MAJOR ARTICLE

Tolevamer, a Novel Nonantibiotic Polymer, Compared with Vancomycin in the Treatment of Mild to Moderately Severe *Clostridium difficile*–Associated Diarrhea

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(See the article by Musher et al. on pages 421–7 and the editorial commentary by Bartlett on pages 428–31)

Background. Current antibiotic therapies for *Clostridium difficile*–associated diarrhea have limitations, including progression to severe disease, recurrent *C. difficile*–associated diarrhea, and selection for nosocomial pathogens. Tolevamer, a soluble, high–molecular weight, anionic polymer that binds *C. difficile* toxins A and B is a unique nonantibiotic treatment option.

Methods. In this 3-arm, multicenter, randomized, double-blind, active-controlled, parallel-design phase II study, patients with mild to moderately severe *C. difficile*–associated diarrhea were randomized to receive 3 g of tolevamer per day ($n = 97$), 6 g of tolevamer per day ($n = 95$), or 500 mg of vancomycin per day ($n = 97$). The primary efficacy parameter was time to resolution of diarrhea, defined as the first day of 2 consecutive days when the patient had hard or formed stools (any number) or ⩽2 stools of loose or watery consistency.

Results. In the per-protocol study population, resolution of diarrhea was achieved in 48 (67%) of 72 patients receiving 3 g of tolevamer per day (median time to resolution of diarrhea, 4.0 days; 95% confidence interval, 2.0–6.0 days), in 58 (83%) of 70 patients receiving 6 g of tolevamer per day (median time to resolution of diarrhea, 2.5 days; 95% confidence interval, 2.0–3.0 days), and in 73 (91%) of 80 patients receiving vancomycin (median time to resolution of diarrhea, 2.0 days; 95% confidence interval, 1.0–3.0 days). Tolevamer administered at a dosage of 6 g per day was found to be noninferior to vancomycin administered at a dosage of 500 mg per day with regard to time to resolution of diarrhea ($P = .02$) and was associated with a trend toward a lower recurrence rate. Tolevamer was well tolerated but was associated with an increased risk of hypokalemia.

Conclusions. Tolevamer, a novel polystyrene binder of *C. difficile* toxins A and B, effectively treats mild to moderate *C. difficile* diarrhea and merits further clinical development.

Clostridium difficile–associated diarrhea (CDAD) is fundamentally a microbial ecologic disorder in which the pathogen, once introduced, is able to thrive in an intestinal environment ablated of normal, competing intestinal flora by antimicrobial chemotherapy [1–3]. The risk of developing clinical disease, rather than asymptomatic colonization, and the risk of recurrent CDAD are increased in persons who do not mount a sufficient antibody response to toxin A [4, 5].

The incidence of CDAD appears to be increasing in Canada, the United Kingdom, and the United States [6–9]. In the past decade, the Health Protection Agency

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of the United Kingdom has reported a 6-fold increase in cases, accounting for 44,000 cases in 2004, which is a case rate that is double that found in 2001 [10]. The 2003–2004 outbreak of CDAD in Quebec, Canada, which was largely the result of the introduction of a new hypertoxigenic strain, has increased case rates to >5 times the national average of 1997 [11–13]. A closely related strain accounted for multiple outbreaks in the United States in 2003–2004 [14].

Increasing CDAD rates highlight antibiotic selection factors, failing infection-control measures, and deficiencies in current therapies for *C. difficile* disease. Therapy with vancomycin and metronidazole produces an expected response rate of 85%–90%, accompanied by a 16%–21% risk of recurrence for both agents [15–17]. Metronidazole is the preferred first-line therapy because of low cost and reduced selective pressure for vancomycin resistance, but presumably, both treatments disrupt the normal colonic flora that provide colonization resistance against *C. difficile* [18–20]. However, recent observational studies have questioned the efficacy of metronidazole for the treatment of CDAD, both in terms of suboptimal primary response and higher-than-expected recurrence rates [21, 22].

Tolevamer is a soluble, high–molecular weight, anionic polymer (>400 kDa) that noncovalently binds *C. difficile* toxins A and B [23, 24]. Syrian hamsters infected with *C. difficile* were durably cured of infection and protected from recurrence by toxin-binding therapy with tolevamer [23]. It is hypothesized that tolevamer's unique mechanism of action—toxin neutralization rather than antibacterial activity—should resolve CDAD and, by allowing restoration of the normal microbiota in the absence of antibiotic suppression, will result in a lower recurrence rate. The present study is a phase II multicenter, randomized, double-blind, active-controlled comparison of 3-g per day or 6-g per day regimens of tolevamer with vancomycin for the treatment of CDAD.

