

## ORIGINAL ARTICLE

## Natalizumab for Active Crohn's Disease

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## ABSTRACT

**BACKGROUND**

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In chronic inflammatory conditions such as Crohn's disease, the migration of leukocytes from the circulation into the parenchyma and their activation within inflammatory sites are mediated in part by  $\alpha_4$  integrins.

**METHODS**

We conducted a double-blind, placebo-controlled trial of the  $\alpha_4$  integrin-specific humanized monoclonal antibody natalizumab in 248 patients with moderate-to-severe Crohn's disease. Patients were randomly assigned to receive one of four treatments: two infusions of placebo; one infusion of 3 mg of natalizumab per kilogram of body weight, followed by placebo; two infusions of 3 mg of natalizumab per kilogram; or two infusions of 6 mg of natalizumab per kilogram. Infusions were given four weeks apart. Outcomes included changes in scores for the Crohn's Disease Activity Index (higher scores indicate more severe disease), the health-related quality of life, and C-reactive protein levels.

\*Members of the Natalizumab Pan-European Study Group are listed in the Appendix.

**RESULTS**

The group given two infusions of 6 mg of natalizumab per kilogram did not have a significantly higher rate of clinical remission (defined by a score of less than 150 on the Crohn's Disease Activity Index) than the placebo group at week 6 (the prospectively defined primary end point in the efficacy analysis). However, both groups that received two infusions of natalizumab had higher remission rates than the placebo group at multiple time points. Natalizumab also produced a significant improvement in response rates (defined by a reduction of at least 70 points in the score on the Crohn's Disease Activity Index). The highest remission rate was 44 percent and the highest response rate was 71 percent (at week 6 in the group given two infusions of 3 mg per kilogram). Overall, the two infusions of 6 mg of natalizumab per kilogram and of 3 mg per kilogram had similar effects. The quality of life improved in all natalizumab groups; C-reactive protein levels improved in groups receiving two infusions of natalizumab. The rates of adverse events were similar in all four groups.

**CONCLUSIONS**

Treatment with the selective adhesion-molecule inhibitor natalizumab increased the rates of clinical remission and response, improved the quality of life and C-reactive protein levels, and was well tolerated in patients with active Crohn's disease.

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THE INTEGRINS ARE A FAMILY OF CELL-surface glycoproteins involved in the adhesion, migration, and activation of immune cells. The  $\alpha_4$  integrins are heterodimeric receptors consisting of an  $\alpha_4$  subunit and either a  $\beta_1$  or  $\beta_7$  subunit. Both  $\alpha_4\beta_1$  and  $\alpha_4\beta_7$  integrin have a role in the migration of leukocytes across the vascular endothelium<sup>1,2</sup> and contribute to cell activation and survival within the parenchyma.<sup>3,4</sup> Specifically,  $\alpha_4\beta_1$  integrin (also known as very late antigen 4, or VLA-4) binds to vascular-cell adhesion molecule-1,<sup>5</sup> which is up-regulated on the vascular endothelium at many sites of chronic inflammation,<sup>6,7</sup> including the intestine in patients with Crohn's disease. The  $\alpha_4\beta_1$  integrin also binds to certain forms of the extracellular-matrix protein fibronectin. The  $\alpha_4\beta_7$  dimer interacts with mucosal addressin-cell adhesion molecule and mediates homing of lymphocytes to the gut.<sup>8,9</sup> The expression of this adhesion molecule on the vascular endothelium is also increased at sites of inflammation in the intestinal tract of patients with inflammatory bowel disease.<sup>10-12</sup>

Preclinical studies have shown that monoclonal antibodies against  $\alpha_4$  integrin reduce inflammation and symptoms of disease in tamarins with inflammatory bowel disease.<sup>13,14</sup> Natalizumab (Antegren, Elan Pharmaceuticals and Biogen), a recombinant, humanized monoclonal antibody against  $\alpha_4$  integrin, improved the signs and symptoms of patients with Crohn's disease or ulcerative colitis in two pilot studies.<sup>15,16</sup> We conducted a large, randomized, placebo-controlled trial of this selective adhesion-molecule inhibitor in patients with moderate-to-severe Crohn's disease.

