EDITORIAL

The Search for Effective Treatment of *Clostridium difficile* Infection

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Since 1996, the incidence of *Clostridium difficile* infection has more than doubled. Some estimates suggest that there may be up to 3 million cases each year in the United States. If that statistic is correct, it would make *C. difficile* infection the most common bacterial cause of diarrhea in the United States. With the rising incidence, we are seeing higher mortality associated with the disease, related to at least two factors: increasing virulence of the *C. difficile* strains and increasing host vulnerability. *C. difficile* infection is particularly problematic when three factors are aligned: coexisting conditions, including advanced age; disturbed intestinal microbiota as a result of antibiotic therapy or antitumor drugs; and exposure to vegetative cells or spores of *C. difficile*.

C. difficile infection has four clinical forms: short-term colonization, which usually develops when a patient is in a health care facility; acute diarrhea, ranging from mild to severe; fulminant diarrhea, which may be associated with pseudomembranous colitis (which in some cases requires colectomy) and leukocytosis and may lead to death; and recurrent *C. difficile* infection, which typically occurs within 60 days after initial treatment for the infection. Current treatments for *C. difficile* infection are inadequate. Metronidazole is an inexpensive treatment that is considered by most authorities to be the standard therapy for nonsevere cases of *C. difficile* infection, despite the fact that it is not approved by the Food and Drug Administration as a treatment for this condition. Unfortunately, metronidazole has unacceptable pharmacokinetic characteristics; it is almost completely absorbed in the gut, resulting in

very low drug levels in the colon and a high rate of treatment failure. Severe cases of *C. difficile* infection are treated preferentially with oral vancomycin. A lack of response to treatment and recurrence of the disease happen with approximately equal frequency after both metronidazole and oral vancomycin treatment. Recurrent disease is seen in 20 to 30% of cases, regardless of which of these two treatments is used.[1,2] Although the reasons for the high rate of disease recurrence are not established, recurrence appears to be related to a combination of a failure to reestablish microbial flora, the presence in the intestines of spores of *C. difficile*, and a defective host immune response to the infecting organism and its toxins. A disturbing number of people have multiple recurrences over many months or years and are exposed to many courses of expensive and potentially toxic antibiotics. The frequent occurrence of intestinal *C. difficile* colonization in hospitalized patients and in patients with acute and recurrent infections results in an important pathogen reservoir that leads to secondary infection among other exposed patients.

Owing to the inadequacies of current therapy for *C. difficile* infection, an impressive search for new and more effective treatments is under way. Because of the importance of intestinal flora in the recovery process, antibiotics that inhibit vegetative cells of *C. difficile* while preserving colonic flora or aiding in the restoration of flora during treatment are being evaluated preferentially. Fidaxomicin, a new macrocyclic antibiotic that has no cross-resistance with other antibiotics, has in vitro activity against strains of *C. difficile*[3] and may

have less deleterious effects on intestinal microbiota than do other commonly used antibacterial agents.[4]

In this issue of the *Journal*, Louie et al.[5] report the results of a phase 3 trial involving 629 patients, in which fidaxomicin was compared with vancomycin in the treatment of *C. difficile* infection. The rates of clinical cure in the two groups were similar, but *C. difficile* infection recurred significantly less often with fidaxomicin than with vancomycin (15% vs. 25% in the modified intention-to-treat population, P=0.005). The data provide evidence that the reduction in recurrence was dependent on the strain of *C. difficile*; when subjects had the more virulent strain known as the North American Pulsed Field type 1 (NAP1), restriction endonuclease analysis (REA) type BI, or polymerase-chain-reaction ribotype 027 strain, fidaxomicin, as compared with vancomycin, did not reduce the rate of recurrence. Additional study of fidaxomicin is needed to evaluate alterations of the colonic microflora during therapy and to confirm the favorable effect of the drug in reducing the recurrence of disease in a wide variety of patients with various strains of *C. difficile*.

The significantly reduced rate of recurrence after fidaxomicin therapy, as compared with standard therapy, represents an important advance in the treatment of *C. difficile* infection. We should be working to reduce the recurrence rate even further than the 15% seen with fidaxomicin in this trial. The most promising agents for future development should be safe, have low levels of systemic absorption, have low potential for the development of resistance among intestinal and extraintestinal bacteria, provide high levels of active drug in the colon, and be associated with a low rate of recurrence of *C. difficile* infection after treatment. Fidaxomicin fits these criteria better than any other agent evaluated so far. Probiotics are also being developed for the management of *C. difficile* infection because of their favorable effects on gut flora, which may be useful in the prevention of or recovery from *C. difficile* infection.[6]

In the trial reported by Louie et al., the treatment was administered for 10 days. Therapy for *C. difficile* infection is generally administered for either 10 or 14 days, with no clinical or microbiologic advantage seen with one of these regimens as compared with the other. With a spore-forming pathogen, is 10 days of treatment sufficient for cure? The recommended duration of treatment of disease caused by spore-forming *Bacillus anthracis* is 2 months. Would commonly used drugs (including metronidazole or oral vancomycin) or fidaxomicin be more effective in reducing recurrences if the initial episode of *C. difficile* infection were treated for 1 month or 6 weeks?