MATERIALS AND METHODS

Patients. Patients (both male and female) ⩾18 years of age with non–life-threatening medical conditions and confirmed (primary or recurrent) or presumed recurrent mild to moderately severe CDAD were screened for study entry. For the 24 h preceding enrollment, patients must have had mild to moderate CDAD symptoms, which included ⩽12 stools, absent to moderate abdominal discomfort, and ⩽1 episode of vomiting. Female patients could not be pregnant and were required to be using contraception. Patients were required to have ⩾3 loose or watery stools in the 24-h period preceding enrollment to meet the study definition for diarrhea. Patients with a first CDAD episode were required to demonstrate a positive *C. difficile* toxin assay result within the 7 days prior to enrollment; patients with presumed recurrent CDAD could either demonstrate a positive *C. difficile* toxin assay result within the 7 days prior to enrollment or have a stool sample collected for testing within 24 h after enrollment and demonstrate a positive assay result within 7 days after enrollment. Toxin was confirmed by the EIA or cytotoxicity assay in current use at each site. Patients who did not demonstrate a positive toxin assay result were discontinued from the study and underwent the end-of-treatment visit safety procedures. The institutional review board or ethics committee at each center approved the study, which was conducted in accordance with United States Good Clinical Practice, the International Conference on Harmonization, the Declaration of Helsinki, and all applicable laws and regulations. All patients provided written, informed consent.

Patients were excluded from the study if they had severe CDAD, defined as the presence of any of the following in the 24-h period preceding enrollment: >12 stools; severe, persistent abdominal pain or distension (>2 h in duration) attributed to CDAD; ⩾2 episodes of vomiting; and a temperature >38.9°C attributed to CDAD. Other exclusion criteria included any of the following serum potassium (K^+) test results in the 24-h period preceding enrollment: K^+ level <2.5 mEq/L; K^+ level <3.0 mEq/L and a history of cardiac ischemia, congestive heart failure, or left ventricular hypertrophy; and K^+ level <3.5 mEq/L and a history of cardiac arrhythmias or current receipt of digoxin. Patients who were expected to continue to receive the CDAD-inducing antibiotic regimen for >14 days were excluded from study entry. Patients with diarrhea due to another known cause, patients with active chronic diarrhea unrelated to CDAD, and patients who received >48 h of vancomycin or metronidazole therapy for the presenting episode of CDAD were excluded.

Objectives. The primary objective of this study was to compare the safety, tolerability, and efficacy of tolevamer and vancomycin for the treatment of mild to moderate CDAD. The secondary objectives were to compare symptom resolution and recurrence during 10 weeks of study.

Study design. This was a phase II multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-design efficacy study conducted at 61 centers in the United States, the United Kingdom, and Canada. Patients were randomized to receive oral capsules of either tolevamer (1 g administered 3 times per day or 2 g administered 3 times per day) for 14 days or vancomycin (administered at a dosage of 125 mg 4 times per day for 10 days) and a matching placebo (figure 1) without regard to concomitant food consumption. For patients requiring continuation of the CDAD-inducing systemic antibiotic therapy (with causality determined by the investigator) for up to 14 days, tolevamer or placebo therapy (but not vancomycin therapy) could be extended for a corresponding period to protect the patient against *C. difficile* toxins while allowing time for repopulation of the gut with normal flora. The maximum therapeutic duration was no more than 28 days. After

