Title: Vedolizumab as induction and maintenance therapy for Crohn's disease.

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Journal: The New England journal of medicine

Year: 2013 Aug 22

Volume: 369

Issue: 8

Pages: 711-21

DOI: 10.1056/NEJMoa1215739

ORIGINAL ARTICLE

Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease

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ABSTRACT

BACKGROUND

The efficacy of vedolizumab, an $\alpha_4\beta_7$ integrin antibody, in Crohn's disease is unknown.

METHODS

In an integrated study with separate induction and maintenance trials, we assessed intravenous vedolizumab therapy (300 mg) in adults with active Crohn's disease. In the induction trial, 368 patients were randomly assigned to receive vedolizumab or placebo at weeks 0 and 2 (cohort 1), and 747 patients received open-label vedolizumab at weeks 0 and 2 (cohort 2); disease status was assessed at week 6. In the maintenance trial, 461 patients who had had a response to vedolizumab were randomly assigned to receive placebo or vedolizumab every 8 or 4 weeks until week 52.

RESULTS

At week 6, a total of 14.5% of the patients in cohort 1 who received vedolizumab and 6.8% who received placebo were in clinical remission (i.e., had a score on the Crohn's Disease Activity Index [CDAI] of ≤150, with scores ranging from 0 to approximately 600 and higher scores indicating greater disease activity) (P=0.02); a total of 31.4% and 25.7% of the patients, respectively, had a CDAI-100 response (≥100-point decrease in the CDAI score) (P=0.23). Among patients in cohorts 1 and 2 who had a response to induction therapy, 39.0% and 36.4% of those assigned to vedolizumab every 8 weeks and every 4 weeks, respectively, were in clinical remission at week 52, as compared with 21.6% assigned to placebo (P<0.001 and P=0.004 for the two vedolizumab groups, respectively, vs. placebo). Antibodies against vedolizumab developed in 4.0% of the patients. Nasopharyngitis occurred more frequently, and headache and abdominal pain less frequently, in patients receiving vedolizumab than in patients receiving placebo. Vedolizumab, as compared with placebo, was associated with a higher rate of serious adverse events (24.4% vs. 15.3%), infections (44.1% vs. 40.2%), and serious infections (5.5% vs. 3.0%).

CONCLUSIONS

Vedolizumab-treated patients with active Crohn's disease were more likely than patients receiving placebo to have a remission, but not a CDAI-100 response, at week 6; patients with a response to induction therapy who continued to receive vedolizumab (rather than switching to placebo) were more likely to be in remission at week 52. Adverse events were more common with vedolizumab. (Funded by Millennium Pharmaceuticals; GEMINI 2 ClinicalTrials.gov number, NCT00783692.)

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N Engl J Med 2013;369:711-21.
DOI: 10.1056/NEJMoa1215739

Crohn's disease is a chronic inflammatory bowel disease.[1] Current treatments include glucocorticoids, immunosuppressive agents (i.e., azathioprine, mercaptopurine, or methotrexate), and tumor necrosis factor (TNF) antagonists.[1-3] Many patients do not have a response to therapy,[4] and treatments are associated with important toxic effects.[5,6]

Natalizumab, a monoclonal antibody that modulates gut and brain lymphocyte migration by antagonizing $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin–mediated interactions,[7] is efficacious in the treatment of multiple sclerosis[8,9] and Crohn's disease.[10-12] Its use in patients with Crohn's disease has been limited by the development in some patients of progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection that is caused by reactivation of latent JC polyomavirus.[13,14]

Vedolizumab (Millennium Pharmaceuticals), a humanized immunoglobulin G1 monoclonal antibody to $\alpha_4\beta_7$ integrin, modulates gut, but not brain, lymphocyte trafficking and therefore should theoretically be less likely to confer a predisposition to PML.[15] Results from phase 2 trials suggested a benefit in patients with inflammatory bowel disease.[16-18] We conducted integrated induction and maintenance trials of vedolizumab in patients with moderately to severely active Crohn's disease.

Methods

Study Oversight

This phase 3, randomized, parallel-group, double-blind, placebo-controlled study consisted of separate induction and maintenance trials. We conducted the study at 285 medical centers in 39 countries from December 2008 to May 2012. (Enrollment was discontinued at 15 of these centers; see the Supplementary Appendix, available with the full text of this article at NEJM.org.) The protocol was approved by the institutional review board at each participating center. All patients gave written informed consent.

The members of the GEMINI 2 steering committee (see the Supplementary Appendix), which was composed of academic investigators, designed the trial in conjunction with the sponsor (Millennium Pharmaceuticals). The study was monitored by means of onsite visits, with audits conducted at centers with high enrollment (see the Supplementary Appendix). The sponsor collected and analyzed the data, and the steering committee and the sponsor jointly interpreted the data. All the authors had full access to the data. The investigators, the participating institutions, and the sponsor agreed to maintain the confidentiality of the data. The first two authors wrote the first draft of the manuscript, and all the authors contributed to subsequent drafts. All the authors made the decision to submit the manuscript for publication and vouch for the veracity and completeness of the data and analyses and for the fidelity of the study to the protocol, available at NEJM.org. Editorial support was provided by Takeda Pharmaceuticals International and by Complete Healthcare Communications and MedLogix Communications, funded by Takeda Pharmaceuticals International.