With data showing that the rate of recurrence of *C. difficile* infection is increased in patients in whom anti–*C. difficile* toxin A IgG antibodies do not develop,[7] immunologic approaches to the prevention and treatment of recurrences are in development and include the use of immunoglobulins,[8] monoclonal anti–*C. difficile* toxin antibodies,[9] and active immunization.[10] Perhaps future therapy for *C. difficile* infection will combine an antibacterial drug with an immunologic approach. Although such therapy would be expensive, the approach may be cost-effective if it prevents the development of complicated disease and reduces the frequency of recurrences.

Future studies are needed to determine the relative value of various treatments in controlling symptoms of *C. difficile* infection and in preventing disease recurrences. Additional study is needed to determine the optimal duration of treatment for *C. difficile* infection. It is recommended that future trials of potentially curative treatments include the study of the metagenomic alterations of colonic microflora before and after treatment. It is likely that we will be better able to identify effective therapies for this emerging infectious disease if we have an enhanced understanding of the microbial community of the lower gut during episodes of *C. difficile* infection and at the time of recovery and more information regarding the selective pressure exerted by various antimicrobial agents directed against *C. difficile* infection.

Although therapy of *C. difficile* infection is fraught with challenges, fidaxomicin appears to be an important advance. Additional studies are needed to confirm its enhanced value in preventing the recurrence of *C. difficile* infection. If studies with fidaxomicin confirm a favorable clinical response and a significant decrease in the rate of recurrence after treatment, this new agent could become a recommended therapy for *C. difficile* infection.

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ORIGINAL ARTICLE

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

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ABSTRACT

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BACKGROUND

Clostridium difficile infection is a serious diarrheal illness associated with substantial morbidity and mortality. Patients generally have a response to oral vancomycin or metronidazole; however, the rate of recurrence is high. This phase 3 clinical trial compared the efficacy and safety of fidaxomicin with those of vancomycin in treating *C. difficile* infection.

METHODS

Adults with acute symptoms of *C. difficile* infection and a positive result on a stool toxin test were eligible for study entry. We randomly assigned patients to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The primary end point was clinical cure (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy). The secondary end points were recurrence of *C. difficile* infection (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment) and global cure (i.e., cure with no recurrence).

RESULTS

A total of 629 patients were enrolled, of whom 548 (87.1%) could be evaluated for the per-protocol analysis. The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004). The lower rate of recurrence was seen in patients with non–North American Pulsed Field type 1 strains. The adverse-event profile was similar for the two therapies.

CONCLUSIONS

The rates of clinical cure after treatment with fidaxomicin were noninferior to those after treatment with vancomycin. Fidaxomicin was associated with a significantly lower rate of recurrence of *C. difficile* infection associated with non–North American Pulsed Field type 1 strains. (Funded by Optimer Pharmaceuticals; ClinicalTrials.gov number, NCT00314951.)

CLOSTRIDIUM DIFFICILE INFECTION GENER-
ally occurs after exposure to broad-spectrum
antibiotics. The incidence and severity of
C. difficile infection are increasing. The increases
have been ascribed to the emergence of a hyper-
virulent *C. difficile* strain, known variously as North
American Pulsed Field type 1 (NAP1), restriction-
endonuclease analysis (REA) type BI, or poly-
merase-chain-reaction ribotype 027 (referred to
collectively as the NAP1/BI/027 strain).[1-4] Further-
more, the rates of death associated with *C. difficile*
infection are rising,[5-7] and the infection is occur-
ring in populations that were previously consid-
ered to be at low risk, such as young, healthy per-
sons living in the community and peripartum
women.[8,9] As compared with observations in the
mid-1990s,[10] the reduced rates of clinical response
and increased recurrence rates seen in more re-
cent studies are cause for concern.[11-14]

Fidaxomicin (previously referred to as OPT-80),
a macrocyclic antibiotic, is more active in vitro
than vancomycin, by a factor of approximately 8,
against clinical isolates of *C. difficile*, including
NAP1/BI/027 strains.[15-19] This activity, in combi-
nation with minimal systemic absorption,[20] high
fecal concentrations, and limited activity in vi-
tro[15-19] and in vivo[21] against components of the
normal gut flora, makes fidaxomicin a promis-
ing candidate that may provide highly active but
more selective therapy for *C. difficile* infection. In
a dose-finding, randomized, open-label, phase 2
trial, treatment with fidaxomicin was associated
with a good clinical response and a low rate of
recurrence.[22] The results of a phase 3 noninferi-
ority study comparing fidaxomicin with vanco-
mycin in 629 patients with *C. difficile* infection are
reported here.

METHODS

STUDY DESIGN

This prospective, multicenter, double-blind, ran-
domized, parallel-group trial was conducted be-
tween May 9, 2006, and August 21, 2008, in
accordance with the ethical principles of the
Declaration of Helsinki and the principles of cur-
rent Good Clinical Practices. The study protocol
and amendments were approved by local or cen-
tral institutional review boards. All patients pro-
vided written informed consent. Optimer Phar-
maceuticals sponsored the study. The data were
monitored and retrieved by INC Research (a con-
tract research organization). The analysis of the

data was performed by all the authors, along with
an additional investigator at Optimer Pharma-
ceuticals. The first draft of the manuscript was
written by one of the authors who is a part-time
employee of Optimer Pharmaceuticals; that au-
thor along with the first two authors wrote sub-
sequent drafts of the manuscript. All the au-
thors, on behalf of the OPT-80-003 clinical trial
study group, made the decision to submit the man-
uscript for publication. The protocol, including
the statistical analysis plan, is available with the
full text of this article at NEJM.org. All the au-
thors vouch for the accuracy and completeness of
the data presented and the fidelity of the report-
ed study to the trial protocol.