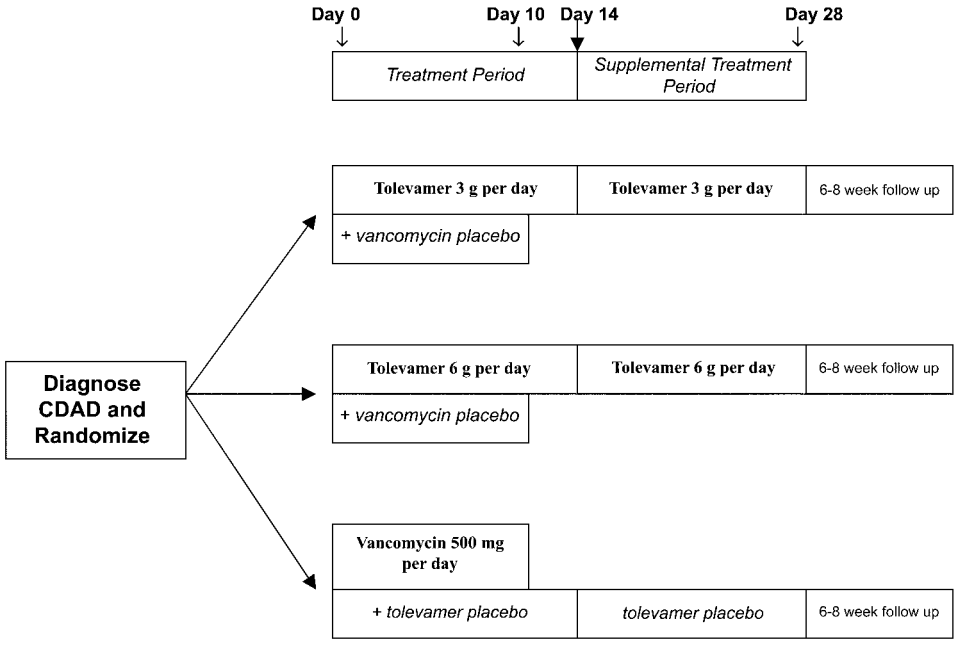

Figure 1. Flow chart showing the study design. The supplemental treatment period consisted of up to 14 days of supplemental tolevamer or placebo in patients continuing to receive the *Clostridium difficile*–associated diarrhea (CDAD)–inciting antibiotic.

the study treatment period, there was a 6–8-week follow-up period, depending on the duration of the study drug dosing period.

Clinical evaluations. Resolution of diarrhea was determined on the basis of stool counts and average consistency, which were recorded daily (on days 1–14) by the clinical trials nurse and/or investigator team after direct assessment and interview of hospitalized patients and by daily telephone interview of outpatients on nonclinic days. Recurrent CDAD after resolution was defined as $\geqslant$3 stools in a 24-h period with loose or watery consistency with a positive toxin assay result or presence of pseudomembranes and no other likely etiology. Adverse events and concomitant medications were assessed daily; serum K^+ level was evaluated a minimum of every 4 days. Outpatients were evaluated during a physical examination on day 8.

Evaluation of efficacy and safety. The primary efficacy parameter was time to resolution of diarrhea (TTROD). Diarrhea was considered to be resolved on the first day of 2 consecutive days on which the patient had any number of stools with an average consistency classified as hard or formed or $\leqslant$2 stools with an average consistency of loose or watery. The secondary efficacy parameters included the following: number of stools, average stool consistency, abdominal discomfort, and recurrence. A consistency score was used to rate the average consistency of stool, as follows: hard, 1; formed, 2; loose, 3; and watery, 4. The safety parameters included clinical and laboratory adverse events.

Statistical methods. The intent-to-treat population consisted of all randomized patients with confirmed CDAD who received at least 1 dose of the study drug and had any post-dosing investigator evaluation data. The per-protocol population consisted of the subset of patients who were not excluded on the basis of prospectively defined evaluability criteria or other major protocol violations.

Balance between treatment arms was assessed with respect to baseline clinical characteristics and demographic data using a 2-way analysis of variance model for continuous factors and the Cochran-Mantel-Haenszel (CMH) test controlling for categorical factors.

If the median TTROD was found to be statistically significantly <2 days longer in the tolevamer 6-g group, compared with the vancomycin 500-mg group, it was concluded that the tolevamer regimen was noninferior to the vancomycin regimen. The per-protocol analysis was the primary assessment of noninferiority. The *P* values were calculated using the CMH test adjusted for site to compare proportions, the log-rank test to compare times to event, the Chow test to assess noninferiority [25], and the Wald χ^2 test to assess hazard ratio. A sample size of 78 patients per arm was calculated to provide 80% power to detect noninferiority.

RESULTS

A total of 289 patients were randomized into the study. Ten patients were not included in the full analysis group: 3 withdrew from the study before receiving medication, 4 were withdrawn

Table 1. Demographic data and baseline characteristics for patients with *Clostridium difficile*–associated diarrhea (CDAD) in the full analysis group.

