MAJOR ARTICLE

Vancomycin, Metronidazole, or Tolevamer for *Clostridium difficile* Infection: Results From Two Multinational, Randomized, Controlled Trials

Stuart Johnson,[1] Thomas J. Louie,[2] Dale N. Gerding,[1] Oliver A. Cornely,[3] Scott Chasan-Taber,[4,a] David Fitts,[5] Steven P. Gelone,[5] Colin Broom,[5] and David M. Davidson[4,b]; for the Polymer Alternative for CDI Treatment (PACT) investigators

[1]Loyola University Medical Center and Hines Veterans Administration Hospital, Chicago, Illinois; [2]University of Calgary, Alberta, Canada; [3]Department of Internal Medicine, Clinical Trials Centre Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Germany; [4]Genzyme, Cambridge, Massachusetts; and [5]ViroPharma Incorporated, Exton, Pennsylvania

(See the Editorial Commentary by Wilcox on pages 355–7.)

Background. *Clostridium difficile* infection (CDI) is a common complication of antibiotic therapy that is treated with antibiotics, contributing to ongoing disruption of the colonic microbiota and CDI recurrence. Two multinational trials were conducted to compare the efficacy of tolevamer, a nonantibiotic, toxin-binding polymer, with vancomycin and metronidazole.

Methods. Patients with CDI were randomly assigned in a 2:1:1 ratio to oral tolevamer 9 g (loading dose) followed by 3 g every 8 hours for 14 days, vancomycin 125 mg every 6 hours for 10 days, or metronidazole 375 mg every 6 hours for 10 days. The primary endpoint was clinical success, defined as resolution of diarrhea and absence of severe abdominal discomfort for more than 2 consecutive days including day 10.

Results. In a pooled analysis, 563 patients received tolevamer, 289 received metronidazole, and 266 received vancomycin. Clinical success of tolevamer was inferior to both metronidazole and vancomycin ($P < .001$), and metronidazole was inferior to vancomycin ($P = .02$; 44.2% [n = 534], 72.7% [n = 278], and 81.1% [n = 259], respectively). Clinical success in patients with severe CDI who received metronidazole was 66.3% compared with vancomycin, which was 78.5%. ($P = .059$). A post-hoc multivariate analysis that excluded tolevamer found 3 factors that were strongly associated with clinical success: vancomycin treatment, treatment-naive status, and mild or moderate CDI severity. Adverse events were similar among the treatment groups.

Conclusions. Tolevamer was inferior to antibiotic treatment of CDI, and metronidazole was inferior to vancomycin.

Trial Registration. clinicaltrials.gov NCT00106509 and NCT00196794.

Keywords. *Clostridium difficile*; infection; vancomycin; metronidazole.

Treatment of *Clostridium difficile* infection (CDI) has become increasingly problematic because of rising incidence [1], severity [2], and frequency of recurrences [3]. Historically, the 2 most commonly used therapeutic agents, metronidazole and vancomycin, were thought to be similar in efficacy [4, 5], although recurrences have been common following treatment with both agents. Clinical practice guidelines suggest that treatment should be chosen based on infection severity, with metronidazole being used for mild or moderate CDI and vancomycin for severe CDI [6, 7]. However, the data upon which these recommendations for treatment of severe CDI were based primarily came from a single-center, randomized comparison of oral metronidazole and

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[a]Present affiliation: Dartmouth Institute for Health Policy and Clinical Practice, Hanover, New Hampshire.

[b]Present affiliation: bluebird bio, Cambridge, Massachusetts.

Correspondence: Stuart Johnson, MD, Research Service, Hines VA Hospital, 5000 So. 5th Ave., Rm. C-344, Hines, IL 60141 (stuart.johnson2@va.gov).

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vancomycin in which patients with severe CDI who received vancomycin had improved cure rates [8].

CDI is a toxin-mediated disease, but antibiotic disruption of the indigenous host microbiota is usually a prerequisite for CDI infection. Antimicrobial treatments for CDI also affect the indigenous microbiota [9] and increase the risk of CDI recurrence. Therefore, a treatment strategy that is based on toxin neutralization without antibiotics may be beneficial. Tolevamer is a high-molecular-weight (≥400 kDa), soluble linear polymer of styrene-sulfonate that binds and neutralizes *C. difficile* toxins in vitro [10].

In the context of recent reports of metronidazole treatment failures [3, 11–14], the limitations of antibiotic treatment for the management of an antibiotic-induced disease, and the emergence of widespread nosocomial outbreaks of a CDI strain that produces high levels of toxins [15, 16], 2 studies were initiated to compare the efficacy and safety of tolevamer with that of metronidazole and vancomycin. Based on a promising phase 2 study in patients with mild to moderate CDI who showed a dose response for tolevamer with 3- or 6-g daily dosages [17], a 9-g dose was chosen, and the salt composition of the formulation was adjusted to minimize the risk of hypokalemia due to intestinal potassium binding to the anionic polymer. The efficacy and safety of vancomycin was also compared with that of metronidazole.