STUDY POPULATION

Patients were enrolled at 52 sites in the United
States and 15 sites in Canada. Eligible patients
were 16 years of age or older with a diagnosis of
C. difficile infection, defined by the presence of di-
arrhea (a change in bowel habits, with more than
three unformed bowel movements in the 24-hour
period before randomization) and *C. difficile* toxin
A, B, or both in a stool specimen obtained within
48 hours before randomization. Patients could
have received up to four doses of metronidazole
or vancomycin in the 24 hour-period before ran-
domization and no other potentially effective con-
current treatments for *C. difficile* infection (e.g.,
oral bacitracin, fusidic acid, or rifaximin). Pa-
tients with life-threatening or fulminant *C. diffi-
cile* infection, toxic megacolon, previous exposure
to fidaxomicin, a history of ulcerative colitis or
Crohn's disease, or more than one occurrence of
C. difficile infection within 3 months before the
start of the study were excluded.

RANDOMIZATION AND TREATMENT

After providing informed consent, patients were
stratified according to whether the current *C. dif-
ficile* infection was the first episode (primary oc-
currence) or second episode (first recurrence) with-
in the 3 months before the start of the study. An
interactive voice-response system and computer-
generated randomization schedule were used to
provide a randomization number and medication-
kit number for each patient. Patients received the
study medication orally each day for 10 days, ac-
cording to an every-6-hour regimen: 200 mg of
fidaxomicin every 12 hours with intervening
matching doses of placebo or 125 mg of vanco-
mycin every 6 hours. The two study medications

and placebo were overencapsulated to look the same. Patients were assessed daily for clinical cure or failure during the 10-day course of therapy. If the criteria for clinical cure were met, the patient was followed for recurrence, by means of a weekly assessment, for 28 days after the last dose of study medication had been administered, with immediate patient-initiated reassessment by the study team if diarrhea recurred.

DEFINITIONS

Clinical cure was defined by the resolution of diarrhea (i.e., three or fewer unformed stools for 2 consecutive days), with maintenance of resolution for the duration of therapy and no further requirement (in the investigator's opinion) for therapy for *C. difficile* infection as of the second day after the end of the course of therapy. Patients who had a marked reduction in the number of unformed stools at the end of treatment but who had residual mild abdominal discomfort were considered by the investigator to have met the criteria for clinical cure, providing that no new anti-infective therapy for *C. difficile* infection was required. Clinical failure was defined by the persistence of diarrhea, the need for additional therapy for *C. difficile* infection, or both, in the opinion of the investigator. Global cure was defined as the resolution of diarrhea without recurrence.

Patients who remained in the study and had a follow-up assessment between days 36 and 40 after randomization were evaluated for recurrence. Clinical recurrence was defined by the reappearance of more than three diarrheal stools per 24-hour period within 4 weeks after the cessation of therapy; *C. difficile* toxin A or B, or both, in stool; and a need for retreatment for *C. difficile* infection.

OUTCOMES

Efficacy Evaluation

The primary efficacy end point was the rate of clinical cure in the modified intention-to-treat and per-protocol populations at the end of therapy or at the time of early withdrawal from the study. The modified intention-to-treat population comprised patients with documented *C. difficile* infection who underwent randomization and received at least one dose of study medication. The per-protocol population comprised patients in the modified intention-to-treat group who received treatment for at least 3 days (in the case of patients with treatment failure) or at least 8 days (in the case of patients with clinical cure), had docu-

mented adherence to the protocol, and underwent an end-of-therapy evaluation. The secondary efficacy end point was recurrence of *C. difficile* infection during the 4-week period after the end of the course of therapy and global cure in the modified intention-to-treat and per-protocol populations.

Microbiologic Evaluation

Fecal samples for toxin assays to verify *C. difficile* infection and microbiologic testing were obtained at the time of screening or enrollment, at the time of early termination or the end-of-therapy visit in the case of patients with clinical failure, and at visits for the diagnosis and treatment of recurrent infection in the case of patients in whom the disease recurred. Toxin tests were performed at individual study sites. Assays for *C. difficile* isolation and susceptibility were performed by R.M. Alden Research Laboratory with the use of the Clinical and Laboratory Standards Institute agar dilution method (CLSI M11-A7). Restriction-endonuclease typing[23,24] was performed at the Edward Hines, Jr., Veterans Affairs Hospital.

Pharmacokinetic Evaluation

Blood samples for pharmacokinetic evaluation were obtained before and 3 to 5 hours after the first dose of the study medication on day 1 and at the end-of-therapy or early-termination visit. Fecal samples were obtained at the end-of-therapy or early-termination visit. Plasma concentrations (Tandem Labs) and fecal concentrations (Micro-Constants) of fidaxomicin were determined with the use of reverse-phase, high-performance liquid chromatography with tandem mass spectrometry.

SAFETY

Safety was assessed from the day informed consent was provided through the day the last dose of the study drug was administered or the last study visit occurred, whichever came later. The assessment included a physical examination, electrocardiography (ERT), and clinical laboratory testing, including hematologic and biochemical tests and urinalysis (Covance). The safety population comprised patients who received at least one dose of the study medication and underwent at least one safety assessment after the first dose of the study medication. Adverse events were classified according to the terms used in the *Medical Dictionary for Regulatory Activities.* An adverse event could be reported more than once for a patient,

but each patient was counted only once in the incidence count for a particular adverse event.