Variable	Tolevamer 3-g group (n = 94)	Tolevamer 6-g group (n = 91)	Vancomycin 500-mg group (n = 94)	All patients (n = 279)
Race				
White	86 (91)	80 (88)	87 (93)	253 (91)
Black	6 (6)	7 (8)	6 (6)	19 (7)
Hispanic	1 (1)	1 (1)	1 (1)	3 (1)
Asian	0	1 (1)	0	1 (0)
Other	1 (1)	2 (2)	0	3 (1)
Sex				
Male	44 (47)	39 (43)	42 (45)	125 (45)
Female	50 (53)	52 (57)	52 (55)	154 (55)
Age, years				
Median	64	69	69	67
Range	27–97	22–94	22–96	22–97
CDAD strata				
Primary	69 (73)	70 (77)	76 (81)	215 (77)
Presumed recurrent	25 (27)	21 (23)	18 (19)	64 (23)
CDAD severity				
Mild[a]	60 (64)	63 (69)	70 (74)	193 (69)
Moderate[b]	34 (36)	27 (30)	23 (24)	84 (30)
Severe[c]	0	1 (1)	1 (1)	2 (1)
Oral vancomycin or metronidazole				
Naive	49 (52)	49 (54)	50 (53)	148 (53)
Previously treated[d]	45 (48)	42 (46)	44 (47)	131 (47)
Treatment duration ⩽1 day	10 (11)	11 (12)	11 (12)	32 (11)
Treatment duration >1 day but ⩽2 days	27 (29)	22 (24)	30 (32)	79 (28)
Country				
Canada	36 (38)	33 (36)	36 (38)	105 (38)
United Kingdom	11 (12)	13 (14)	15 (16)	39 (14)
United States	47 (50)	45 (49)	43 (46)	135 (48)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Defined as <7 stools in the 24-h period preceding screening; moderate, 7–12 stools in the 24-h period preceding screening; severe, >12 stools in the 24-h period preceding screening.

[b] Defined as 7–12 stools in the 24-h period preceding screening.

[c] Defined as >12 stools in the 24-h period preceding screening.

[d] Vancomycin or metronidazole use for CDAD within 4 days prior to screening.

because of negative toxin assay results, and 3 had no post-dose investigator evaluations. The full analysis group comprised 279 patients enrolled from 61 centers in the United States (135 [48%] of 279), Canada (105 [38%] of 279), and the United Kingdom (39 [14%] of 279). Of the 279 full analysis patients, 57 were excluded from the per-protocol analysis for the following reasons: <5 days of therapy (35 patients), <70% compliance with study medication (30 patients), negative toxin assay result and/or no endoscopic confirmation (6 patients), no diarrhea (4 patients), chronic diarrhea (6 patients), CDAD for >30 days (3 patients), presence of other enteric pathogen (1 patient), and >48 h of prior therapy (8 patients). The exclusions were similarly distributed in each of the study arms. The per-protocol population consisted of 222 patients, 72 receiving 3 g of tolevamer per day, 70 receiving 6 g of tolevamer per day, and 80 receiving vancomycin. The supplemental treatment period was used for ~10% of the patients (distributed similarly among the groups) and likely had minimal impact on outcomes.

Demographic data and other baseline characteristics for patients in the full analysis group are shown in table 1. No statistically significant differences were observed across the 3 treatment groups. Similar demographic profiles were seen in the per-protocol analysis.

The patient history of CDAD is presented in table 2. Diarrhea severity at study entry was similar between groups. No statis-

Table 2. ***Clostridium difficile*–associated diarrhea (CDAD) history at screening for patients in the full analysis group.**

Variable	Tolevamer 3-g group (n = 94)	Tolevamer 6-g group (n = 91)	Vancomycin 500-mg group (n = 94)
History of CDAD			
Yes	25 (27)	22 (24)	18 (19)
No	69 (73)	69 (76)	76 (81)
Time since last episode, median months (range)[a]	1 (0–20)[b]	1 (0–7)[c]	1 (0–5)[d]
Duration of diarrhea, median days (range)[e]	6 (2–78)[f]	7 (2–36)[g]	6 (1–278)[f]
C. difficile toxin assay result			
Negative	1 (1)	2 (2)	1 (1)
Positive	93 (99)	89 (98)	93 (99)
Type of toxin assay			
EIA	79 (84)	72 (79)	78 (83)
Cellular cytotoxicity assay	15 (16)	18 (20)	16 (17)
Other	0	1 (1)	0
Receiving metronidazole or vancomycin			
Yes[h]	45 (48)	42 (46)	44 (47)
No	49 (52)	49 (54)	50 (53)
No. of stools per day before illness, median (range)	1 (1–6)	1 (0–3)[i]	1 (1–6)[f]
No. of stools in 24-h period before screening, median (range)	6 (2–12)	5 (2–13)	5 (3–13)
Average consistency of stools in 24-h period before screening			
Hard	0	0	0
Formed	0	1 (1)	0
Loose	38 (40)	40 (44)	42 (45)
Watery	56 (60)	50 (55)	52 (55)
Maximum severity of abdominal discomfort in 24-h period before screening			
Absent	22 (23)	26 (29)	27 (29)
Mild	33 (35)	26 (29)	33 (35)
Moderate	39 (41)	39 (43)	34 (36)
Severe	0	0	0
Maximum temperature in 24-h period before screening, median °C (range)	37.1 (36.0–39.7)[i]	37.0 (34.9–40.0)	37.0 (35.8–39.3)[f]

