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Treatment with Monoclonal Antibodies against *Clostridium difficile* Toxins

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ABSTRACT

BACKGROUND

New therapies are needed to manage the increasing incidence, severity, and high rate of recurrence of *Clostridium difficile* infection.

METHODS

We performed a randomized, double-blind, placebo-controlled study of two neutralizing, fully human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1). The antibodies were administered together as a single infusion, each at a dose of 10 mg per kilogram of body weight, in patients with symptomatic *C. difficile* infection who were receiving either metronidazole or vancomycin. The primary outcome was laboratory-documented recurrence of infection during the 84 days after the administration of monoclonal antibodies or placebo.

RESULTS

Among the 200 patients who were enrolled (101 in the antibody group and 99 in the placebo group), the rate of recurrence of *C. difficile* infection was lower among patients treated with monoclonal antibodies (7% vs. 25%; 95% confidence interval, 7 to 29; P<0.001). The recurrence rates among patients with the epidemic BI/NAP1/027 strain were 8% for the antibody group and 32% for the placebo group (P=0.06); among patients with more than one previous episode of *C. difficile* infection, recurrence rates were 7% and 38%, respectively (P=0.006). The mean duration of the initial hospitalization for inpatients did not differ significantly between the antibody and placebo groups (9.5 and 9.4 days, respectively). At least one serious adverse event was reported by 18 patients in the antibody group and by 28 patients in the placebo group (P=0.09).

CONCLUSIONS

The addition of monoclonal antibodies against *C. difficile* toxins to antibiotic agents significantly reduced the recurrence of *C. difficile* infection. (ClinicalTrials.gov number, NCT00350298.)

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During the past decade, there has been a striking increase in the prevalence of *Clostridium difficile* infection and in associated mortality in the United States, Canada, and Europe.[1-5] The widespread use of broad-spectrum antibiotics places patients at risk for *C. difficile* diarrhea or colitis and has changed the epidemiology of *C. difficile* infection. This has been characterized by the emergence of a hypervirulent strain of *C. difficile* (BI/NAP1/027) and an increasing risk of treatment failure and recurrent infection.[1,6-14]

We developed one fully human monoclonal antibody targeted against *C. difficile* toxin A (CDA1) and a second against toxin B (CDB1). We have found significant efficacy for the combined antibodies in an established hamster model of *C. difficile* infection, as well as safety in a phase 1 study in healthy volunteers.[15] We now report a phase 2 randomized, double-blind, placebo-controlled trial of the efficacy of CDA1 plus CDB1 in preventing the recurrence of *C. difficile* infection. We also examined the safety of this therapy and its effects on the duration and severity of the initial episode of infection and on duration of hospitalization.

Methods

Patients

From July 2006 through April 2008, patients were enrolled at 30 study sites in the United States and Canada. Eligible patients were at least 18 years of age and had diarrhea associated with a positive stool test for a *C. difficile* toxin in the 14 days before enrollment. The enzyme immunoassay method for stool toxin detection that was in use at each study site was also used for this study. Patients were required to be receiving either metronidazole or oral vancomycin for the treatment of the *C. difficile* infection, with the choice of antibiotic made by the treating physician. Diarrhea was defined as three or more unformed stools per day for at least 2 consecutive days or more than six unformed stools in 1 day.[16] Patients could have started receiving antibiotic treatment at any time before enrollment but must have had diarrhea on the day of enrollment. The protocol was approved by the institutional review board or ethics committee at each study site and by the governmental regulatory authorities in the United States and Canada. All patients provided written informed consent.

Study Design and Oversight

This study was designed and supervised by the sponsors, MassBiologics and Medarex. Data were collected by principal investigators at each study site, and statistical analyses were performed by an independent statistician who was supervised by the sponsors. An independent data and safety monitoring board was responsible for monitoring the safety of the patients during the trial and the performance of the primary end-point analysis at the time of breaking the blind. Two authors who are employed by the sponsors wrote the first draft of the manuscript. All the authors vouch for the accuracy and completeness of the data reported.