STATISTICAL ANALYSIS

The trial was designed as a noninferiority study. A one-sided lower 97.5% confidence interval was used in the analysis of the primary end point, the rate of clinical cure, with a noninferiority margin of –10 percentage points. If the lower boundary of the confidence limit was within the 10-percentage-point margin, clinical noninferiority was demonstrated. The secondary end points of recurrence and overall cure, which were prospectively defined as descriptive end points, were analyzed by means of post hoc hypothesis tests with the use of two-sided tests of population proportions that were based on the normal approximation to the binomial distribution, at a significance level of 0.05. Treatment differences according to age, inpatient versus outpatient status, prior occurrence of *C. difficile* infection versus no prior occurrence, disease severity (mild disease, defined by the presence of 4 to 5 unformed bowel movements per day or a white-cell count of ≤12,000 per cubic millimeter; moderate disease, defined by the presence of 6 to 9 unformed bowel movements per day or a white-cell count of 12,001 to 15,000 per cubic millimeter; or severe disease, defined by the presence of ≥10 unformed bowel movements per day or a white-cell count of ≥15,001 per cubic millimeter), and strain type were also assessed by means of post hoc analyses. The time to resolution of diarrhea, defined as the interval, in hours, from the start of treatment until the time the last unformed bowel movement occurred on the day before resolution of diarrhea, was analyzed with the use of the Kaplan–Meier method, with a Gehan–Wilcoxon test for comparison of resolution time curves. All summary statistics are presented as means ±SD for continuous variables and as numbers and percentages for categorical variables.

RESULTS

PATIENTS

A total of 629 patients were enrolled and underwent randomization: 302 received fidaxomicin, and 327 received vancomycin. Figure 1 shows the randomization and follow-up of patients in the study. A total of 596 patients were included in the modified intention-to-treat analysis (287 in the fidaxomicin group and 309 in the vancomycin group) and 548 were included in the per-protocol

analysis (265 in the fidaxomicin group and 283 in the vancomycin group). Adherence to the study medication was similar in the two treatment groups; in the modified intention-to-treat population, 91.7% in the fidaxomicin group and 91.4% in the vancomycin group took the assigned doses, and in the per-protocol population, 95.8% and 96.1% in the two groups, respectively, took the assigned doses. The safety population comprised 623 patients — 300 in the fidaxomicin group and 323 in the vancomycin group. The two treatment groups did not differ significantly with respect to baseline characteristics (Table 1).

CLINICAL OUTCOMES

The overall outcomes are shown in Figure 2. The criterion for noninferiority with respect to the primary end point of clinical cure was met in both the modified intention-to-treat and per-protocol populations. In the modified intention-to-treat population, 88.2% of patients in the fidaxomicin group (253 of 287 patients) and 85.8% of those in the vancomycin group (265 of 309) met the criteria for clinical cure (with a lower boundary of the 97.5% confidence interval [CI] for the difference in cure rates of –3.1 percentage points). In the per-protocol population, 92.1% of the patients in the fidaxomicin group (244 of 265 patients) and 89.8% of the patients in the vancomycin group (254 of 283) were considered to have met the criteria for clinical cure (with a lower boundary of the 97.5% CI of –2.6 percentage points). Subgroup analyses of the rates of clinical cure according to the patients' age, inpatient versus outpatient status, prior occurrence of *C. difficile* infection versus no prior occurrence, treatment for *C. difficile* infection versus no treatment within 24 hours before the start of the study, baseline severity of the disease, infecting strain type, no response versus response to previous metronidazole therapy, and use versus nonuse of concomitant systemic antimicrobial therapy showed no significant differences between treatments in both the modified intention-to-treat and per-protocol populations (Table 2).