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Month of informed consent minus month of last episode. Only patients with a history of CDAD are included.
[b] n = 24.
[c] n = 22.
[d] n = 17.
[e] Calculated on the basis of the date of onset of diarrhea to the date of informed consent.
[f] n = 91.
[g] n = 88.
[h] Includes patients receiving metronidazole or vancomycin for CDAD within 4 days before signing informed consent forms.
[i] n = 90.

tically significant differences were observed across the 3 treatment groups in either the full analysis or per-protocol analysis data sets.

Primary efficacy end points. There was a <1-day difference in median TTROD between the tolevamer 6-g group (2.5 days) and the vancomycin 500-mg group (2.0 days), and noninferiority was established with respect to a noninferiority margin of 2 days (P = .02 by Chow test; table 3). However, the 3-g dose of tolevamer was found to be inferior to the 500-mg dose of vancomycin (P = .53 by Chow test) for TTROD. A total of 48 (67%) of 72 patients who received 3-g doses of tolevamer achieved resolution, compared with 58 (83%) of 70 patients who received 6-g doses of tolevamer (P = .02 by CMH test) and 73 (91%) of 80 patients who received 500-mg doses of vancomycin (P < .01 by CMH test). However, the difference in the proportion of patients achieving resolution with vancomycin and the proportion of patients achieving resolution with the 6-g dose of tolevamer was not statistically significant (P = .18 by CMH test). Kaplan-Meier estimates of cumulative distribution of TTROD for both per-protocol analysis and full

Table 3. Time to resolution of diarrhea (TTROD) for patients with *Clostridium difficile*–associated diarrhea (CDAD) in the per-protocol analysis group.

Variable	Tolevamer 3-g group (n = 72)	Tolevamer 6-g group (n = 70)	Vancomycin 500-mg group (n = 80)
Patients with resolution of CDAD			
No. (%) of patients	48 (67)	58 (83)	73 (91)
TTROD, median days (95% CI)	4.0 (2.0–6.0)	2.5 (2.0–3.0)	2.0 (1.0–3.0)
P value vs. vancomycin 500-mg group			
By log-rank test of difference in TTROD	<.01	.53	…
By Chow test of noninferiority	.53	.02	…
No. of patients with recurrence during treatment period[a]	4	2	0
Patients with resolution of CDAD with no recurrence during study treatment			
No. (%) of patients	44 (60)	56 (79)	73 (91)
TTROD, median days (95% CI)	5 (2.0–7.0)	2.5 (2.0–3.0)	2 (1.0–3.0)
P value vs. vancomycin 500-mg group			
By log-rank test of difference in TTROD	<.01	.31	…
By Chow test of noninferiority	0.47	0.03	…

[a] During the period 10–14 days after initiation of treatment with the study drug. Two additional patients—1 in the tolevamer 3-g group and 1 in the tolevamer 6-g group—had recrudescence of diarrhea while receiving the study drug, but both patients had negative toxin assay results. Including these patients in the analysis as having experienced recurrence during treatment results in a median TTROD of 3 days for the tolevamer 6-g group, with noninferiority to the vancomycin 500-mg group retained (P = .03 by Chow test). The median TTROD for the tolevamer 3-g group is unchanged.

analysis are shown in figure 2. In the per-protocol analysis, these were similar for the tolevamer 6-g group and the vancomycin 500-mg group (P = .53 by log-rank test), but the tolevamer 3-g group experienced slower resolution of diarrhea (P = .02 for tolevamer 3-g group vs. tolevamer 6-g group by log-rank test; P < 0.01 for tolevamer 3-g group vs. vancomycin 500-mg group by log-rank test). The results based on the full analysis population were similar, but noninferiority for the tolevamer 6-g regimen and the vancomycin 500-mg regimen were not supported (P = .09 by Chow test; figure 2*B*). These treatment effects were found to be consistent across subgroups of patients with respect to treatment-naive patients (i.e., those who had received no prior treatment) versus patients previously treated with vancomycin or metronidazole for ⩽48 h, CDAD severity, primary versus recurrent CDAD, and concomitant antibiotic use.