## METHODS

### PATIENTS

After receiving approval from the local ethics committee, centers screened male and female patients at least 18 years of age who had clinical evidence of moderate-to-severe Crohn's disease, defined by a score on the Crohn's Disease Activity Index of at least 220 but no more than 450. The Crohn's Disease Activity Index incorporates eight related variables: the number of liquid or very soft stools per day, the severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of an abdominal mass, the use of anti-diarrheal drugs, hematocrit, and body weight.<sup>17,18</sup> Scores range from 0 to 600, with higher scores in-

dicating more severe disease activity. A total of 301 patients were screened, and 248 patients underwent randomization at 35 study centers in Belgium, the Czech Republic, Denmark, Germany, Israel, the Netherlands, Sweden, and the United Kingdom between September 1999 and August 2000. Enrollment at each center ranged from 1 to 19 patients. All patients gave written informed consent. Patients who had received methotrexate, cyclosporine, or any investigational agents within three months before randomization were excluded; patients who were receiving azathioprine or mercaptopurine were required to have been taking a stable dose for at least four months before randomization. Other criteria for exclusion included prior treatment with any antibody agent, current use of oral prednisolone at a dose of more than 25 mg per day or another corticosteroid at an equivalent dose, current use of an elemental diet or parenteral nutrition, infectious or neoplastic diseases of the bowel, bowel surgery within three months before randomization, the presence of an ostomy, the presence of symptoms due mainly to fibrotic strictures, and a clinical impression that the patient was likely to require abdominal surgery soon.

The study data were gathered by the investigators and by an independent organization (PPD Development), and the data were held and analyzed by Elan and Biogen. The principal investigators on the writing team had access to all data.

### STUDY DESIGN AND RANDOMIZATION

Eligible patients were randomly assigned to one of four treatment regimens according to a computer-generated, site-stratified, block randomization schedule. Each group received two intravenous infusions four weeks apart. The four treatment regimens consisted of two infusions of placebo, one infusion of natalizumab at a dose of 3 mg per kilogram of body weight and one infusion of placebo, two infusions of natalizumab at a dose of 3 mg per kilogram, and two infusions of natalizumab at a dose of 6 mg per kilogram. Neither the study personnel nor the patients were aware of the treatment assignments.

### STUDY PROCEDURES AND END POINTS

The primary efficacy measure was the Crohn's Disease Activity Index. A clinical remission was defined by a score of less than 150. A clinical response was defined by a decrease in the score of at least 70 points from base line. Additional outcomes includ-

ed the serum level of C-reactive protein and the health-related quality of life, as measured by the Inflammatory Bowel Disease Questionnaire.<sup>19</sup> Scores on this instrument can range from 32 to 224, with higher scores indicating a better quality of life.

Safety evaluations, which included all reports of adverse events and clinical laboratory tests, were conducted throughout the study. Investigators were informed of the patients' absolute neutrophil counts but not the white-cell or differential counts, so that the increase in circulating lymphocytes observed in natalizumab-treated patients would not prompt unblinding of the treatment assignments. An independent data and safety monitoring committee oversaw the study. Serum samples were collected at each visit and analyzed for antibodies against natalizumab by an enzyme-linked immunosorbent assay.

#### STATISTICAL ANALYSIS

The prospective primary hypothesis was that two infusions of 6 mg of natalizumab per kilogram would result in a higher proportion of patients in clinical remission (defined as a score of less than 150 on the Crohn's Disease Activity Index) at week 6 than would two infusions of placebo. All other efficacy analyses were prespecified as secondary outcomes. All efficacy analyses were conducted according to the intention-to-treat principle, with the last observation carried forward, and thus included all 248 patients who underwent randomization. Patients who dropped out of the study, including those who received rescue medications, had the data obtained at their last visit carried forward. The analysis of adverse events included all 244 patients who underwent randomization and received at least one dose of the assigned treatment. Four patients did not receive either dose, because after undergoing randomization, they were found to be ineligible.

All statistical tests were two-sided, with an alpha level of 0.05. P values for secondary analyses were not adjusted for multiple comparisons. Remission and response rates were compared with use of the Cochran–Mantel–Haenszel chi-square test (general association),<sup>20</sup> according to the country in which patients were treated. We analyzed scores on the Crohn's Disease Activity Index using the area under the curve, and we used linear mixed modeling of repeated-measurements methods for a post hoc evaluation of treatment effects.<sup>21,22</sup>

We estimated that 60 patients would be needed in each group in order to detect a significant differ-

ence in response rates among the groups at a power of 80 percent and a 5 percent level of significance. We assumed that the natalizumab groups would have a rate of response of 40 percent and the placebo group would have a response rate of 15 percent.