Randomization and Follow-up

Enrolled patients were randomly assigned to receive an intravenous infusion of either CDA1–CDB1 or 0.9% sodium chloride as placebo in a 1:1 ratio. Stool specimens were collected at enrollment and were processed for the identification of *C. difficile* by culture on selective prereduced taurocholate–cefoxitin–cycloserine–fructose agar (TCCFA) and typed by restriction endonuclease analysis in a blinded fashion, as described previously.[17,18] Current epidemic *C. difficile* isolates have been identified as group BI on restriction endonuclease analysis, NAP1 on pulsed-field gel electrophoresis, and 027 on ribotyping (BI/NAP1/027) with the use of polymerase-chain-reaction (PCR) assay.[18]

On the first day of the study, during a 2-hour period, patients received a single intravenous infusion of 10 mg each of CDA1 and CDB1 per kilogram of body weight in a total volume of 200 ml (with 0.9% sodium chloride as the diluent) or placebo. Stool counts were recorded daily for the 84-day study period with the use of a memory aid to track the number and type of stools. This information was reviewed by study staff, either in person or through telephone contact. Patients were contacted on a daily basis through day 14 after infusion, weekly through day 56, and then monthly until day 84, with in-person visits on days 3±1, 10±2, 28±3, 56±7, and 84±10, which included blood-sample collection. The first 20 patients who were enrolled had an additional visit on day 168±14 to obtain a blood sample for immunogenicity analysis.

Efficacy Assessments

The primary end point, which was the recurrence of *C. difficile* infection, was defined as a new episode

of diarrhea associated with a new positive stool toxin test after the resolution of the initial CDI diarrheal episode and after discontinuation of metronidazole or vancomycin. Only the first episode of CDI recurrence was evaluated in the efficacy analyses. Secondary end points included the number of days to the resolution of the initial episode, severity of the initial episode, and failure of antibiotic treatment (as defined as a change in antibiotics or persistence of diarrhea at day 14 of antibiotic administration). Levels of serum antibodies against toxins A and B were measured in all patients by enzyme-linked immunosorbent assay (ELISA) with the use of fragment 4 of the toxins as the target[19] (for details, see the Laboratory Assays section in the Supplementary Appendix, available with the full text of this article at NEJM.org).

SAFETY ASSESSMENTS

Evaluation for safety included the measurement of vital signs, the taking of an interim medical history, and physical assessment if clinically indicated for adverse events at all study visits. Laboratory testing of hematologic and serum chemical values and urinalysis were performed at study visits through day 28±3. Solicited reports of adverse events were collected by study personnel during the infusion and the 2-hour period after infusion. Adverse events were graded according to the Adult Toxicity Table (May 2001), as adapted by the National Institute of Allergy and Infectious Diseases. The detection of human antihuman antibody in response to the monoclonal antibodies was determined with the use of a bridging ELISA[19] (see the Laboratory Assays section in the Supplementary Appendix).

STATISTICAL ANALYSIS

The target study enrollment of 200 patients was based on an ability to observe a reduction in recurrence rates from 20% in the placebo group to 6% in the antibody group with a power of 80%. All statistical methods were specified before study enrollment, and the final statistical-analysis plan was approved before blinding was broken. All analyses were performed with JMP software, version 7.0 (SAS Institute), and StatXact (Cytel Software).

We analyzed primary and secondary efficacy end points (as prespecified in the statistical-analysis plan) on the intention-to-treat principle and included all patients who underwent randomization (see the Methods section in the Supplementary Appendix). Each subgroup (except for the subgroups defined according to hospitalization status) was prespecified in the statistical-analysis plan at enrollment. Analysis of additional hospitalizations during the study period was performed post hoc. Nominal variables were compared between the study groups with the use of a two-sided Fisher's exact test with 95% confidence intervals. Continuous variables were compared with the use of a two-sided t-test. Kaplan–Meier plots were used to analyze time-to-event variables, which were compared by means of log-rank tests. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PATIENTS

Of 7396 patients who were assessed for eligibility, 484 were screened, and 200 patients from 30 participating centers were enrolled. The mean age of the patients was 64 years (range, 20 to 101). Of these patients, 101 were randomly assigned to receive CDA1–CDB1 antibody treatment and 99 to receive placebo (Fig. 1 in the Supplementary Appendix). Baseline characteristics were similar between the two study groups, except for a higher mean number of unformed stools at screening and at the time of infusion in the antibody group than in the placebo group (Table 1). Exposure to antibiotics other than metronidazole or vancomycin from the day of study infusion through day 84 occurred in 40 patients (40%) in the antibody group and 48 patients (48%) in the placebo group (P=0.26).