Secondary efficacy end points. Secondary efficacy end points and post hoc analysis of recurrence are summarized in table 4. Although stool counts improved such that, by day 11, they were similar across all groups, the median values for number of stools per day over the 14-day treatment period favored vancomycin (P < .01), and mean stool consistency was more solid for vancomycin-treated patients (P < .01). Severity of abdominal discomfort improved in all groups, shifting to absent (73%–85%) or mild (9%–16%) by day 11 with no clinically or statistically significant differences between groups.

Recurrence of diarrhea was not statistically different between treatment groups, with similar results according to per-protocol analysis and full analysis, but there was a trend toward a lower recurrence rate in the tolevamer 6-g group (10%, compared with 19% for the vancomycin group in the per-protocol analysis; P = .19 by log-rank test). As a sensitivity analysis, we also evaluated a more relaxed definition of recurrence that did not require a positive toxin assay result or pseudomembranes, and the results were consistent.

In a post hoc adjustment of responses for the per-protocol patients, 4 patients receiving the 3-g regimen of tolevamer and 2 patients receiving the 6-g regimen of tolevamer who experienced recrudescence of diarrhea within the 14-day treatment period were reclassified as having experienced treatment failure after having been originally classified as attaining diarrhea resolution with subsequent recurrent CDAD. No patients in the vancomycin group required reclassification. These episodes of recurrent diarrhea were all of mild to moderate severity; study medication was discontinued for these subjects, and they were treated with standard antibiotics for CDAD. With this adjusted analysis for TTROD (table 3), 60% of the tolevamer 3-g group, 79% of the tolevamer 6-g group, and 91% of the vancomycin group achieved diarrhea resolution. Noninferiority between the tolevamer 6-g regimen and the vancomycin regimen still achieved statistical significance (P = .03 by Chow test), and rates of CDAD recurrence (table 4) were 16% for the tolevamer 3-g group, 7% for the tolevamer 6-g group, and 19% for the

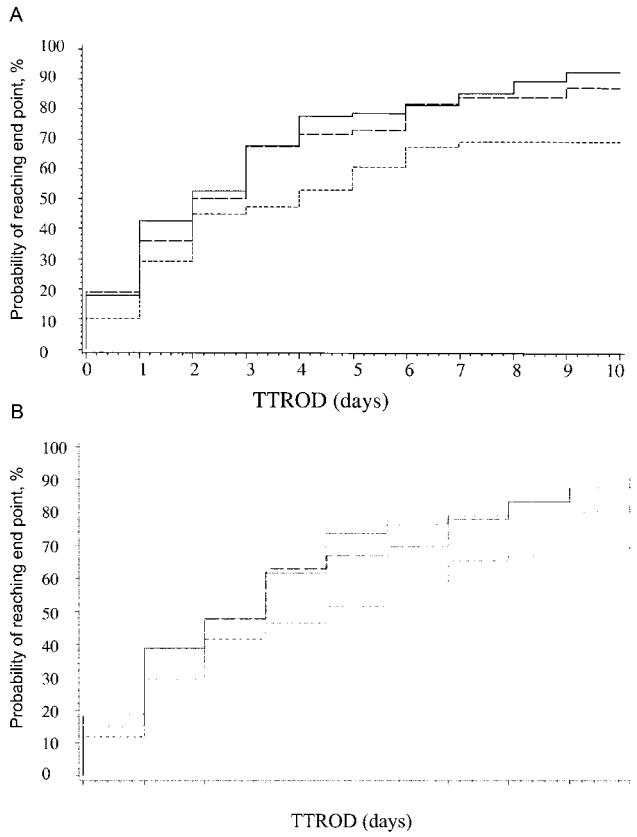

Figure 2. Kaplan-Meier estimates of cumulative distribution of time to resolution of diarrhea (TTROD) for patients receiving 500 mg per day of vancomycin *(solid line),* 6 g per day of tolevamer *(dashed line),* or 3 g per day of tolevamer *(dotted line)* according to whether they are included in the per-protocol data set *(A)* or the full analysis data set *(B).*

vancomycin group ($P = .05$ by log-rank test for the tolevamer 6-g group vs. the vancomycin group).