Treatment with fidaxomicin was associated with a significantly lower rate of recurrence than was treatment with vancomycin in both the modified intention-to-treat population (15.4% [39 of 253 patients] vs. 25.3% [67 of 265]; a reduction with fidaxomicin of 9.9 percentage points; 95% CI, –16.6 to –2.9; P=0.005) and the per-protocol population (13.3% [28 of 211 patients] vs. 24.0%
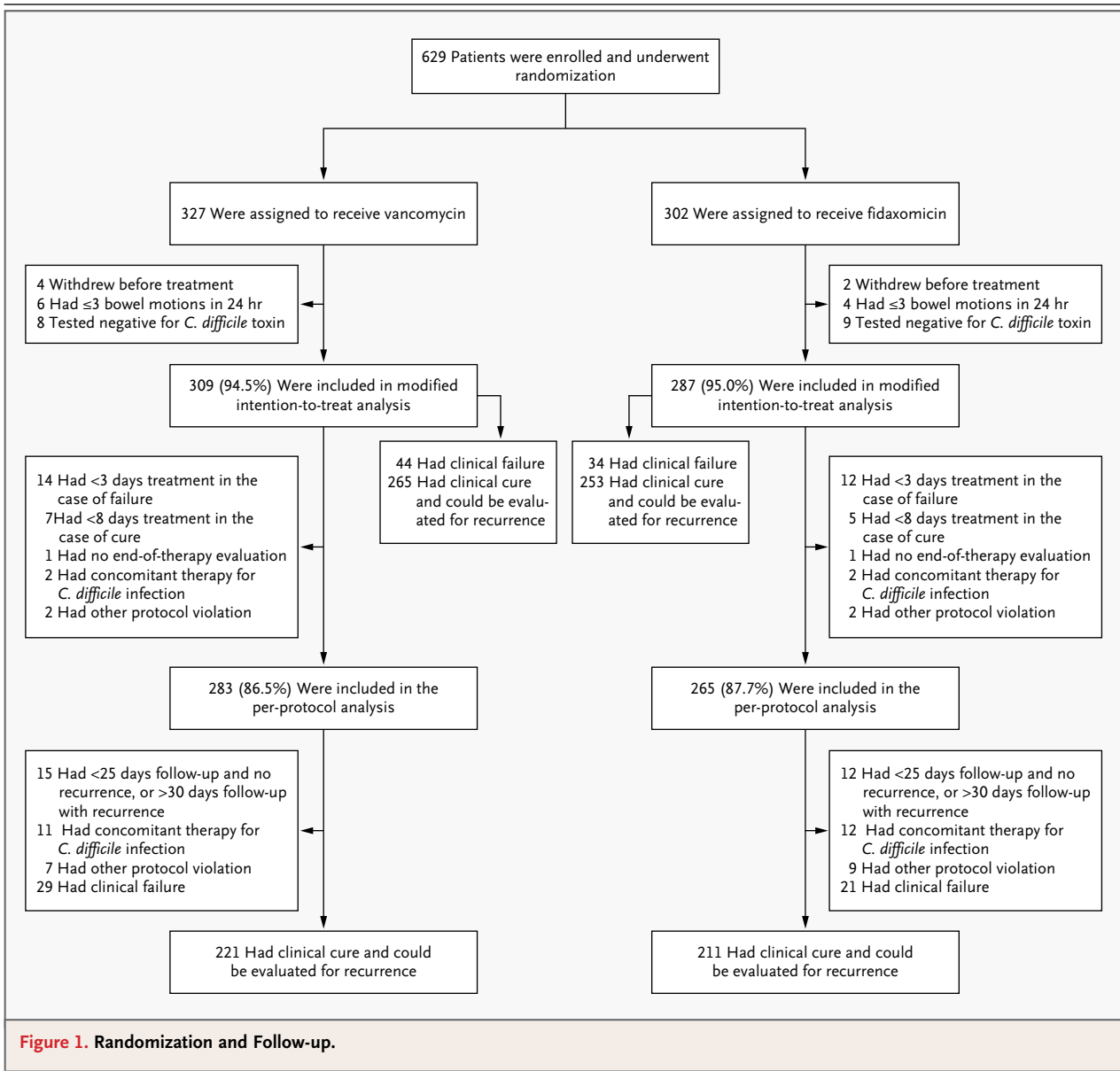
Figure 1. Randomization and Follow-up.

[53 of 221]; a reduction with fidaxomicin of 10.7 percentage points; 95% CI, –17.9 to –3.3; P=0.004). Fidaxomicin treatment was also associated with lower rates of recurrence when the analysis was performed according to subgroups in both the modified intention-to-treat and per-protocol populations (Table 3). The rates of recurrence in the fidaxomicin and vancomycin groups were similar among patients with the NAP1/BI/027 strain: 24.4% (11 of 45 patients) and 23.6% (13 of 55), respectively (P=0.93). Among patients with other strains, however, the rate of recurrence was lower with fidaxomicin: 7.8% (8 of 103 patients), versus 25.5% (27 of 106) with vancomycin (a reduc-

tion with fidaxomicin of 17.7 percentage points; 95% CI, –27.5 to –7.9; P<0.001). This represents a 69% relative reduction in recurrences with fidaxomicin as compared with vancomycin in the subgroup of patients with non–NAP1/BI/027 strains. The relative risk of recurrence for patients with a non–NAP1/BI/027 strain was approximately 3.3 times as high (95% CI, 1.6 to 6.9) among patients receiving vancomycin as among patients receiving fidaxomicin. At the time a recurrence occurred, the same REA strain type as that in the initial occurrence was recovered in 12 of 14 patients in the fidaxomicin group and in 27 of 33 patients in the vancomycin group.

Table 1. Demographic and Baseline Clinical Characteristics of the Patients in the Modified Intention-to-Treat and Per-Protocol Populations.*

Characteristic	Modified Intention-to-Treat Population			Per-Protocol Population		
	Fidaxomicin (N=287)	Vancomycin (N=309)	Total (N=596)	Fidaxomicin (N=265)	Vancomycin (N=283)	Total (N=548)
Age (yr)	60.3±16.9	62.9±16.9	61.6±16.9	59.9±17.1	62.7±17.0	61.3±17.1
Female sex (%)	57.1	54.7	55.9	57.4	54.8	56.0
Unformed stools per day (no.)	8.1±4.2	8.3±5.4	8.2±4.8	8.2±4.3	8.4±5.5	8.3±4.9
Inpatient (%)	58.2	60.5	59.4	55.1	57.2	56.2
Lack of response to metronidazole (%)	4.5	5.5	5.0	4.9	5.7	5.3
Treatment for *C. difficile* infection in previous 24 hr (%)	38.3	39.8	39.1	37.4	38.5	38.0
Previous episode of *C. difficile* infection (%)	16.7	17.5	17.1	16.2	17.0	16.6
BI/NAP1/027 strain (%)†	37.5	38.6	38.1	35.3	36.4	35.9

* Plus–minus values are means ±SD. There were no significant between-group differences.
† Percentages are based on the 415 patients who had a strain type that could be evaluated.