The comparisons of changes from base line in the scores on the inflammatory bowel disease questionnaire and in the C-reactive protein levels between each of the three natalizumab groups and the placebo group were performed with use of the Wilcoxon–Mann–Whitney test. C-reactive protein levels were compared in all patients, as well as in a prospectively identified subgroup with a base-line value above the normal range.

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#### RESULTS

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There were no significant differences in demographic characteristics, Crohn's Disease Activity Index scores, sites of disease, and medications among the groups at base line (Table 1). Although not statistically significant, the incidence of fistulizing disease at base line was higher in the group given two infusions of 6 mg of natalizumab per kilogram (25 percent, as compared with 10 percent in the placebo group, 16 percent in the group given one infusion of 3 mg of natalizumab per kilogram, and 12 percent in the group given two infusions of 3 mg of natalizumab per kilogram). At base line (week 0), most patients were receiving other medications for Crohn's disease, including 5-aminosalicylate compounds (48 to 62 percent), oral corticosteroids (46 to 63 percent), or azathioprine or mercaptopurine (18 to 38 percent), with or without other agents. At base line, 10 to 19 percent of the patients were not receiving any other therapy for Crohn's disease, 16 to 24 percent were receiving monotherapy with 5-aminosalicylate compounds, 7 to 25 percent were receiving monotherapy with oral corticosteroids, and 0 to 9 percent were receiving monotherapy with azathioprine or mercaptopurine. Of the 244 patients who received at least one dose of the assigned study drug, 27 withdrew from the study before completing 12 weeks: 10 in the placebo group, 6 in the group given one infusion of 3 mg of natalizumab per kilogram, 5 in the group given two infusions of 3 mg of natalizumab per kilogram, and 6 in the group given two infusions of 6 mg of natalizumab per kilogram. The reasons for withdrawal were ineligibility (in the case of two patients), adverse events (eight), lack of efficacy (seven), patient's request (three), loss to follow-up (two), and investi-

**Table 1. Demographic Characteristics and Medications at Base Line.**

Characteristic	Placebo (N=63)	1 Infusion of 3 mg of Natalizumab/kg (N=68)	2 Infusions of 3 mg of Natalizumab/kg (N=66)	2 Infusions of 6 mg of Natalizumab/kg (N=51)
Age — yr				
Mean	34	36	36	35
Range	18–68	18–66	19–64	19–62
Duration of disease — yr				
Mean	8.9	8.4	8.1	7.8
Range	0.3–64.3	0.5–27.6	0.5–21.9	0.6–29.0
Crohn's Disease Activity Index Score*				
Mean	300	288	300	298
Range	186–449	211–427	219–449	210–429
Disease site — no. (%)				
Ileum	15 (24)	9 (13)	17 (26)	12 (24)
Colon	11 (17)	16 (24)	16 (24)	16 (31)
Ileum and colon	37 (59)	43 (63)	33 (50)	23 (45)
Fistulizing disease — no. (%)	6 (10)	11 (16)	8 (12)	13 (25)
Female sex — no. (%)	33 (52)	41 (60)	36 (55)	26 (51)
Weight — kg				
Mean	68	66	64	69
Range	42–100	41–95	44–97	44–98
Concomitant medications — no. (%)				
None for Crohn's disease†	12 (19)	10 (15)	9 (14)	5 (10)
5-Aminosalicylate compounds	30 (48)	41 (60)	41 (62)	30 (59)
Oral corticosteroids	31 (49)	31 (46)	37 (56)	32 (63)
Azathioprine or mercaptopurine with or without corticosteroids	22 (35)	26 (38)	17 (26)	9 (18)

\* Eight of 248 patients had a Crohn's Disease Activity Index score of less than 220 at base line. Five of these eight patients were eligible on the basis of their screening hematocrit, but they had scores of less than 220 when they were subsequently recalculated with use of the base-line hematocrit. The scores for the other three patients were incorrectly calculated at the time of randomization but are included in the intention-to-treat analysis.