METHODS

Randomization

Two identical, phase 3, multicenter, randomized, double-dummy, double-blind, active-controlled, parallel-design efficacy studies enrolled patients at 91 sites in the United States and Canada (study 301, NCT00106509) and at 109 sites in Europe, Australia, and Canada (study 302, NCT00196794) between 2005 and 2007. In both studies, patients were randomly assigned in a 2:1:1 ratio to receive tolevamer (GT267-004; 9 g [45 mL of liquid] loading dose followed by 3 g [15 mL of liquid] every 8 hours for 14 days), vancomycin (one 125-mg capsule every 6 hours for 10 days), or metronidazole (one 375-mg capsule every 6 hours for 10 days).

Patients

Hospitalized or ambulatory patients aged ≥18 years with non–life-threatening medical conditions and confirmed primary CDI or presumed or confirmed recurrent CDI were screened. CDI was defined as 3 or more bowel movements in a 24-hour period (BM/day) with a loose or watery consistency, a positive *C. difficile* toxin assay result (enzyme immunoassay or cellular cytotoxicity assay) or pseudomembranes on endoscopy, and no other likely etiology for the diarrhea. Toxin confirmation was required within 72 hours prior to enrollment, except for patients who had been treated for a prior CDI episode within 30 days of enrollment. Those patients were presumed to have recurrent CDI until the diagnosis was confirmed with a positive toxin assay result within 24 hours following enrollment. Patients were excluded if they had fulminant CDI, intestinal ileus, vomiting more than twice in 24 hours, inability to swallow oral medication (protocol GD3-170-302 also allowed enteral feeding via nasogastric or jejunostomy tube), hypokalemia (serum $K^+ < 3.0$ mEq/L or serum $K^+ < 3.5$ mEq/L and a history of cardiac arrhythmias or currently receiving digoxin), continued exposure to CDI-inducing antibiotic(s) for more than 7 days, hepatic failure and biliary obstruction, diarrhea of other known cause, existence of active chronic diarrhea unrelated to CDI, more than 48 hours of oral vancomycin or intravenous or oral metronidazole or other effective alternate treatment for CDI within 5 days of enrollment, allergy to vancomycin or metronidazole, participation in an investigational drug study within 30 days, pregnancy or lactation, inability to abstain from alcohol during the 14-day treatment period, prior treatment with tolevamer, or presence of an acute life-threatening condition that would preclude completion of the study. Women of child-bearing potential were required to have a negative pregnancy test result and to use effective contraception for the duration of the study. Patients who were unable to voluntarily sign and date the written informed consent must have had a legally authorized representative willing to consent to all visits and procedures.

Assessments

After the 2-week treatment period, patients were followed for 4 weeks. The primary efficacy endpoint was clinical success, defined as resolution of diarrhea and absence of severe abdominal discomfort due to CDI for more than 2 consecutive days including day 10. Resolution of diarrhea was defined as attainment of bowel movements with a hard or formed consistency on average or 2 or fewer BM/day with a loose or watery consistency on average. The secondary endpoints included (a) the time to resolution of diarrhea (TTROD), defined as the beginning of diarrhea resolution that was sustained for the treatment period (10 days for metronidazole and vancomycin and 14 days for tolevamer), and (b) recurrence of CDI, defined as a confirmed CDI diagnosis during the 4-week follow-up period according to the criteria listed above in patients who had previously met the criteria for resolution of diarrhea. Assessments were made by blinded interviewers. Microbial methods are described in the Supplementary material.

Nonresponse was defined as an increase in diarrhea or increased abdominal discomfort for more than 48 hours, development of symptomatic ileus or toxic megacolon, persistent fever >38.6°C orally or 39°C rectally, or recurrence of diarrhea attributed to CDI while on study medication. Patients with persistent diarrhea for more than 6 days were evaluated by the investigator to determine if study medication should be continued. A change in therapy was scored as a failure. Safety assessments included clinical and laboratory adverse events.

The safety analysis set included all randomized patients who received any treatment. The full analysis set (FAS) included all randomized patients who received any treatment and had any post-dose evaluation. The per protocol set (PPS) was a subset of patients from the FAS who had 7 or more days of treatment and met all CDI diagnostic criteria described above and had no diagnosis or history at screening of active chronic diarrhea unrelated to CDI, had no diagnosis at screening or during study treatment of enteritis from pathogens other than *C. difficile* causing diarrhea, had ≤48 hours of antibacterial therapies specific for CDI (eg, vancomycin or metronidazole) within the 5 days preceding enrollment, and were compliant with study medication.