Patients

Eligible patients were 18 to 80 years of age, had had Crohn's disease for at least 3 months, had a score of 220 to 450 on the Crohn's Disease Activity Index (CDAI, on which scores range from 0 to approximately 600, with higher scores indicating greater disease activity[19]), and had one of the following: a serum C-reactive protein level higher than 2.87 mg per liter, colonoscopic findings showing 3 or more large ulcers or 10 or more aphthous ulcers, or fecal calprotectin concentrations of more than 250 μg per gram of stool plus evidence of ulcers on computed tomography or magnetic resonance enterography, small-bowel radiography, or capsule endoscopy. Eligible patients had had no response to or had had unacceptable side effects from one or more of the following: glucocorticoids, immunosuppressive agents (i.e., azathioprine, mercaptopurine, or methotrexate), or TNF antagonists (Table S1 in the Supplementary Appendix). Stable doses of oral prednisone (≤30 mg per day) or budesonide (≤9 mg per day), immunosuppressive agents, mesalamine, and antibiotics were permitted. Patients were not eligible if they had received previous treatment with vedolizumab, natalizumab, efalizumab, or rituximab. Treatment with adalimumab within 30 days before enrollment and treatment with infliximab or certolizumab pegol within 60 days before enrollment was not permitted. Patients with a stoma, more than three small-bowel resections, the short-bowel syndrome, extensive colonic resection, intestinal stricture, abdominal abscess, active or latent tuberculosis, or cancer were excluded.

Screening assessments included physical and neurologic examinations; questionnaires designed

to identify possible symptoms of PML (see the Supplementary Appendix); blood and stool tests, including measurement of fecal calprotectin and C-reactive protein levels; and the Inflammatory Bowel Disease Questionnaire (IBDQ, on which scores range from 32 to 224, with higher scores indicating better quality of life).

RANDOMIZATION

In the double-blind induction trial (cohort 1), patients were randomly assigned, in a 3:2 ratio, to receive intravenous vedolizumab, at a dose of 300 mg, or placebo at weeks 0 and 2 and were followed through week 6, at which time disease status was assessed. Randomization was stratified according to status with respect to concomitant use of glucocorticoids and according to status with respect to concomitant use of immunosuppressive agents, prior use of TNF antagonists, or both. The proportion of patients with previous exposure to TNF antagonists was limited to 50%.

To fulfill the sample-size requirements for the maintenance trial, additional patients were enrolled in an open-label group (cohort 2), which received the same vedolizumab induction regimen that was used for the patients assigned to vedolizumab in cohort 1. Patients from both cohorts who had a clinical response (i.e., ≥70-point decrease in the CDAI score) with vedolizumab at week 6 were randomly assigned, in a 1:1:1 ratio, to continue in a blinded fashion to receive vedolizumab every 8 weeks, vedolizumab every 4 weeks, or placebo, for up to 52 weeks. Randomization was stratified according to participation in cohort 1 or 2 during induction; concomitant use of glucocorticoids; and concomitant use of immunosuppressive agents, prior use of TNF antagonists, or both. Patients who did not have a clinical response at week 6 to vedolizumab induction therapy received vedolizumab at a dose of 300 mg every 4 weeks and were followed through week 52. Patients in the placebo group of cohort 1 continued to receive placebo and were also followed through week 52.

Randomization was computer-generated and was performed at a central location. Glucocorticoids were tapered in patients who had a response at week 6, according to a prespecified regimen; immunosuppressive agents were discontinued in patients at U.S. sites (see the Supplementary Appendix). The use of other concomitant medications remained constant.

FOLLOW-UP

Study visits were scheduled at weeks 0, 2, 4, and 6 in the trial of induction therapy and every 4 weeks thereafter during the trial of maintenance therapy until week 52. Adverse events, CDAI score, neurologic symptoms of PML as assessed by means of questionnaires (see the Supplementary Appendix), the use of concomitant medications, and the presence or absence of fistulae were evaluated at all visits. Blood testing, including measurement of C-reactive protein levels, serum vedolizumab concentrations, and antibodies against vedolizumab, was performed at baseline and throughout the study. Testing for JC virus antibodies was not performed because a validated assay was not available.