EFFICACY

The primary efficacy end point was laboratory-documented recurrence of *C. difficile* infection, which was observed in 32 patients: 7% in the antibody group and 25% in the placebo group (95% confidence interval [CI], 7 to 29; P<0.001). Significant reductions were also observed for less rigorous and more inclusive definitions of recurrence in both the intention-to-treat and per-protocol populations. In a comparison of recurrent diarrhea with or without laboratory confirmation of *C. difficile* infection and with or without antibiotic treatment for *C. difficile* infection, 28% of patients in the antibody group had recurrent diarrhea, as com-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Monoclonal Antibody (N=101)	Placebo (N=99)	P Value
Mean age — yr	63	64	0.62
Female sex — no. (%)	61 (60)	71 (72)	0.10
Race or ethnic group — no. (%)†			
White	91 (90)	84 (85)	0.34
Black	6 (6)	6 (6)	
Hispanic	4 (4)	6 (6)	0.54
Other	4 (4)	9 (9)	
Inpatient — no. (%)	50 (50)	52 (53)	0.67
Treatment with metronidazole or vancomycin before enrollment — days			
Mean	3	3	0.88
Range	1–10	1–14	
Horn's index score for severity of underlying illness‡	2.1	2.2	0.43
Antibiotic treatment for CDI — no. (%)			
Metronidazole	71 (70)	77 (78)	0.26
Vancomycin§	30 (30)	22 (22)	0.26
CDI severity			
Severe disease at enrollment — no. (%)¶	44 (44)	36 (36)	0.32
Mean no. of unformed stools per day			
At screening	8.2	6.5	0.008
At infusion	7.9	6.3	0.01
More than one previous episode of CDI — no. (%)‖	29 (29)	32 (33)	0.64
Presence of BI/NAP1/027 strain — no. (%)**	25 (32)	19 (26)	0.38

* CDI denotes *Clostridium difficile* infection.
† Race or ethnic group was self-reported.
‡ Scores on the modified Horn's index range from 1 to 3, with a higher score indicating a greater severity of illness.
§ Included in this category were seven patients in the antibody group and four patients in the placebo group who were also receiving metronidazole on the day of infusion.
¶ Severe disease was defined as the occurrence of at least five unformed stools per day for 2 consecutive days.
‖ Data were missing for one patient in the placebo group.
** Data were missing for 24 patients in the antibody group and 25 patients in the placebo group.

pared with 50% of those in the placebo group (P=0.002) (see the Methods section and Table 1 in the Supplementary Appendix).

Kaplan–Meier analysis showed that the time to recurrence of *C. difficile* infection differed significantly between the two study groups (P<0.001) (Fig. 1). The relative risk of recurrence on the basis of total days of follow-up for each study group was significantly lower in the antibody group (relative risk, 0.23; 95% CI, 0.08 to 0.54; P=0.01).

The effect of CDA1–CDB1 on the severity of diarrhea during the initial episode was also assessed as a secondary end point. Severe diarrhea was defined as at least five unformed stools per day for at least 2 consecutive days, starting with the stool counts recorded on day 1 through cessation of diarrhea and discontinuation of antibiotic treatment for the initial episode. There were no significant differences between the antibody group and the placebo group in the severity of diarrhea during the initial episode of *C. difficile* infection, the median or mean number of days to the resolution of the initial episode, or the proportion of patients in whom treatment failed, according to the protocol definition of failure of antibiotic treatment.

SUBGROUP ANALYSES

For subgroups of patients that were prespecified in the statistical-analysis plan, CDA1–CDB1 treatment was effective with either concomitant vancomycin or metronidazole treatment, in patients with epidemic strain BI/NAP1/027 or nonepidemic strains of *C. difficile*, and in patients with their first episode of infection or those with multiple previous episodes (Table 2). All recurrent episodes in the antibody group were in patients who had been hospitalized during their initial episode. The subgroup analysis for hospitalization status was performed post hoc. Inpatients were significantly older and had a significantly higher score on Horn's index (indicating greater severity of underlying illness) than did outpatients, and there was a trend toward more severe infection at enrollment among such patients (Table 2 in the Supplementary Appendix). A post hoc analysis showed that among patients with a recurrence, 2 of the 7 patients in the antibody group (29%) had severe diarrhea during the recurrent episode, as compared with 16 of 25 (64%) in the placebo group (P=0.20 by Fisher's exact test).