Table 5 summarizes outcomes for per-protocol analysis patients who received at least 10 days of study therapy. Improved results are seen; it is of note that no recurrences occurred in patients in the tolevamer 6-g group who enrolled in the study with recurrent CDAD ($P = .07$ by log-rank test).

Safety. Adverse events regardless of causality were similar between study groups. The most frequent adverse events in all 3 treatment groups were minor gastrointestinal complaints. Adverse events commonly associated with CDAD and adverse events that could be related to polymer therapy regardless of causality are summarized in table 6. Most of the adverse events that were considered to be related to the study drug were mild in intensity. The study medication was discontinued because of an adverse event for 8 patients in the tolevamer 3-g group, 11 patients in the tolevamer 6-g group, and 7 patients in the vancomycin group. Hypokalemia was most common among patients in the tolevamer 6-g group (23%, compared with 17% in the tolevamer 3-g group and 7% in the vancomycin group). No other clinically significant laboratory differences between treatment groups were observed. Eighteen patients with a mean age of 78 years (range, 55–94 years) died during this study, including 4 (4%) of 96 patients in the tolevamer 3-g group, 9 (10%) of 94 patients in the tolevamer 6-g group, and 5 (5%) of 96 patients in the vancomycin group. The adverse events that caused death included cardiac disease (5 patients), a cerebrovascular and/or CNS event (2), respiratory failure and/or pneumonia (6), multiorgan failure and/or septic shock (3), disseminated carcinoma (1), and pseudomembranous colitis (1). One death that was attributed to *C. difficile* colitis occurred

Table 4. Recurrence of diarrhea and other secondary efficacy end points for patients with *Clostridium difficile*–associated diarrhea (CDAD) in the per-protocol analysis group.

Variable	Tolevamer 3-g group ($n = 72$)	P[a]	Tolevamer 6-g group ($n = 70$)	P[a]	Vancomycin 500-mg group ($n = 80$)
Patients with resolution of CDAD					
No. (%) of patients	48 (67)		58 (83)		73 (91)
Proportion (%) of patients with recurrence	11/48 (23)	.61[b]	6/58 (10)	.19[b]b	14/73 (19)
Patients with resolution of CDAD with no recurrence during study treatment					
No. (%) of patients	44 (60)		56 (79)		73 (91)
Proportion (%) of patients with recurrence	7/44 (16)	.62	4/56 (7)	.05	14/73 (19)
No. of stools per day during the treatment period, median (range)	3.5 (1–16)	<.01[c]	3.0 (1–10)	<.01[c]	2.4 (0–8)
Stool consistency score per day during the treatment period, mean ± SD	2.8 ± 0.5	<.01[c]	2.8 ± 0.6	<.01[c]	2.5 ± 0.4
No. of stools at day 11, mean ± SD	2.7 ± 1.9	.24[d]	2.6 ± 2.1	Not calculable	2.3 ± 1.7

[a] *P* value versus the vancomycin 500-mg group.
[b] By log-rank test.
[c] By Wilcoxon rank sum test.
[d] By Cochran-Mantel-Haenszel test.

Table 5. Resolution of *Clostridium difficile*–associated diarrhea (CDAD) and recurrence among patients with at least 10 days of study treatment in the per-protocol analysis group.

Variable	Tolevamer 3-g group	*P*	Tolevamer 6-g group	*P*	Vancomycin 500-mg group
Patients with resolution of CDAD					
Proportion (%) of patients	41/52 (79)		51/55 (93)		71/76 (93)
Proportion (%) of patients with recurrence	8/41 (20)	.99	5/51 (10)	.16	14/71 (20)
With primary CDAD cases	4/30 (13)	.60	5/39 (13)	.52	10/56 (18)
With recurrent CDAD cases	4/11 (36)	.56	0/12 (0)	.07	4/15 (27)
Patients with resolution of CDAD with no recurrence during study treatment					
Proportion (%) of patients	37/52 (71)		49/55 (89)		71/76 (93)
Proportion (%) of patients with recurrence	4/37 (11)	.23	3/49 (6)	.04	14/71 (20)
With primary CDAD cases	2/28 (7)	.18	3/37 (8)	.18	10/56 (18)
With recurrent CDAD cases	2/9 (22)	.82	0/12 (0)	.07	4/15 (27)

[a] *P* value versus the vancomycin 500-mg group by the log-rank test.

in the tolevamer 6-g group in a patient who discontinued the study drug after only 1 day because of vomiting and died 2 weeks later. No deaths were judged by the investigators to be related to the study drug, and the deaths likely reflect the elderly and debilitated population at risk for CDAD.