† The patients were not receiving 5-aminosalicylate compounds, corticosteroids, or immunosuppressants.

gator's decision (five). Lack of efficacy was the reason for the withdrawal of three patients in the placebo group (5 percent), as compared with none in the group given one infusion of 3 mg of natalizumab per kilogram, three in the group given two infusions of 3 mg of natalizumab per kilogram (5 percent), and one in the group given two infusions of 6 mg of natalizumab per kilogram (2 percent). Similar numbers of patients in each group withdrew because of adverse events (two [3 percent], one [1 percent], two [3 percent], and three [6 percent], respectively).

#### CLINICAL REMISSIONS AND RESPONSES

The group given two infusions of 6 mg of natalizumab per kilogram did not have a significantly higher rate of clinical remission than the placebo group at week 6 (the prospectively defined primary end point in the efficacy analysis). This group did

have significantly higher rates of remission than the placebo group at four and eight weeks. The rate of remission in the placebo group was relatively high at week 6 (27 percent), as compared with week 2 (10 percent), week 4 (14 percent), and week 8 (16 percent). At week 4, before the second infusion, all three natalizumab groups had significantly higher rates of clinical remission than the placebo group, and the group given two infusions of 3 mg of natalizumab per kilogram also had significantly higher rates at weeks 6, 8, and 12 (Table 2).

The rate of clinical response was significantly higher in all three natalizumab groups at weeks 4, 6, and 8 than in the placebo group, with the highest rate (71 percent) occurring at six weeks in the group given two infusions of 3 mg of natalizumab per kilogram (Table 2). An additional benefit was observed after the second infusion of natalizumab, and this benefit persisted through week 12. Trends toward

**Table 2. Rates of Remission and Clinical Response.\***

Week	Placebo (N=63)	1 Infusion of 3 mg of Natalizumab/kg (N=68)	2 Infusions of 3 mg of Natalizumab/kg (N=66)	2 Infusions of 6 mg of Natalizumab/kg (N=51)
Remission				
Week 2	6 (10)	10 (15)	13 (20)	6 (12)
P value		0.328	0.127	0.745
Week 4	9 (14)	21 (31)	19 (29)	15 (29)
P value		0.02	0.027	0.028
Week 6 (primary end point)	17 (27)	20 (29)	29 (44)	16 (31)
P value		0.757	0.030	0.533
Week 8	10 (16)	19 (28)	27 (41)	22 (43)
P value		0.107	<0.001	<0.001
Week 12	17 (27)	19 (28)	28 (42)	20 (39)
P value		0.992	0.042	0.122
Response				
Week 2	19 (30)	31 (46)	36 (55)	22 (43)
P value		0.081	0.004	0.136
Week 4	18 (29)	32 (47)	41 (62)	27 (53)
P value		0.029	<0.001	0.006
Week 6	24 (38)	40 (59)	47 (71)	29 (57)
P value		0.022	<0.001	0.039
Week 8	22 (35)	38 (56)	44 (67)	28 (55)
P value		0.018	<0.001	0.028
Week 12	27 (43)	34 (50)	40 (61)	33 (65)
P value		0.503	0.033	0.018

\* Remission was defined by a score of less than 150 on the Crohn's Disease Activity Index. A response was defined by a decrease in the score of at least 70 points from base line. P values are for the comparison with the placebo group.

an improvement in the response rates were observed as early as two weeks after the first treatment.

That natalizumab was better than placebo was further supported by post hoc analyses of the area under the curve of the scores on the Crohn's Disease Activity Index ( $P < 0.02$  for each natalizumab group), and these differences remained significant at a level of less than 0.05 after Bonferroni's adjustment for multiple comparisons for the groups given two infusions of 3 mg of natalizumab per kilogram ( $P = 0.002$ ) and two infusions of 6 mg of natalizumab per kilogram ( $P = 0.009$ ). Repeated-measures analysis of the scores (with use of linear mixed-model methods) also provided supportive evidence of the beneficial effects of natalizumab ( $P < 0.05$  for all pairwise comparisons of the three natalizumab groups with the placebo group at weeks 2, 4, 6, and 8). An analysis of the treatment effects according to the country in which treatment

was received indicated that the observed benefits of natalizumab were similar in all geographic areas. During the 12 weeks of the study 11 patients in the placebo group used rescue medication (17 percent), as compared with 14 in the group given one infusion of 3 mg of natalizumab per kilogram (21 percent), 10 in the group given two infusions of 3 mg of natalizumab per kilogram (15 percent), and 6 in the group given two infusions of 6 mg of natalizumab per kilogram (12 percent); none of these differences were statistically significant.