END-POINT MEASURES

The two primary end points in the trial of induction therapy were clinical remission (CDAI score of ≤150 points[19]) and CDAI-100 response (≥100-point decrease in the CDAI score) at week 6; the secondary end point was the mean change in C-reactive protein levels from baseline to week 6. In the trial of maintenance therapy, the primary end point was clinical remission at week 52, and the secondary end points (in ranked order) were CDAI-100 response, glucocorticoid-free remission (defined as clinical remission at week 52 without glucocorticoid therapy), and durable clinical remission (defined as clinical remission at ≥80% of study visits, including the final visit) at week 52. Adverse events were classified according to the *Medical Dictionary for Regulatory Activities*,[20] version 15, and were analyzed in the safety population, which included all patients who received any amount of study drug during the course of the study.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize demographic characteristics. The proportions of patients with clinical remission and a CDAI-100 response at week 6 were analyzed with the use of a Cochran–Mantel–Haenszel chi-square test with adjustment for stratification factors. Patients who withdrew from the study prematurely were classified as having had treatment failure (Table S2 in the Supplementary Appendix).

A combination of the Hochberg method and sequential testing was used to maintain the overall type I error rate at a 5% significance

level. If the P value for one of the two primary end points was greater than 0.05, the other P value was considered to indicate statistical significance only if it was 0.025 or lower. Nine subgroup analyses were prespecified; risk differences and 95% confidence intervals were determined for the proportions of patients in the vedolizumab and placebo groups who were in remission and who had CDAI-100 responses at week 6.

The proportions of patients who met the criteria for the end points during the trial of maintenance therapy were analyzed in a similar way. End points in that trial were tested for significance in a prespecified ranked order, with the Hochberg method applied to maintain the alpha level at 5% in the comparison of the two vedolizumab regimens with placebo. Exploratory analyses of end points were not adjusted for multiple comparisons. Continuous outcomes with respect to CDAI score, IBDQ score, and glucocorticoid use over time were examined by means of an analysis of covariance; data on C-reactive protein levels were analyzed with the use of the Wilcoxon rank-sum test.

For the trial of induction therapy, we calculated that with 370 patients, the study would have 91% power to detect a 16% difference in clinical remission rates and 82% power to detect a 15% difference in CDAI-100 response rates between the vedolizumab and placebo groups, assuming clinical remission rates of 37% and 21% with vedolizumab and placebo, respectively, and CDAI-100 response rates of 46% and 31%,

Table 1. Demographic and Baseline Clinical Characteristics and History of Crohn's Disease Medication among Patients in the Induction Trial.*

Characteristic	Placebo (N=148)	Vedolizumab			Total (N=1115)
		Cohort 1 (N=220)	Cohort 2 (N=747)	Combined (N=967)	
Age — yr	38.6±13.2	36.3±11.6	35.6±12.0	35.7±11.9	36.1±12.1
Male sex — no. (%)	69 (46.6)	105 (47.7)	346 (46.3)	451 (46.6)	520 (46.6)
White race — no. (%)†	124 (83.8)	182 (82.7)	689 (92.2)	871 (90.1)	995 (89.2)
Body weight — kg	68.7±18.9	67.1±19.1	70.8±19.6	69.9±19.5	69.8±19.4
Current smoker — no. (%)	34 (23.0)	54 (24.5)	210 (28.1)	264 (27.3)	298 (26.7)
Duration of disease — yr	8.2±7.8	9.2±8.2	9.2±7.6	9.2±7.8	9.0±7.8
CDAI score‡	325±78	327±71	322±67	323±68	324±69
Median C-reactive protein — mg/liter§	13.7	15.3	10.2	10.6	11.5
Median fecal calprotectin — μg/g¶	653	852	657	688	686
Disease site — no. (%)					
Ileum only	21 (14.2)	37 (16.8)	123 (16.5)	160 (16.5)	181 (16.2)
Colon only	43 (29.1)	62 (28.2)	211 (28.2)	273 (28.2)	316 (28.3)
Ileum and colon	84 (56.8)	121 (55.0)	413 (55.3)	534 (55.2)	618 (55.4)
Concomitant medications for Crohn's disease — no. (%)‖					
Glucocorticoids only	45 (30.4)	67 (30.5)	269 (36.0)	336 (34.7)	381 (34.2)
Immunosuppressive agents only	25 (16.9)	37 (16.8)	119 (15.9)	156 (16.1)	181 (16.2)
Glucocorticoids and immunosuppressive agents	26 (17.6)	38 (17.3)	125 (16.7)	163 (16.9)	189 (17.0)
No glucocorticoids or immunosuppressive agents	52 (35.1)	78 (35.5)	234 (31.3)	312 (32.3)	364 (32.6)
Prednisone-equivalent dose — mg					
Median	20.0	20.0	20.0	20.0	20.0
Interquartile range	10.0–30.0	10.0–20.0	12.5–30.0	10.0–30.0	10.0–30.0

Table 1. (Continued.)