DISCUSSION

In an era of increasing antibiotic resistance, a nonantibiotic treatment for an infectious disease that avoids additional adverse microbial ecologic selection pressure is timely and novel. This is the first study to verify that a treatment to neutralize *C. difficile* toxins A and B is clinically effective for treating CDAD. In this study, 67% of patients who received 3 g of tolevamer per day achieved resolution of diarrhea; increasing the dosage of tolevamer to 6 g per day produced an 83% response rate, a result that was comparable to the 91% response rate achieved by vancomycin administered at a dosage of 500 mg per day. When patients with recurrent diarrhea during study treatment were reclassified as having experienced treatment failure in a post-hoc analysis, response rates of 60%, 79%, and 91% were observed for the tolevamer 3-g group, the tolevamer 6-g group, and the vancomycin group, respectively, and a lower recurrence rate was observed with a tolevamer regimen of 6 g per day (4 [7%] of 55 patients) than with vancomycin administered at 500 mg per day (14 [19%] of 73 patients) ($P = .05$). The mechanism of action leading to improved clinical response and less recurrence with the higher tolevamer dose is postulated to be more-complete toxin neutralization with improved healing of damaged tissues and greater restoration of the normal microbiota.

Tolevamer was found to be safe and well tolerated, but it was associated with an increase in hypokalemia. Tolevamer is an anionic polymer, and, as such, it is capable of binding cations, of which potassium is abundant in colonic fluid. For current studies, tolevamer has undergone 2 modifications: development of a liquid formulation to improve compliance and allow for higher doses, and addition of potassium as a counterion in an amount estimated to achieve net neutral potassium balance and mitigate the risk of hypokalemia. This new formulation was safe and well tolerated in a phase I study, and patients receiving it maintained normal potassium levels in serum and urine [26].

A new nonantimicrobial treatment for CDAD may solve deficiencies associated with current therapies [22, 27–34]. In addition to primary treatment of CDAD, toxin binding could reduce disease severity or, in the future, be considered an option for patients with relapsing disease. The recent emergence of a hypertoxigenic ribotype 027/North American pulsotype 1 strain of *C. difficile* [11, 35] highlights the need for prevention and multimodality treatment strategies, in which toxin binding may play an important role.

Table 6. Adverse events commonly associated with *Clostridium difficile*–associated diarrhea (CDAD) and adverse events that might result from polymer therapy regardless of causality.

Adverse event	No. (%) of patients		
	Tolevamer 3-g group ($n = 96$)	Tolevamer 6-g group ($n = 94$)	Vancomycin 500-mg group ($n = 96$)
Nausea	15 (16)	12 (13)	20 (21)
Hypokalemia	16 (17)	22 (23)[a]	7 (7)
Vomiting NOS	9 (9)	7 (7)	5 (5)
Constipation	5 (5)	2 (2)	11 (11)
Abdominal pain NOS	7 (7)	4 (4)	5 (5)
Flatulence	4 (4)	6 (6)	1 (1)
Antibiotic-associated colitis	3 (3)	2 (2)	2 (2)

NOTE. NOS, no other symptoms.

[a] Statistically significant difference versus the vancomycin 500-mg group. $P < .05$, by Fisher's exact test.

Because the proportion of patients achieving diarrhea resolution was higher with vancomycin than with tolevamer, and in light of the observed dose response and safety of tolevamer, a higher dose of polymer is being examined in ongoing phase 3 studies that compare a daily 9-g regimen of the new formulation with both vancomycin and metronidazole.

In conclusion, tolevamer administered at 6 g per day was shown to be no less effective than vancomycin administered at 500 mg per day with respect to TTROD and was also associated with a strong trend towards a lower recurrence rate. The potential for reducing antibiotic resistance, improving primary outcomes, and reducing recurrence merits further clinical development of tolevamer as a nonantibiotic treatment for CDAD.

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