Treatment with fidaxomicin resulted in significantly higher rates of resolution of diarrhea without recurrence than did treatment with vancomycin: 74.6% (214 of 287 patients) versus 64.1% (198 of 309) in the modified intention-to-treat population (an increase with fidaxomicin of 10.5 percentage points; 95% CI, 3.1 to 17.7; P=0.006) and 77.7% (206 of 265 patients) versus 67.1% (190 of 283) in the per-protocol population (an increase with fidaxomicin of 10.6 percentage points; 95% CI, 3.1 to 17.9; P=0.006).

The median time to resolution of diarrhea was shorter in the fidaxomicin group than in the vancomycin group (58 hours vs. 78 hours in the modified intention-to-treat population and 55 hours vs. 69 hours in the per-protocol population) among both inpatients (91 hours vs. 120 hours and 72 hours vs. 78 hours in the two populations, respectively) and outpatients (47 hours vs. 61 hours and 47 hours vs. 60 hours in the two populations, respectively). None of these differences were significant.

SAFETY

There were no significant differences between the fidaxomicin group and the vancomycin group in the rates of adverse events or serious adverse events (see Tables 1 and 2 in the Supplementary Appendix, available at NEJM.org). The occurrence of any adverse event during the treatment period until 7 days after treatment was reported in 62.3% of th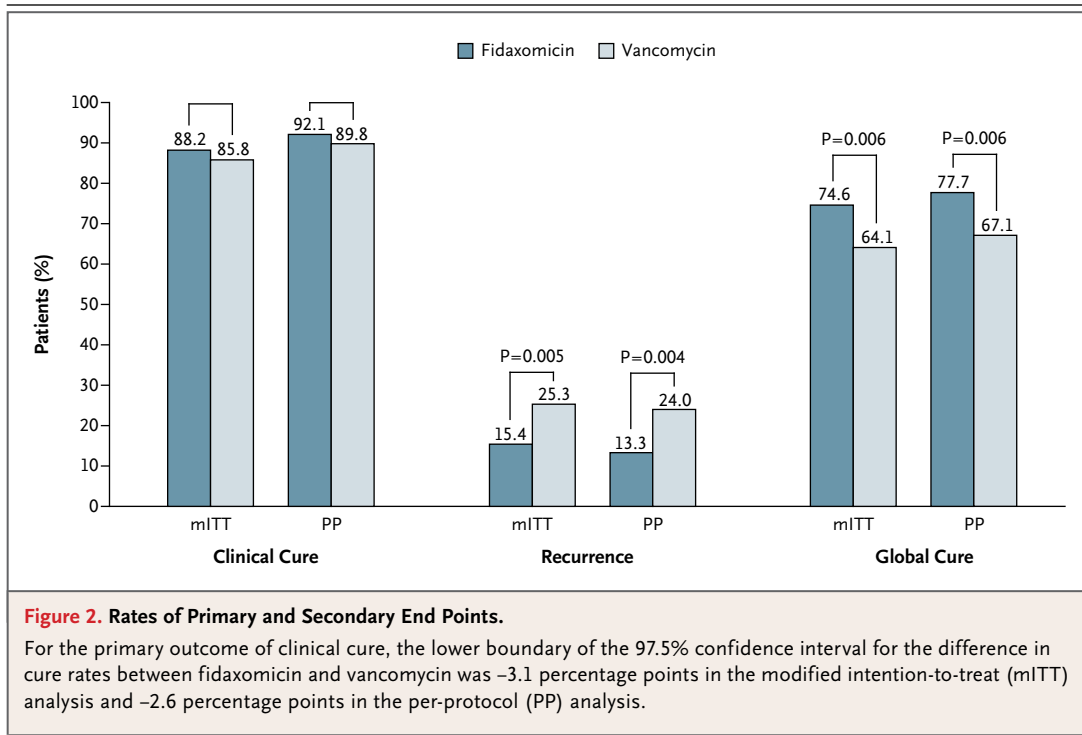e patients in the fidaxomicin group and 60.4% of the patients in the vancomycin group; the occurrence of any serious adverse event was reported in 25.0% and 24.1% of the patients in the two groups, respectively. Adverse events possibly or definitely related to the study treatment were mild gastrointestinal and nonspecific symptoms; the rate of these events was similar in the two groups (9.7% and 9.0% in the fidaxomicin and vancomycin groups, respectively). Significantly more serious adverse events related to laboratory test results occurred in the fidaxomicin group than in the vancomycin group (4.7% vs. 1.2%, P=0.01), without an obvious pattern (Table 5 in the Supplementary Appendix). No subjects discontinued the study as a result of intolerance or allergy to the study medications.

MICROBIOLOGIC EVALUATION

Measurement of in vitro antimicrobial activity against *C. difficile* showed minimum inhibitory concentrations at or below 0.25 μg per milliliter for 90% of isolates in the case of fidaxomicin and 2.0 μg per milliliter in the case of vancomycin. There was no relationship between the minimum inhibitory concentration of baseline clinical isolates and the clinical outcome (cure or recurrence). No shifts in susceptibility to fidaxomicin or vancomycin occurred during the study.