Characteristic	Placebo (N=148)	Vedolizumab			Total (N=1115)
		Cohort 1 (N=220)	Cohort 2 (N=747)	Combined (N=967)	
Prior TNF antagonist therapy for Crohn's disease — no./total no. (%)					
Receipt of ≥1 TNF antagonist	72/148 (48.6)	111/220 (50.5)	506/747 (67.7)	617/967 (63.8)	689/1115 (61.8)
Failure of TNF antagonist therapy					
≥1 TNF antagonist	70/148 (47.3)	105/220 (47.7)	470/747 (62.9)	575/967 (59.5)	645/1115 (57.8)
Inadequate response**	41/70 (58.6)	56/105 (53.3)	223/470 (47.4)	279/575 (48.5)	320/645 (49.6)
Loss of response††	22/70 (31.4)	40/105 (38.1)	189/470 (40.2)	229/575 (39.8)	251/645 (38.9)
Unacceptable side effects	7/70 (10.0)	9/105 (8.6)	58/470 (12.3)	67/575 (11.7)	74/645 (11.5)
≥2 TNF antagonists	42/148 (28.4)	56/220 (25.5)	300/747 (40.2)	356/967 (36.8)	398/1115 (35.7)
Hemoglobin concentration — g/liter	124.7±18.6	121.6±18.4	125.2±16.8	124.4±17.3	124.4±17.4
White-cell count — $\times 10^{-9}$/liter	8.8±3.0	9.0±3.3	9.2±3.4	9.2±3.4	9.1±3.4
Prior surgery for Crohn's disease — no. (%)	54 (36.5)	98 (44.5)	314 (42.0)	412 (42.6)	466 (41.8)
History of fistulizing disease — no. (%)	56 (37.8)	90 (40.9)	264 (35.3)	354 (36.6)	410 (36.8)
Draining fistulae at baseline — no. (%)	23 (15.5)	38 (17.3)	104 (13.9)	142 (14.7)	165 (14.8)

* Plus–minus values are means ±SD. Cohort 1 included patients who were randomly assigned, in a 3:2 ratio, as part of the double-blind trial of induction therapy, to receive intravenous vedolizumab, at a dose of 300 mg, or placebo at weeks 0 and 2. Cohort 2 included patients who received open-label vedolizumab at a dose of 300 mg at weeks 0 and 2. There were no significant differences (at $P<0.05$) between the placebo group and the vedolizumab group in cohort 1. TNF denotes tumor necrosis factor.

† Race was determined by the investigator.

‡ The Crohn's Disease Activity Index (CDAI) consists of eight components, each of which is adjusted by a weighting factor. The components are subsequently added together to yield a composite score; scores range from 0 to approximately 600, with higher scores indicating more severe disease activity.

§ Data on C-reactive protein levels were available for 147 patients in the placebo group, 220 patients in vedolizumab cohort 1, and 747 patients in vedolizumab cohort 2, for a total of 1114 patients. Among these, 127 patients in the placebo group (86.4%), 183 in vedolizumab cohort 1 (83.2%), and 617 in vedolizumab cohort 2 (82.6%) (800 patients [82.7%] in the combined vedolizumab groups and 917 patients [83.2%] in the total population) had elevated C-reactive protein levels (>2.87 mg per liter).

¶ Data on fecal calprotectin concentrations were available for 142 patients in the placebo group, 210 in vedolizumab cohort 1, and 719 in vedolizumab cohort 2.

‖ The glucocorticoids used included prednisone, methylprednisolone, prednisolone, budesonide, hydrocortisone, and triamcinolone. The immunosuppressive agents included azathioprine, mercaptopurine, and methotrexate.

** Included in this category were patients who did not have an initial response.

†† Loss of response indicates that the patient had a response initially but subsequently did not have a response.

respectively.[11,16,21-26] For the trial of maintenance therapy, we calculated that with 501 patients, the study would have 89% power to detect a 16% difference in clinical remission rates, assuming rates of 38% and 22% with vedolizumab and placebo, respectively.[11,16,21-26]

RESULTS

PATIENTS

A total of 1920 patients were screened (Fig. S1 in the Supplementary Appendix), and 1115 were enrolled and included in the analyses; 7.6% of them did not meet at least one inclusion criterion or met at least one exclusion criterion (Table S3 in the Supplementary Appendix). In the randomized trial of induction therapy involving 368 patients (cohort 1), the baseline characteristics were similar in the placebo and vedolizumab groups (Table 1). Approximately 50% of patients had previously received TNF antagonist therapy. In the randomized trial of maintenance therapy involving 461 patients, the baseline characteristics were similar in the placebo and vedolizumab groups (Table S4 in the Supplementary Appendix) as well as in patients who entered the main-

