24 (47)	20 (39)
Arthralgia	7 (14)	9 (18)
Headache	10 (20)	3 (6)
Nasopharyngitis	6 (12)	6 (12)
Nausea	5 (10)	5 (10)
Abdominal pain	4 (8)	3 (6)
Back pain	2 (4)	5 (10)
Frequent bowel movements	4 (8)	2 (4)
Upper respiratory tract infection	5 (10)	1 (2)
Gastroenteritis	2 (4)	3 (6)
Influenza	4 (8)	1 (2)
Dyspnea	0	3 (6)
Adverse event assessed by the investigator as related to vedolizumab or placebo	12 (24)	11 (22)
Severity of adverse events		
Mild	15 (29)	11 (22)
Moderate	29 (57)	28 (55)
Severe	3 (6)	5 (10)
Adverse event leading to discontinuation of vedolizumab or placebo	1 (2)	5 (10)
Serious adverse events		
Any serious adverse event	3 (6)	4 (8)
Abdominal pain	0	1 (2)
Pouchitis	2 (4)	1 (2)
Intestinal obstruction	0	1 (2)
Gastroenteritis	1 (2)	0
Basal-cell carcinoma	0	1 (2)
Serious adverse event assessed by the investigator as related to vedolizumab or placebo	0	1 (2)
Serious adverse event leading to discontinuation of vedolizumab or placebo	0	0
Fatal event	0	0

* The safety analysis set was identical to the full analysis set.

The mean (±SD) number of ulcers and erosions combined changed from 15.1±16.4 at baseline to 5.0±4.9 at week 14 in the vedolizumab group and from 11.8±11.3 at baseline to 13.4±18.4 at week 14 in the placebo group (mean difference, –10.1; 95% CI, –17.7 to –2.5) (Fig. S5). The percentage of patients in the vedolizumab group who had SES-CD–defined endoscopic remission increased from 2% at baseline to 21% at week 14 and to 23% at week 34; in contrast, the change in the placebo group was minimal (8%, 6%, and 10%, respectively). The difference between the groups in the percentage of patients with SES-CD–defined endoscopic remission was 15 percentage points (95% CI, 1 to 30) at week 14 and 13 percentage points (95% CI, –2 to 28) at week 34 (Fig. S6). The mean change from baseline in the RHI total score did not differ substantially between the two groups; the mean between-group difference was –2.7 points (95% CI, –8.1 to 2.8) at week 14 and –3.1 points (95% CI, –9.5 to 3.2) at week 34 (Table S7). Additional histologic data are provided in Tables S8 and S9.

SAFETY

Adverse events were reported in 47 patients (92%) in the vedolizumab group and in 44 patients (86%) in the placebo group (Table 3). Pouchitis was reported as an adverse event in more patients in the vedolizumab group than in the placebo group (47% [24 of 51 patients] vs. 39% [20 of 51 patients]). The incidence of upper respiratory tract infections was also higher among patients who received vedolizumab than among those who received placebo (10% [5 of 51 patients] vs. 2% [1 of 51 patients]), as was the incidence of headache (20% [10 of 51 patients] vs. 6% [3 of 51 patients]. Serious adverse events were reported in 3 of 51 patients (6%) in the vedolizumab group and in 4 of 51 patients (8%) in the placebo group. Additional details about adverse events are provided in Tables S11 and S12.

DISCUSSION

In this double-blind, placebo-controlled trial involving patients with chronic pouchitis, vedolizumab was more effective than placebo with respect to the primary end point of mPDAI-defined remission at week 14, with a 21 percentage-point difference between the groups in the percentage of patients with remission. The early treatment effect appeared to be sustained through week 34. Approximately two thirds of the patients who received vedolizumab met the criteria for a response at week 14 as compared with one third of those who received placebo. Although a subgroup analysis suggested higher percentages of patients with mPDAI-defined remission in the vedolizumab group than in the placebo group in many of the subgroups, the numbers of patients in the subgroups are insufficient to draw firm conclusions.

Controlling mucosal inflammation ultimately prevents bowel damage. Vedolizumab inhibits the recruitment of lymphocytes expressing $\alpha_4\beta_7$ integrin to inflamed intestinal mucosa and is effective in treating ulcerative colitis.[26] In this trial, we observed a reduction of mucosal inflammation in the pouch. The incidence of upper respiratory tract infections and headache in this trial was higher in the vedolizumab group than in the placebo group. Pouchitis was reported more often as an adverse event among patients who received vedolizumab than among those who received placebo; the reporting of pouchitis as an adverse event was based on symptoms alone rather than on clinical, endoscopic, and histologic assessments.

Our trial has some limitations. First, although the PDAI and mPDAI are established measures for the evaluation of pouchitis, these instruments have not been fully validated.[18] Nonetheless, they incorporate assessments that are relevant to the well-being of patients, assessment of the inflammatory process, and clinical care. Second, concomitant antibiotic use after week 4 was reported in a higher percentage of patients in the vedolizumab group than in the placebo group, a finding that was unexpected. However, the use of additional antibiotics was not considered to be a treatment failure because antibiotics are the current standard of care for chronic pouchitis. The analysis of mPDAI-defined remission in which patients who took additional antibiotics during the trial were compared with those who did not receive additional antibiotics suggested that there was no substantial difference between the two groups. Third, although the trial included a 34-week blinded evaluation, longer-term assessment of the efficacy and safety of vedolizumab in patients with pouchitis is warranted.

Among patients who had chronic pouchitis after undergoing IPAA for ulcerative colitis, treatment with vedolizumab was more effective than placebo in the induction of remission.

Supported by Takeda.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in the trial and their caregivers, the trial investigators and members of the EARNEST trial team, and Adele Blair, Ph.D., and Vardit Dror, Ph.D., of Envision Pharma Group for medical writing support.

APPENDIX

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