#### QUALITY OF LIFE

All three natalizumab groups had a significant improvement in mean scores on the inflammatory bowel disease questionnaire at week 6, as compared with the value in the placebo group. By week 12, only the groups that received two infusions of natalizumab continued to have scores that were

**Table 3. Scores on the Inflammatory Bowel Disease Questionnaire.\***

Week	Placebo (N=63)	1 Infusion of 3 mg of Natalizumab/kg (N=68)	2 Infusions of 3 mg of Natalizumab/kg (N=66)	2 Infusions of 6 mg of Natalizumab/kg (N=51)
	<i>median score (range)</i>			
Week 0	130 (66–192)	130 (52–188)	136 (79–194)	123 (55–194)
Week 6	145 (61–219)	155 (81–221)	163 (99–211)	155 (67–224)
P value		0.008	<0.001	<0.001
Week 12	145 (61–217)	149 (81–221)	161 (86–221)	155 (64–215)
P value		0.486	0.021	0.014

\* Scores can range from 32 to 224. Higher scores indicate a better quality of life. P values are for the comparison with the placebo group.

significantly higher than that in the placebo group (Table 3).

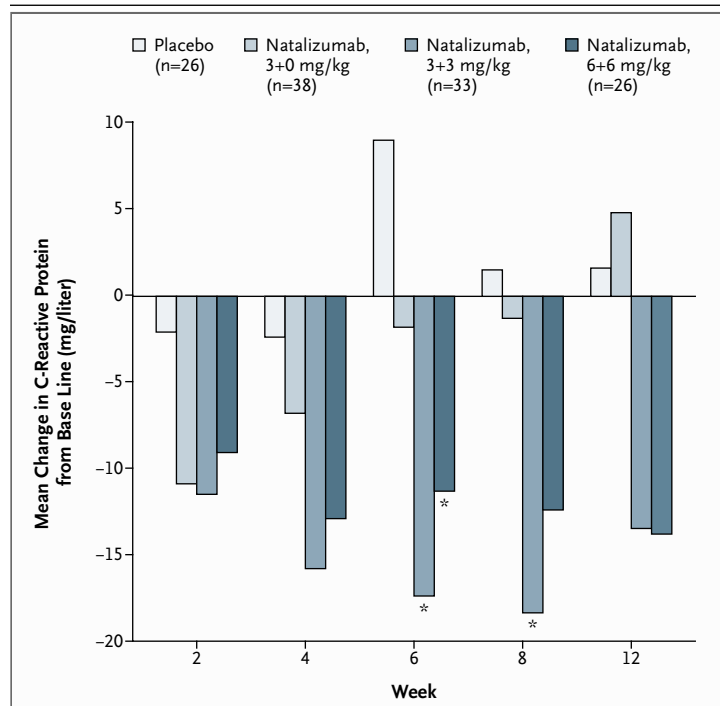
**C-REACTIVE PROTEIN**

Patients treated with natalizumab had a decline from base line in the serum levels of C-reactive protein, whereas patients in the placebo group did not. This decline was significant at week 6 for both groups that received two infusions of natalizumab, both when all patients were included in the analysis and when the analysis was confined to the subgroup of patients with elevated C-reactive protein levels at base line (Fig. 1).

**SAFETY AND TOLERABILITY**

Both doses of natalizumab were well tolerated throughout the 12 weeks of observation. During this period, 26 patients had a serious adverse event: 7 in the placebo group (11 percent), 7 in the group given one infusion of 3 mg of natalizumab per kilogram (11 percent), 6 in the group given two infusions of 3 mg of natalizumab per kilogram (9 percent), and 6 in the group given two infusions of 6 mg of natalizumab per kilogram (12 percent). No serious adverse events were considered by physicians during blinded treatment to be causally related to treatment. Most consisted of hospital admissions for complications or symptoms associated with Crohn's disease. There were no deaths. The numbers of patients who had adverse events during or after treatment were similar in the four groups: 51 in the placebo group (81 percent), and 50 in the group given one infusion of 3 mg of natalizumab per kilogram (77 percent), 57 in the group given two infusions of 3 mg of natalizumab per kilogram (88 percent), and 40 in the group given two infu-

sions of 6 mg of natalizumab per kilogram (78 percent). Table 4 shows adverse events that occurred in more than 10 percent of at least one group. The incidence of the various types of adverse events was generally similar among the four groups. There was a sustained increase in the mean lymphocyte count, ranging from 1.3 to 1.9 times the base-line value, in each natalizumab group. The lymphocyte counts



**Figure 1. Mean Changes in Serum C-Reactive Protein Levels in a Subgroup of Patients Who Had Elevated Levels (>8 mg per liter) at Base Line.**

Asterisks indicate a significant difference (P<0.05) from the placebo group.