PHARMACOKINETIC EVALUATION

The mean (±SD) plasma level of fidaxomicin after administration of the drug on day 1 was

Figure 2. Rates of Primary and Secondary End Points.

For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was −3.1 percentage points in the modified intention-to-treat (mITT) analysis and −2.6 percentage points in the per-protocol (PP) analysis.

22.8±26.5 ng per milliliter (range, 0.4 to 185.0). In addition, no plasma accumulation was found between day 1 and the end of therapy. The mean end-of-therapy fecal concentration of fidaxomicin was 1225.1±759.0 μg per gram (range, 31.7 to 4640.0), which is 4900 times as high as the minimum inhibitory concentration of 0.25 μg per milliliter for 90% of isolates against *C. difficile.*

DISCUSSION

During the past decade, the clinical profile of *C. difficile* infection has worsened, with increased numbers of cases, greater morbidity, an increased incidence of complications requiring colectomy, and rising mortality. These worsening disease markers have occurred in parallel with the emergence of the new and more virulent BI/NAP1/027 *C. difficile* strain, although efforts to link a poor outcome of infection to the hypervirulent strain have not been uniformly successful.[4,25-29] Regardless of the cause, *C. difficile* infection has become a more serious disease in North America and Europe, even in countries with a relatively low incidence of the BI/NAP1/027 strain.

The initial therapeutic approach to a diagnosed case of *C. difficile* infection is to discontinue the antibiotic that precipitated the infection. Although a minority of cases will resolve with cessation of

antibiotic selection pressure, the risk of worsening disease mandates that treatment be directed against the pathogen. The standard treatments are metronidazole and vancomycin. Both drugs have liabilities. Metronidazole is efficiently absorbed, so that only small quantities reach the colon,[30] which is a pharmacodynamic disadvantage in a primarily mucosal or luminal infection. In addition, it has systemic side effects, such as nausea, headache, taste perversion, and peripheral neuropathy. Furthermore, several studies have shown that metronidazole therapy, as compared with vancomycin therapy, is associated with more failures and higher rates of recurrence, especially among severely ill patients.[31,32] Concern has been expressed that oral administration of metronidazole or vancomycin may induce the emergence of vancomycin-resistant enterococci.[33]

One of the most problematic aspects of *C. difficile* infection is the rate of recurrence. After successful initial treatment with metronidazole or vancomycin, 20 to 30% of patients have a recrudescence of illness within 60 days — but usually within the first 2 weeks.[34] Retreatment with metronidazole or vancomycin resolves the condition in most patients, but approximately one third (or more) of patients have one or more additional recurrences. Severe illness and deaths associated with relapses have been reported at approximately

Table 2. Rates of Clinical Cure at the End of Therapy, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.*

Subgroup	Modified Intention-to-Treat Population		Per-Protocol Population	
	Fidaxomicin	Vancomycin	Fidaxomicin	Vancomycin
	number/total number (percent)			
Age				
<65 yr	150/165 (90.9)	134/157 (85.4)	145/152 (95.4)	132/145 (91.0)
≥65 yr	103/122 (84.4)	131/152 (86.2)	99/113 (87.6)	122/138 (88.4)
Hospital status				
Inpatient	136/167 (81.4)	146/187 (78.1)	128/146 (87.7)	136/162 (84.0)
Outpatient	117/120 (97.5)	119/122 (97.5)	116/119 (97.5)	118/121 (97.5)
Previous episode of *C. difficile* infection				
No	211/239 (88.3)	217/255 (85.1)	203/222 (91.4)	209/235 (88.9)
Yes	42/48 (87.5)	48/54 (88.9)	41/43 (95.3)	45/48 (93.8)
Treatment for current episode of *C. difficile* infection in previous 24 hr				
Yes	88/110 (80.0)	97/123 (78.9)	85/99 (85.9)	92/109 (84.4)
No	165/177 (93.2)	168/186 (90.3)	159/166 (95.8)	162/174 (93.1)
Severity of disease				
Mild	59/64 (92.2)	68/80 (85.0)	56/59 (94.9)	63/71 (88.7)
Moderate	102/111 (91.9)	88/106 (83.0)	99/105 (94.3)	84/97 (86.6)
Severe	92/112 (82.1)	109/123 (88.6)	89/101 (88.1)	107/115 (93.0)
Strain type				
NAP1/BI/027	59/75 (78.7)	67/83 (80.7)	56/65 (86.2)	61/72 (84.7)
Non–NAP1/BI/027	117/125 (93.6)	121/132 (91.7)	115/119 (96.6)	119/126 (94.4)
Lack of response to metronidazole before study				
Yes	13/13 (100.0)	15/17 (88.2)	13/13 (100.0)	14/16 (87.5)
No	240/274 (87.6)	250/292 (85.6)	231/252 (91.7)	240/267 (89.9)
Concomitant systemic antimicrobial therapy				
Yes	67/83 (80.7)	72/94 (76.6)	63/71 (88.7)	67/80 (83.8)
No	186/204 (91.2)	193/215 (89.8)	181/194 (93.3)	187/203 (92.1)

* There were no significant between-group differences according to subgroup.

the same rate as those associated with the primary event.