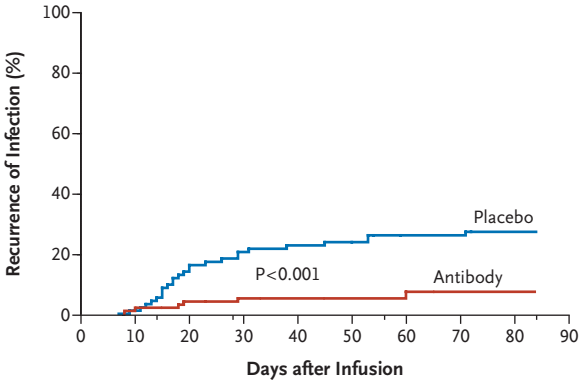

Figure 1. Time to Recurrence of *Clostridium difficile* Infection (CDI).

The cumulative percentages of 32 patients with laboratory-documented recurrent CDI during the 84-day study period are shown for the two study groups: 7% in the antibody group and 25% in the placebo group. Five patients had a second episode of CDI recurrence: two in the antibody group and three in the placebo group. The P value was calculated by means of the log-rank test.

HOSPITAL ADMISSION AFTER FIRST EPISODE

The mean length of hospitalization for the initial episode of *C. difficile* infection did not differ significantly between the antibody group and the placebo group (9.5 and 9.4 days, respectively), nor did the total number of hospital days during the 84-day study period (data not shown). However, in a post hoc analysis, the proportion of patients who were admitted to the hospital after the study infusion differed significantly: 9% of the patients in the antibody group as compared with 20% of those in the placebo group (P=0.03). An exploratory analysis of the admission diagnoses for these hospitalizations suggests that coexisting illnesses that were related to *C. difficile* infection (e.g., diarrhea, dehydration, and hypotension) were responsible for many of these hospitalizations, accounting for 5 of the 9 admissions in the antibody group and 16 of the 20 admissions in the placebo group, even if they did not meet the criteria for recurrent infection at that admission.

PHARMACOKINETICS

Serum levels of antitoxin A and antitoxin B were measured in all patients before and after the study infusion (Fig. 2). For patients in the antibody group, the mean (±SD) half-life of the terminal portion of the disposition phase was 26±8.4 days for antitoxin A and 22±13 days for antitoxin B. For patients in the placebo group whose serum antitoxin antibodies represented their endogenous response over time, the majority of patients who had a recurrence of infection had low or no detectable levels of antibodies against either toxin.

ADVERSE EVENTS

There were no significant differences in vital signs between the two study groups during and up to 2 hours after infusion. Adverse events were reported in 14 patients (9 in the antibody group and 5 in the placebo group) during infusion and in 11 patients (6 in the antibody group and 5 in the placebo group) during the 2-hour period after infusion. All adverse events were mild to moderate in nature, with headache reported most frequently in both groups. There were seven deaths in the antibody group and eight in the placebo group during the study period (P=0.79); no deaths were attributed to a study drug (see the Results section in the Supplementary Appendix). At least one serious adverse event was reported by 18 patients in

Table 2. Recurrence of *Clostridium difficile* Infection (CDI), According to Subgroup.

Variable	Monoclonal Antibody (N=101)	Placebo (N=99)	Difference in Rate (95% CI)	P Value
	no. with recurrence/total no. (%)		*percentage points*	
Hospitalization status at enrollment				
Inpatient	7/50 (14)	13/52 (25)	11 (–5 to 27)	0.21
Outpatient	0/51	12/47 (26)	26 (14 to 40)	<0.001
Antibiotic treatment at enrollment				
Vancomycin	3/30 (10)	7/22 (32)	22 (–1 to 46)	0.08
Metronidazole	4/71 (6)	18/77 (23)	17 (6 to 29)	0.003
Presence of BI/NAP1/027 strain at enrollment*				
Yes	2/25 (8)	6/19 (32)	24 (1 to 50)	0.06
No†	4/52 (8)	11/55 (20)	12 (–1 to 26)	0.09
No. of previous CDI episodes‡				
Multiple	2/29 (7)	12/32 (38)	31 (10 to 50)	0.006
Single	5/72 (7)	12/66 (18)	11 (0 to 23)	0.07