**Table 4. Adverse Events Occurring in More Than 10 Percent of Patients, the Incidence of Infusion Reactions Leading to the Interruption or Cessation of Infusion, and the Incidence of Antibodies against Natalizumab.**

Variable	Placebo (N=63)	1 Infusion of 3 mg of Natalizumab/kg (N=65)	2 Infusions of 3 mg of Natalizumab/kg (N=65)	2 Infusions of 6 mg of Natalizumab/kg (N=51)
<b>Adverse event</b>				
Abdominal pain	11 (17)	8 (12)	10 (15)	9 (18)
Arthralgia	7 (11)	6 (9)	8 (12)	5 (10)
Colitis	9 (14)	10 (15)	8 (12)	5 (10)
Influenza syndrome	5 (8)	9 (14)	7 (11)	10 (20)
Headache	20 (32)	18 (28)	25 (38)	14 (27)
Infection	8 (13)	7 (11)	8 (12)	4 (8)
Nausea	10 (16)	2 (3)	9 (14)	6 (12)
Pain	5 (8)	4 (6)	4 (6)	9 (18)
Pharyngitis	5 (8)	9 (14)	6 (9)	4 (8)
<b>Other events</b>				
Infusion reaction	0	0	1 (2)	1 (2)
Antibodies against natalizumab	0	8 (12)	4 (6)	1 (2)

generally remained within the normal range (data not shown).

Antibodies binding to natalizumab were detected in 13 natalizumab-treated patients (7 percent) at week 12. Two patients had infusion reactions, both of which occurred during the second infusion of natalizumab. A patient in the group given two infusions of 3 mg of natalizumab per kilogram had mild itching and erythema and was subsequently found to be positive for antibodies against natalizumab. A patient in the group given two infusions of 6 mg of natalizumab per kilogram had mild itching and coughing that resolved without treatment. This patient was subsequently found to have no detectable antibodies against natalizumab.

#### DISCUSSION

This randomized, controlled trial evaluated natalizumab, a humanized monoclonal antibody that is a selective inhibitor of leukocyte adhesion mediated by both types of  $\alpha_4$  integrin heterodimers, in patients with Crohn's disease. Although the rate of remission in the group given two infusions of 6 mg of natalizumab per kilogram was not significantly different from the rate in the placebo group at week 6 (the prospectively defined primary end point), at

weeks 4 and 8, the remission rate among the patients who received two 6-mg doses was significantly superior to the rate in the placebo group. In addition, the group given two infusions of 3 mg of natalizumab per kilogram had a significantly higher rate of clinical remission at weeks 4, 6, 8, and 12 than did the placebo group.

The secondary analyses showed that all three natalizumab groups had a significantly higher rate of clinical response than did the placebo group at weeks 4, 6, and 8, and at week 12 for the two groups that received two infusions of natalizumab. The onset of the treatment effect was rapid, evident as early as two weeks after the initiation of treatment, and the response was sustained for up to eight weeks after the last infusion in patients who received two infusions of natalizumab.

The effects of natalizumab on clinical remission and response rates that were based on improvements in the scores on the Crohn's Disease Activity Index were corroborated by the significant improvements in health-related quality of life measured by the inflammatory bowel disease questionnaire and by the improvement in serum levels of C-reactive protein, an acute-phase reactant whose measurement is used to quantify generalized inflammation. These secondary analyses provide evidence of the

efficacy of natalizumab in the short-term treatment of moderate-to-severe Crohn's disease.