This was a phase 3 trial of fidaxomicin, a macrocyclic antibiotic that has a narrow antimicrobial spectrum, with activity against *C. difficile* and most strains of staphylococci and enterococci but negligible activity against gram-negative organisms and fungi. Fidaxomicin is poorly absorbed from the intestinal tract and is associated with the same low incidence of systemic side effects as oral vancomycin. The major benefits of fidaxomicin in this comparative study with vancomycin were a 45% relative reduction in recurrences and a correspondingly improved rate of global cure,

an outcome that is termed "symptomatic cure" by Nelson.[35] For the 35.9% of patients with the BI/NAP1/027 strain, the rates of cure and recurrence in the per-protocol analysis were the same as those with vancomycin, but for the 64.1% of patients with other strain types, the recurrence rate was 7.8% with fidaxomicin as compared with 25.5% with vancomycin (a 69% relative reduction). Besides the obvious benefit to the patient, the prevention of recurrence would eliminate the costs of treating additional episodes of *C. difficile* infection and should reduce the rate of person-to-person transmission.

Certain microbiologic characteristics may ex-

Table 3. Rates of Recurrence of *C. difficile* Infection, According to Subgroups, in the Modified Intention-to-Treat and Per-Protocol Populations.

Subgroup	Modified Intention-to-Treat Population			Per-Protocol Population		
	Fidaxomicin	Vancomycin	P Value	Fidaxomicin	Vancomycin	P Value
	no./total no. (%)			*no./total no. (%)*		
Age						
<65 yr	19/150 (12.7)	27/134 (20.1)	0.09	12/126 (9.5)	22/118 (18.6)	0.04
≥65 yr	20/103 (19.4)	40/131 (30.5)	0.05	16/85 (18.8)	31/103 (30.1)	0.08
Hospital status						
Inpatient	24/136 (17.6)	40/146 (27.4)	0.05	19/106 (17.9)	29/111 (26.1)	0.15
Outpatient	15/117 (12.8)	27/119 (22.7)	0.05	9/105 (8.6)	24/110 (21.8)	0.007
Previous episode of *C. difficile* infection						
No	30/211 (14.2)	52/217 (24.0)	0.01	22/175 (12.6)	41/183 (22.4)	0.02
Yes	9/42 (21.4)	15/48 (31.2)	0.30	6/36 (16.7)	12/38 (31.6)	0.14
Treatment for current episode of *C. difficile* infection in previous 24 hr						
Yes	16/88 (18.2)	25/97 (25.8)	0.22	13/73 (17.8)	19/81 (23.5)	0.39
No	23/165 (13.9)	42/168 (25.0)	0.01	15/138 (10.9)	34/140 (24.3)	0.003
Severity of disease at baseline						
Mild	7/59 (11.9)	20/68 (29.4)	0.02	4/44 (9.1)	13/55 (23.6)	0.06
Moderate	20/102 (19.6)	18/88 (20.5)	0.89	15/90 (16.7)	18/71 (25.4)	0.18
Severe	12/92 (13.0)	29/109 (26.6)	0.02	9/77 (11.7)	22/95 (23.2)	0.05
Strain type						
NAP1/BI/027	16/59 (27.1)	14/67 (20.9)	0.42	11/45 (24.4)	13/55 (23.6)	0.93
Non–NAP1/BI/027	12/117 (10.3)	34/121 (28.1)	<0.001	8/103 (7.8)	27/106 (25.5)	<0.001
Concomitant systemic antimicrobial therapy						
Yes	14/81 (17.3)	25/90 (27.8)	0.10	8/56 (14.3)	20/65 (30.8)	0.03
No	25/172 (14.5)	42/175 (24.0)	0.03	20/155 (12.9)	33/156 (21.2)	0.05

plain the favorable results with respect to recurrence. Fidaxomicin rapidly kills *C. difficile* (i.e., it is bactericidal), whereas vancomycin inhibits growth (i.e., it is bacteriostatic). Along with its narrow antimicrobial spectrum,[15-18] fidaxomicin also has a prolonged postantibiotic effect against *C. difficile*, which is not observed in the case of vancomycin. Vancomycin treatment results in the suppression of organisms of the bacteroides group in the fecal flora, which are considered to be markers of normal anaerobic microflora,[21] whereas fidaxomicin preserves these organisms in the flora of patients.[36] The anaerobic bowel flora maintains "colonization resistance," which prevents the introduction or persistence of pathogens and may inhibit the reemergence of *C. difficile*. Preservation of the intestinal flora should also theoretically reduce the likelihood of selection for overgrowth of vancomycin-resistant enterococci.

In conclusion, fidaxomicin and vancomycin have similar effectiveness with respect to the clinical resolution of acute diarrheal disease due to *C. difficile* infection, but more sustained or durable resolution of disease (i.e., improved global cure) is achieved with fidaxomicin — a finding that may be attributable to lesser impairment of the intestinal microbiome during treatment of the infection.

Weiss, receiving honoraria or consulting fees from Abbott, Bayer, Pfizer, and Genzyme; Dr. Shue, being an employee of and owning stock options in Optimer Pharmaceuticals; Dr. Sears, being an employee of and owning stock options in Optimer Pharmaceuticals and being listed as an inventor on a fidaxomicin patent; and Dr. Gorbach, being a part-time employee of Optimer Pharmaceuticals, receiving honoraria from and owning stock options in Cempra, and holding a patent on lactobacillus GG probiotic and β-glucan. No other potential conflict of interest relevant to this article was reported.

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

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431