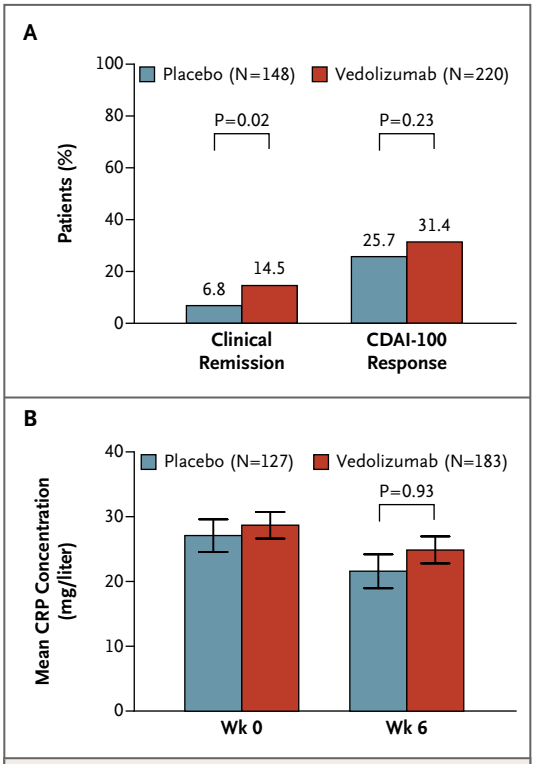


Figure 1. Primary End Points in the Trial of Induction Therapy.

Panel A shows the proportions of patients who were in clinical remission and patients who had a CDAI-100 response (a decrease of 100 points or more in the score on the Crohn's Disease Activity Index [CDAI], with scores ranging from 0 to approximately 600, and with higher scores indicating greater disease activity) at week 6. Panel B shows the mean C-reactive protein (CRP) concentrations at week 0 and week 6. I bars indicate standard errors. For patients with insufficient data at the designated analysis time point, the last value was carried forward. The P value (two-sided) in Panel B was calculated with the use of the Wilcoxon rank-sum test for the change from baseline values in CRP concentrations with vedolizumab versus placebo.

tenance trial from cohort 1 (96 patients) and those who entered from cohort 2 (365 patients).

END POINTS IN THE TRIAL OF INDUCTION THERAPY

In an analysis of the two primary end points in cohort 1, a total of 32 of the 220 patients who received vedolizumab (14.5%) and 10 of the 148 who received placebo (6.8%) had a clinical remission (P=0.02) at week 6; 69 (31.4%) and 38 (25.7%), respectively, had a CDAI-100 response (P=0.23) (Fig. 1A). The efficacy of vedolizumab was generally consistent across subgroups (Fig. S2 in the Supplementary Appendix). Among the 747 patients in cohort 2, a total of 132 (17.7%) had a clinical remission and 257 (34.4%) had a CDAI-100 response at week 6.

In cohort 1, the mean changes in C-reactive protein levels from baseline to week 6 were similar in the vedolizumab and placebo groups (Fig. 1B). In a post hoc analysis, the proportion of patients who had had C-reactive protein levels above 2.87 mg per liter at baseline and whose levels returned to the normal range (i.e., ≤2.87 mg per liter) by week 6 was similar in the two groups (Fig. S3 in the Supplementary Appendix).