We chose the doses of natalizumab on the basis of earlier work that showed that binding of natalizumab to  $\alpha_4$  integrins on peripheral-blood leukocytes approaches saturation at doses of 1 mg per kilogram and that nearly saturating levels of drug are maintained for four to six weeks after a single intravenous infusion of 3 or 6 mg per kilogram, but only for one to two weeks after an infusion of 1 mg per kilogram. Although we found that two infusions of natalizumab administered four weeks apart resulted in more durable clinical responses and apparently higher overall rates of response than a single infusion, two infusions of 6 mg per kilogram had no advantage over two infusions of 3 mg per kilogram.

The increase in circulating lymphocytes in natalizumab-treated patients in this and earlier studies may be a manifestation of the interruption of  $\alpha_4$  integrin-mediated migration of lymphocytes to extravascular sites, resulting in increased numbers of intravascular lymphocytes. This effect may represent a clinically significant mechanism of action of natalizumab, though our findings cannot provide definitive evidence of this mechanism.

In this short-term study, no serious adverse events were considered to be related to natalizumab treatment. The percentage of patients who had detectable levels of antibodies against natalizumab was low. There were no serious adverse events associated with these antibodies. Two infusion reactions occurred during the study, one in a patient with binding antibodies.

On the basis of our short-term study, the efficacy of natalizumab for reducing signs and symptoms of Crohn's disease appears to be at least similar to that of the tumor necrosis factor  $\alpha$ -inhibitor infliximab.<sup>23,24</sup> Although our findings provide evidence of the efficacy and tolerability of natalizumab-mediated inhibition of  $\alpha_4$  integrin in the short-term treatment of moderate-to-severe Crohn's disease, the longer-term benefit and safety of this treatment and its value relative to other therapies for this condition remain to be defined.

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Drs. Rask-Madsen and Rutgeerts report having served as paid consultants on advisory boards to Elan and Biogen. Dr. Rask-Madsen reports owning equity in Elan. Dr. Rutgeerts reports having been a paid lecturer for Elan. Ms. Palmer and Dr. Donoghue are employees of Elan Pharmaceuticals.

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#### APPENDIX

The members of the Natalizumab Pan-European Study Group are as follows: Belgium — J. Belaiche, E. Louis, Domaine Universitaire du Sart Tilman; M. De Vos, University Hospital Gent; P. Rutgeerts, G. Van Assche, University Hospital Gasthuisberg; A. Van Gossum, M. Adler, Hospital Erasme; Czech Republic — J. Hoch, J. Schwarz, R. Keil, J. Golanova, Fakultni nemocnice v Motole; M. Lukas, A. Novotny, Vseobecna fakulni nemocnice; P. Vyhnaek, J. Hajek, Nemocnice Pardubice; Z. Zadorova, M. Kment, Fakultni nemocnice Kralovske Vinohrady; V. Zboril, L. Prokopova, Fakultni nemocnice Brno; Denmark — J. Fallingborg, B. Jacobsen, Aalborg Hospital; K. Lauritsen, J. Kjeldsen, Odense University Hospital; S.N. Rasmussen, P. Schmidt, Hvidovre Hospital; J. Rask-Madsen, O.H. Nielsen, O. Ostergaard-Thomsen, B. Vainer, Herlev Hospital; Germany — W. Kreisel, P. Deibert, Universität Freiburg; N. Lügering, M. Schmidt, Westfälische Wilhelms-Universität; H. Malchow, R. Glombitza, Klinikum Leverkusen; Israel — N. Arber, I. Dotan, Ichilov Hospital; A. Fich, H.S. Odes, Soroka Medical Center; Z. Fireman, A. Sterenberg, Hillel Yaffe Medical Center; E. Goldin, A. Migdal, Hadassah Medical Center; A. Lavy, T. Rainis, Bney-Zion Medical Centre; Y. Niv, G. Fraser, Rabin Medical Center; B. Novis, G. Lichtman, Meir Hospital; Sweden — R. Hultcrantz, R. Befriss, Karolinska Hospital; L. Löf, A. Rönnblom, Uppsala University Hospital; the Netherlands — S.J.H. Van Deventer, D.W. Hommes, Academic Medical Centre; United Kingdom — M. Allison, J. Ramesh, Royal Gwent Hospital; S. Ghosh, D. Watts, Western General Hospital; C. Hawkey, J. Jones, Queen's Medical Centre; M. Pitcher, Northwick Park Hospital; J. Plevis, The Royal Infirmary of Edinburgh; R. Pounder, F. Gordon, Royal Free Hospital School of Medicine; J. Shaffer, Hope Hospital.

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