* No *C. difficile* bacteria were isolated in stool samples from 20 patients in the antibody group and from 21 patients in the placebo group; 1 sample in the antibody group and 1 in the placebo group could not be typed. Stool samples were not available at enrollment for 3 patients in the antibody group and 3 patients in the placebo group.
† This category includes nonspecific or unknown groups of bacteria identified on restriction endonuclease analysis and other commonly identified epidemic or endemic groups aside from BI/NAP1/027, such as J, K, Y, and G.
‡ Data were missing for one patient in the placebo group with recurrent CDI.

the antibody group and 28 patients in the placebo group (P=0.09).

The proportions of patients with the most frequent grade 3 or 4 adverse events were similar in the two study groups, except for significantly fewer reports of hypotension in the antibody group (Table 3). Analysis of adverse events during the overall study period revealed several nonserious adverse events (including anorexia, anxiety, diarrhea, depression, and insomnia) that were significantly less common in the antibody group than in the placebo group (Table 3 in the Supplementary Appendix).

To examine the immunogenicity of the monoclonal antibodies, human antihuman antibody titers in response to CDA1 and CDB1 were assessed before and after study infusion at multiple time points. Two patients in the antibody group had a positive titer before infusion; one of these patients had no detectable titer after infusion, and the other patient's titer was unchanged after infusion. In 20 patients (8 in the antibody group and 12 in the placebo group) who were followed for 6 months (last assessment, day 168 plus or minus 14) after infusion, human antihuman antibody titers were not detected.

DISCUSSION

In our study, the administration of fully human monoclonal antibodies favorably affected the natural history of *C. difficile* infection when added to treatment with metronidazole or vancomycin. A single infusion of two monoclonal antibodies against *C. difficile* toxins A and B (CDA1 and CDB1) resulted in a reduction of the rate of recurrent infection among patients treated with standard-of-care antibiotics. Although the primary end point of the study was a reduction in the rate of recurrence, secondary end points evaluated the effect of monoclonal-antibody treatment on the initial episode of infection. The time to the resolution of diarrhea, number of days of hospitalization for the initial episode, and severity of diarrhea during the initial episode were similar in the two study groups. CDA1 and CDB1 are fully human antibodies, each of which targets an exogenous antigen. Immunogenicity was not detected in any patient during the study period.

Larger studies will need to be conducted to confirm the findings of this phase 2 study. Our results are consistent with those of previous studies that correlated serum levels of antitoxin an-