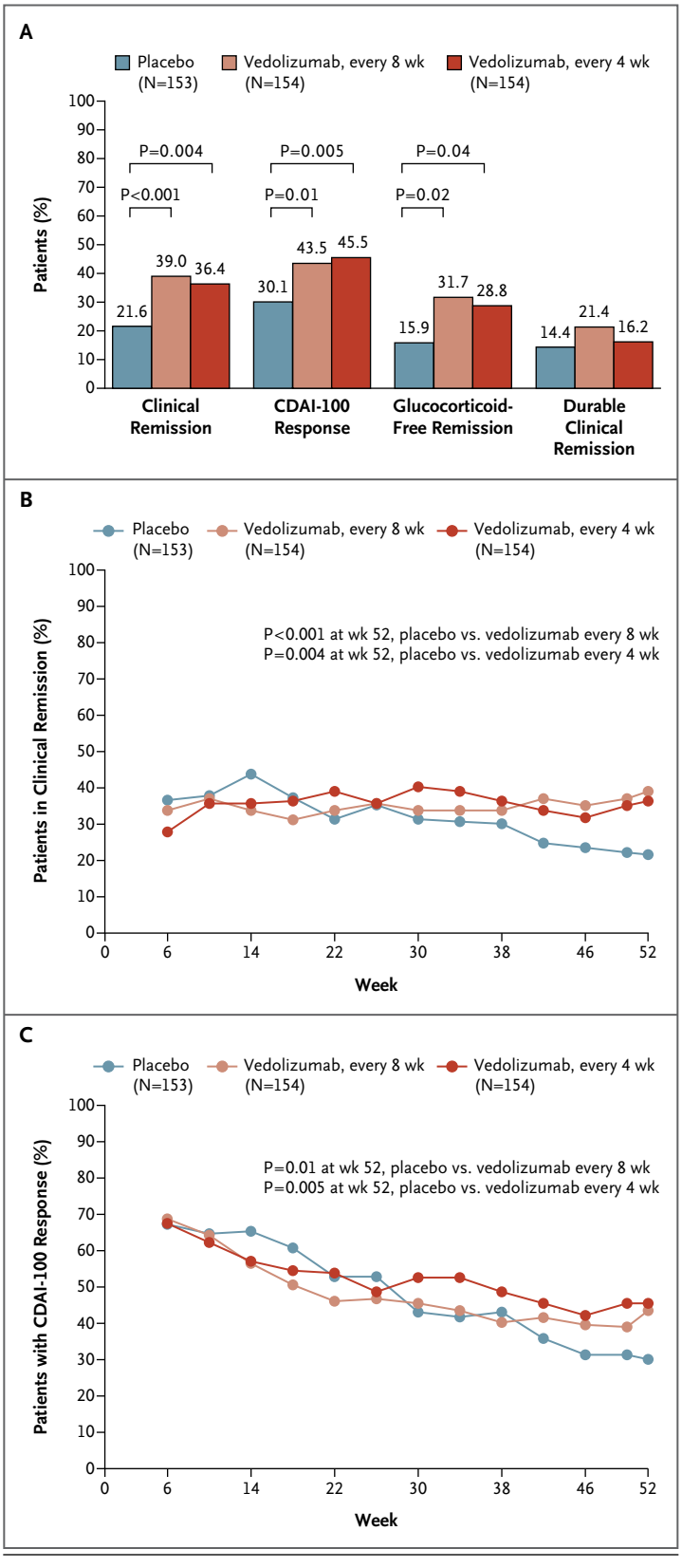
END POINTS IN THE TRIAL OF MAINTENANCE THERAPY

At week 52, a total of 60 of the 154 patients (39.0%) receiving vedolizumab every 8 weeks and 56 of the 154 patients (36.4%) receiving vedolizumab every 4 weeks were in clinical remission, as compared with 33 of the 153 patients (21.6%) receiving placebo (P<0.001 and P=0.004 for the comparison of the two vedolizumab groups, respectively, with placebo) (Fig. 2A). The efficacy of vedolizumab was generally consistent across subgroups (Fig. S4 in the Supplementary Appendix).

In an analysis of secondary end points at week 52, the proportions of patients who had a CDAI-100 response and who had glucocorticoid-free remission were significantly greater in the groups receiving vedolizumab every 8 weeks and every 4 weeks than in the placebo group; however, the proportion of patients with a durable clinical remission did not differ significantly among the groups (Fig. 2A). Figure 2 shows the proportions of patients who met the criteria for clinical remission and who had a CDAI-100 response; Figure S5 in the Supplementary Appendix shows the mean CDAI scores from week 6 to week 52, the mean changes from week 6 in the IBDQ score, the mean C-reactive protein levels in patients who had had elevated levels at baseline, and the median change in the glucocorticoid dose over time. Information regarding draining fistulae is shown in Figure S6 in the Supplementary Appendix. In a post hoc analysis of data from patients who had had elevated C-reactive protein levels at week 6, levels returned to the normal range (i.e., ≤2.87 mg per liter) by week 52 in a greater proportion of patients receiving vedolizumab than of patients receiving placebo (Fig. S7 in the Supplementary Appendix).

Figure 2. End Points in the Trial of Maintenance Therapy.

Panel A shows the proportions of patients, among those who had had clinical remission at week 6, who were still in clinical remission at week 52, who had a CDAI-100 response at week 52, and who had glucocorticoid-free remission (i.e., clinical remission without glucocorticoid therapy) at week 52 (with data for this end point available for 82 patients receiving placebo, 82 patients receiving vedolizumab every 8 weeks, and 80 patients receiving vedolizumab every 4 weeks), as well as the proportion of patients who had a durable clinical remission (defined as a clinical remission at ≥80% of study visits, including the final visit) at week 52. Panel B shows the proportions of patients who were in clinical remission from week 6 to week 52, and Panel C, the proportions of patients who had a CDAI-100 response from week 6 to week 52.



SAFETY

Nasopharyngitis occurred more frequently, and headache and abdominal pain less frequently, with vedolizumab than with placebo during the trial of maintenance therapy (Table 2, and Table S6 in the Supplementary Appendix). The incidences of infections and of serious infections were higher with vedolizumab than with placebo (Table S6 in the Supplementary Appendix). During the 6-week trial of induction therapy, breast cancer developed in one patient who was receiving vedolizumab. During the trial of maintenance therapy, one case each of latent tuberculosis, carcinoid tumor in the appendix, squamous-cell carcinoma, and basal-cell skin carcinoma was diagnosed in the vedolizumab groups; a borderline ovarian tumor developed in one patient in the placebo group. The incidence of any serious adverse event was higher among patients who received vedolizumab than among those who received placebo (24.4% vs. 15.3%).