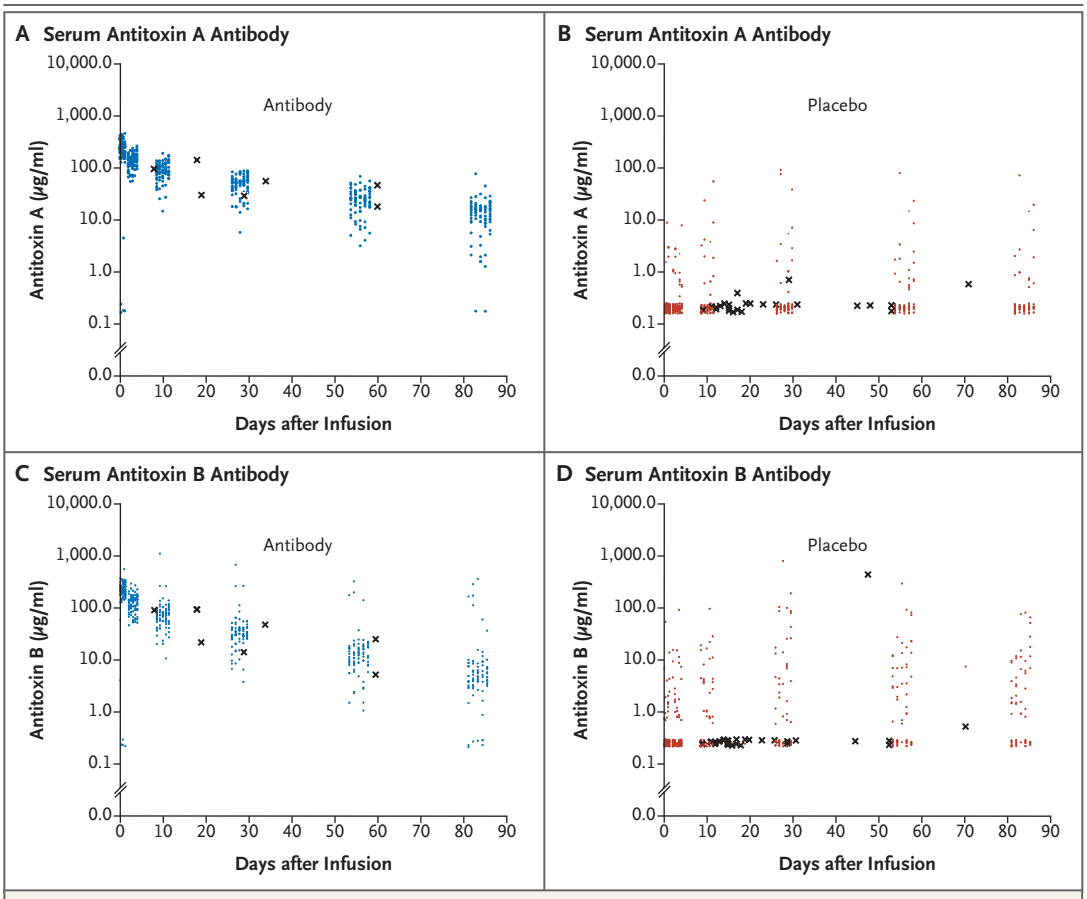

Figure 2. Serum Antibodies against Toxins A and B.

Shown are the responses among patients in the group that received two neutralizing fully human monoclonal antibodies against *Clostridium difficile* toxins A (Panel A) and B (Panel C), as compared with patients who received placebo, the majority of whom had low or no detectable endogenous antibodies against either toxin (Panels B and D). The x's in each of the panels represent the linear interpolation of levels of antibodies against toxins A and B at the time of recurrence for each of the 32 patients with recurrent *C. difficile* infection (7 in the antibody group and 25 in the placebo group.

tibodies with protection against *C. difficile* infection.[16,20-22] The efficacy of neutralizing antibodies against toxins A and B administered as combined treatment is also consistent with data in animal models.[23-26] Although recent evidence in a hamster model of disease indicated that toxin B is essential for virulence and toxin A may not be,[27] the treatment of human disease may benefit from the presence of high-affinity antibodies against both toxins. The doses of CDA1 and CDB1 that were chosen for our study were based on protective doses in animal models[15] and observed pharmacokinetics in humans.

All cases of recurrence in the antibody group were in patients who were hospitalized at the time of enrollment in the study. At enrollment, the inpatients were significantly older and had a significantly higher index of severity of underlying illness than did outpatients — two factors associated with an increased risk of recurrence.[20] For the seven inpatients who had a recurrence of *C. difficile* infection despite CDA1–CDB1 treatment, serum levels of antitoxin antibodies did not appear to be lower than those in patients in the antibody group who did not have a recurrence. The reasons for recurrence in these patients despite high levels of neutralizing antitoxin antibodies are not clear but may be related to impairment of local or other systemic host immune mechanisms. Also, serum levels of neutralizing antibodies may not always reflect adequate levels in the intestinal mucosa. Although higher doses of CDA1–CDB1

Table 3. Most Common Grade 3 or 4 Adverse Events.*

Adverse Event	Monoclonal Antibody (N=101)	Placebo (N=99)	P Value
	number (percent)		
Serious†			
Atrial fibrillation	0	3 (3)	0.12
Cardiorespiratory arrest	1 (1)	2 (2)	0.62
Dehydration	0	4 (4)	0.06
Diarrhea	0	3 (3)	0.12
Hypotension	0	6 (6)	0.01
Leukocytosis‡	0	4 (4)	0.06
Pulmonary embolism	0	4 (4)	0.06
Sepsis or septic shock	1 (1)	5 (5)	0.12
Tachycardia	0	3 (3)	0.12
Not serious			
Abdominal pain	3 (3)	0	0.25
Diarrhea	5 (5)	12 (12)	0.08
Leukocytosis‡	5 (5)	6 (6)	0.76
Nausea	3 (3)	0	0.25
Pyrexia	0	3 (3)	0.12

* The results were not adjusted for multiple events per patient. Listed are all grade 3 or 4 adverse events that occurred in at least 3% of patients. For a list of grade 1 to 4 adverse events that differed significantly between the study groups, see Table 3 in the Supplementary Appendix.