Five deaths occurred during the study period (see the Supplementary Appendix), four among patients receiving vedolizumab (one death each from Crohn's disease with sepsis, intentional overdose of prescription medication, myocarditis, and septic shock) and one in the placebo group (from bronchopneumonia). The sepsis and septic-shock events (both culture-negative) involved, respectively, a patient with extensive preexisting pulmonary emboli and a thrombus in the inferior vena cava and a patient with medically managed pneumoperitoneum after colonoscopy. Myocarditis and intravenous injec-

Table 2. Adverse Events Affecting at Least 5% of Patients Who Received Vedolizumab.*

Event	Placebo (N=301)	Vedolizumab (N=814)
	no. (%)	
Adverse event		
Crohn's disease exacerbation	65 (21.6)	164 (20.1)
Arthralgia	40 (13.3)	110 (13.5)
Pyrexia	40 (13.3)	103 (12.7)
Nasopharyngitis	24 (8.0)	100 (12.3)
Headache	47 (15.6)	97 (11.9)
Nausea	30 (10.0)	90 (11.1)
Abdominal pain	39 (13.0)	79 (9.7)
Upper respiratory tract infection	17 (5.6)	54 (6.6)
Fatigue	14 (4.7)	53 (6.5)
Vomiting	23 (7.6)	49 (6.0)
Back pain	12 (4.0)	38 (4.7)
Any serious adverse event	46 (15.3)	199 (24.4)
Any serious infection†	9 (3.0)	45 (5.5)
Any cancer‡	1 (0.3)	4 (0.5)

* The analysis of adverse events was performed on data from the safety population, which included all patients who received at least one dose of the study drug. For this analysis, the vedolizumab group includes patients who received maintenance therapy with vedolizumab (i.e., those who had had a response to vedolizumab induction therapy and were randomly assigned to receive vedolizumab every 8 weeks or every 4 weeks as maintenance therapy plus those who did not have a response to vedolizumab induction therapy and continued to receive vedolizumab every 4 weeks during the maintenance trial); the placebo group includes patients who did not receive maintenance therapy with vedolizumab (i.e., those who were randomly assigned to placebo during the induction trial plus those who had had a response to vedolizumab induction therapy and were randomly assigned to placebo for the maintenance trial). See Tables S5 and S6 in the Supplementary Appendix for a further breakdown of individual treatment groups. Adverse events were classified according to the System Organ Class categorization and preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15. Patients with more than one event in a category were counted only once if the start and stop dates of the multiple events overlapped or if the start and stop dates were the same; if the start and stop dates of the multiple events did not overlap, they were counted as separate events.

† A serious infection was defined as a serious adverse event of infection according to the classification for adverse event reporting in MedDRA.

‡ The cancer in the placebo group was a borderline ovarian carcinoma, which is defined as a subset of epithelial ovarian tumors that are considered to be of low malignant potential. The cancers in the vedolizumab group included one case each of basal-cell skin carcinoma, breast cancer, carcinoid tumor in the appendix, and squamous-cell carcinoma of the skin.

tion of drugs intended for oral use were diagnosed at autopsy in a patient who had a history of endocarditis and deep-vein thrombosis.

Patients were actively monitored for PML (see the Supplementary Appendix); no cases were identified. Clinically important infusion reactions were infrequent; only one patient discontinued the study treatment because of a serious infusion reaction. No cases of anaphylaxis were reported.

PHARMACOKINETICS AND IMMUNOGENICITY

The mean (±SD) trough vedolizumab concentration in the 827 patients with pharmacokinetic data that could be evaluated was 26.8±17.5 μg per milliliter at week 6. At steady state, the mean vedolizumab concentrations were 13.0±9.1 μg per milliliter in the group receiving vedolizumab every 8 weeks (72 patients with data that could be evaluated) and 34.8±22.6 μg per milliliter in the group receiving vedolizumab every 4 weeks (247 patients with data that could be evaluated). Correlations between drug level and response in the trials of induction and maintenance therapy are shown in Figures S8 and S9, respectively, in the Supplementary Appendix. Both doses were associated with target saturation that exceeded 95% in more than 95% of the study population. Among 814 vedolizumab-treated patients with samples that could be evaluated for antibodies against vedolizumab, 33 patients (4.1%) had at least one sample with positive test results and 3 (0.4%) had two or more consecutive samples with positive results. Concomitant immunosuppressive therapy was associated with decreased immunogenicity (data not shown).

DISCUSSION

Among patients with moderately to severely active Crohn's disease in whom conventional therapy failed, patients treated with vedolizumab induction therapy were more likely than those receiving placebo to have a remission at week 6; however, they were not more likely to have a CDAI-100 response. In an analysis of patients who had a response to induction therapy with vedolizumab, the rates of clinical remission, CDAI-100 response, and glucocorticoid-free remission at week 52 were higher among patients receiving vedolizumab every 8 weeks or every 4 weeks than among patients who were switched to placebo.