† Colitis that was associated with *Clostridium difficile* infection was not included among serious adverse events.

‡ Leukocytosis was considered a serious adverse event if it resulted in hospitalization.

could potentially further improve the outcome, the large effect size of a 72% reduction in recurrence seen with these doses supports the use of the current doses in future studies.

The combined administration of CDA1 and CDB1 human monoclonal antibodies in addition to antibiotics significantly reduced the recurrence of *C. difficile* infection. Furthermore, the administration of a single intravenous dose of antibody may be advantageous, depending on the patient's ability to take oral medications. This novel treatment deserves further study as a means to reduce the morbidity and health care burden of *C. difficile* infection in the face of the increased incidence and severity of the disease worldwide.

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Drs. Lowy and Nichol report being employees of Medarex and having an equity interest in the company; Dr. Lowy, being named as a coinventor on relevant patents with all rights or royalties assigned to Medarex and having an equity interest in Merck; Drs. Molrine and Thomas, being named as coinventors on relevant patents and sharing a partial interest in them; Dr. Baxter, receiving grant support from MassBiologics and Medarex; Dr. Gerding, receiving lecture fees from Robert Michael Associates, receiving consulting fees from or serving on an advisory board for ViroPharma, GOJO Industries, Salix, Schering-Plough, Cepheid, Merck, TheraDoc, and Optimer, receiving research grants from MassBiologics, GOJO, Optimer, Cepheid, Merck, Genzyme, and ViroPharma, and holding patents for the treatment of *C. difficile* infection licensed to ViroPharma. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following principal investigators screened patients for enrollment in the study: **Investigators** — *United States*: A. Bacon, Christiana Care Health Systems, Newark, DE; I. Baird, Remington–Davis Clinical Research, Columbus, OH; R. Baxter, Kaiser Permanente Vaccine Study Center, Oakland, CA; M. Buitrago, Idaho Falls Infectious Disease, Idaho Falls, ID; K. Casey, Jersey Shore University Medical Center, Neptune, NJ; D. Chen, MultiCare Health System, Tacoma, WA; C.D. Cochran, Saint Luke's Hospital of Kansas City, Kansas City, MO; H. DuPont, St. Luke's Episcopal Hospital, Houston; R. Greenberg, University of Kentucky Medical Center, Lexington; T. Kovacs, UCLA CURE Digestive Disease Research Center, Los Angeles; R. Mason, LAC/USC Medical Center, Los Angeles; L. McFarland, Puget Sound Veterans Affairs Medical Center, Seattle; M. Meadors, All-Trials Clinical Research, Winston-Salem, NC; T. Nowak, Central Indiana Gastroenterology Group, Anderson; D. Pardi, Mayo Foundation, Rochester, MN; J. Prieto, Dr. Kiran C. Patel Research Institute, Tampa, FL; J. Pullman, Mercury Street Medical Group, Butte, MT; J. Reyno, Rapid City Regional Hospital, Rapid City, SD; H. Sacks, Mount Sinai Hospital, New York; A. Silverman, Henry Ford Health System–Columbus, Novi, MI; M. Tan, Summa Health Systems, Akron, OH; J. White, Scott and White Memorial Hospital, Temple, TX. *Canada*: C. Bernstein, Health Science Centre, Winnipeg, MB; D. Daly, Vancouver Island Health Research Centre, Victoria, BC; A. Dhar, Windsor Regional Hospital, Windsor, ON; G. Evans, Kingston General Hospital, Kingston, ON; D. Grimard, Centre de Santé et Services Sociaux de Chicoutimi, Chicoutimi, QC; T. Louie, University of Calgary–Foothills Medical Centre, Calgary, AB; A. Poirier, Centre Hospitalier Régional de Trois Rivières, Trois-Rivières, QC. **Data and Safety Monitoring Board** — W. Blackwelder and A. Cross, University of Maryland School of Medicine, Baltimore; M. Samore, University of Utah School of Medicine, Salt Lake City.

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