Many patients with moderately to severely active Crohn's disease do not have a response to currently available treatments or have an initial response that is not sustained.[23,26-28] The efficacy of a second TNF antagonist in patients who

no longer have a response to a first TNF antagonist is lower than the efficacy of the first TNF antagonist in patients who have never received TNF-antagonist therapy.[24] Although natalizumab is efficacious in Crohn's disease, it is used infrequently[10-12] because of the risk of PML.[13] Thus, novel treatment strategies are needed.[16-18] Selective blockade of $\alpha_4\beta_7$-expressing, gut-homing lymphocytes with vedolizumab represents one potential approach.[16-18]

The modest effect of vedolizumab on the induction of clinical remission and its nonsignificant effect on the CDAI-100 response at week 6 require consideration. Whether these effects are attributable primarily to modest efficacy or to potential confounders is unknown. One possible confounder is the severity of disease in the study population, which may have precluded a robust inductive effect. Patients had a mean baseline CDAI score of 324 points, a median C-reactive protein concentration of 11.5 mg per liter, and a median fecal calprotectin value of 686 μg per gram; 37% had a history of fistulizing disease, and 42% had undergone at least one previous surgery for Crohn's disease. Approximately 50% of patients had had treatment failure (which was defined in the protocol as a lack of initial response, loss of response, or unacceptable side effects) with one or more TNF antagonists; half of these patients did not have an initial response. Approximately 30% of patients had had treatment failure with two or more TNF antagonists. A population with such refractory disease has not been evaluated in previous trials of TNF antagonists. However, a recent clinical trial of ustekinumab in a similar population also showed a modest induction effect with respect to the CDAI-100 response at week 6 but did not show a significant effect on remission rates.[29] Protracted medical management with multiple medications, including TNF antagonists, may contribute to the refractoriness of the disease. Alternatively, pharmacologic inhibition of lymphocyte migration to the gut may require more time for full induction efficacy than that required with TNF blockade. In addition, anti-integrin therapy could be relatively slower acting in Crohn's disease, given the transmural nature of the disease, with the predominant benefit seen during the maintenance phase (Fig. 2, and Fig. S5 in the Supplementary Appendix). Previous studies of natalizumab showed modest induction benefits, rising response and remission rates over the course of 12 weeks, and robust maintenance effects, suggesting that vedolizumab may have similar kinetic characteristics.[10-12] Differences between the vedolizumab and placebo groups during the trial of maintenance therapy were not apparent until week 28 or later (Fig. 2B and 2C), possibly owing to the time required for vedolizumab clearance after two induction doses.

During the maintenance phase, serious infections occurred in 5.5% of the patients receiving vedolizumab, as compared with 3.0% of the patients receiving placebo. PML developed in none of the 1115 patients who entered this study — a finding consistent with that in a parallel study of patients with ulcerative colitis, which appears elsewhere in this issue of the *Journal*.[30] This trial did not have a long enough duration or a large enough sample to exclude the possibility of an association of vedolizumab with the risk of PML; longer-term observational data are needed.

Among approximately 3000 patients exposed to vedolizumab for a median of 18.8 months (mean, 20.9 months; range, 4 to 67), no cases of PML were reported as of February 2013 (unpublished data from Millennium clinical trials). Approximately 80% of patients had received immunosuppressive agents previously, and 900 patients (approximately 30%) had more than 24 months of vedolizumab exposure. Owing to the lack of a commercially available validated assay, JC virus antibody status was not assessed. However, seropositivity rates of at least 50% have been reported in similar populations with Crohn's disease.[31-38] In patients with multiple sclerosis receiving natalizumab therapy, the overall incidence of PML is more than 1 case in 500 patients (2.0 per 1000; range, approximately 1 in 3000 [0.3 per 1000] with ≤24 months of exposure and no prior immunosuppressive therapy to approximately 1 in 150 [6.7 per 1000] with >24 months of exposure and prior immunosuppressive therapy).[13]

The rate of 5 deaths per 1115 patients observed in this study (see the Supplementary Appendix) is similar to crude rates of death associated with other biologic medications.[11,23,25-27] Cancer was reported in 4 patients treated with vedolizumab (two solid tumors and two nonmelanoma skin cancers). Long-term epidemio-

logic studies are needed to fully characterize the safety of vedolizumab.

This study leaves some questions unanswered, including which specific patients with Crohn's disease may derive the most benefit from vedolizumab. In addition, the study design did not allow for adequate assessment of potential synergistic effects of combining vedolizumab with immunosuppressive agents.

In conclusion, patients with moderately to severely active Crohn's disease who were treated with vedolizumab, as compared with those receiving placebo, were more likely to have a clinical remission at week 6 but were not more likely to have a CDAI-100 response. Among patients who had a response to vedolizumab at week 6, the rates of clinical remission at week 52 were significantly higher among patients receiving vedolizumab every 8 weeks or every 4 weeks than among those receiving placebo.

Supported by Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceuticals.

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

We thank Tiffany Brake, Ph.D., and Candace Lundin, D.V.M. (Complete Healthcare Communications), Audrey Suh, Pharm.D. (Takeda Pharmaceuticals International), and Elizabeth Barton, M.S., and Stefanie Dorlas, B. Math. (MedLogix Communications), for editorial support; and Tim Wyant, Ph.D., for critical review of an earlier version of the manuscript.

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