For each study, randomization of 464 patients in a 2:1:1 ratio to tolevamer, metronidazole, and vancomycin would provide 90% power to demonstrate noninferiority of tolevamer to vancomycin. Noninferiority was defined as tolevamer achieving a clinical success rate that was 10 percentage points less than that of control. This calculation was based on a 2-group, large-sample normal approximation test of proportions with a 2-sided, 5%, type I error rate, assuming a clinical success rate among control patients of 90%.

Data from the 2 clinical trials were combined with equal weight into a single dataset. Balance across studies among demographic and clinical attributes was evaluated for categorical factors with the Cochran–Mantel–Haenszel (CMH) test stratified by study and for continuous characteristics with 2-way analysis of variance. Efficacy outcomes were evaluated for association with demographic and clinical covariates as well as for differences due to treatment. CMH was also used to evaluate clinical success and recurrence, with stratification by levels of the covariate. The log-rank test was used to evaluate time to event data, such as TTROD and time to recurrence. Association between efficacy and treatment controlling for covariates was assessed via logistic regression. Unadjusted alpha of 0.05 was used as a threshold for statistical significance.

RESULTS

Analysis of Studies 301 and 302 Individually

A total of 1118 patients were randomly assigned to treatment in the 2 studies, 574 in the 301 study (safety set n = 558, FAS n = 543, PPS n = 471) and 544 in the 302 study (safety set n = 538, FAS n = 528, PPS n = 421; Figure 1). Because the analyses of PPS and FAS yielded similar results, we present the FAS results here, except where noted. Patients were similarly matched across the 3 treatment arms within each study (Table 1); however, there were differences between the studies in terms of age, body weight, inpatient status, and concomitant antibiotic use (Table 1). Patients in the 301 study were more likely to be infected with the BI strain of *C. difficile* (136 patients [34%] vs 40 patients [11%] among those with isolates typed; $P < .001$) than those in the 302 study. However, the overall distribution of BI, non-BI, and unknown strains (no isolates available for typing) was not significantly different between the 2 studies (Table 1). Additional description of *C. difficile* strain results is in the Supplementary material.

CDI characteristics were well matched across the treatment arms in both studies, including the duration of diarrhea, consistency of bowel movements, and severity of abdominal discomfort (Supplementary Table 1). CDI was confirmed by toxin immunoassay in 81.1% (869/1071), cell culture cytotoxicity in 14.8% (159/1071), and other laboratory tests (eg, rapid toxin tests, polymerase chain reaction) in 2.2% (24/1071); for the remaining 1.8% (19/1071), the confirmation method was by endoscopy or the specific assay documentation was missing. Endoscopy was performed in only 65 patients (6.1%), among whom pseudomembranes were seen in 36 (55%).

Tolevamer was inferior to both metronidazole and vancomycin with regard to clinical success in both studies (Figure 2*A*). Rates of clinical success for metronidazole were numerically lower than those for vancomycin in both studies, with this result reaching statistical significance in the PPS of the 302 study (87/112 [77.7%] vs 88/99 [88.9%], respectively; $P = .031$; Supplementary Table 2). In the FAS, the percentage of patients with severe CDI in the vancomycin group who achieved clinical success (28/33, 84.8%) was significantly greater than that of the metronidazole group (37/57, 64.9%; $P = .042$) in the 301 study but not in the 302 study (23/32 [71.9%] vs 24/35 [68.6%], respectively; Supplementary Table 2).

In both studies, TTROD for patients with diarrhea resolution was significantly longer in the tolevamer group compared with the metronidazole and vancomycin groups (Supplementary Table 2). The median (95% confidence interval) TTROD was 12 days (10, 13) for tolevamer, 5 days (4, 6) for metronidazole, and 5 days (4, 6) for vancomycin in the 301 study and 12 days (11, not estimable), 4 days (3, 6), and 4 days (4, 5), respectively, in the 302 study ($P < .001$; tolevamer vs metronidazole and vancomycin). However, CDI recurrence rates in patients who demonstrated diarrhea resolution were significantly lower for patients who received tolevamer compared with those who received both metronidazole and vancomycin ($P < .05$; Figure 2*C*).

Analysis of 301 and 302 Studies Combined

The pattern of clinical success in the combined 301/302 analysis was similar to that of the individual studies, with tolevamer inferior to both metronidazole and vancomycin (Figure 2*A*). The nonstatistically significant difference in clinical success with vancomycin compared with metronidazole that was observed in the individual studies was statistically significant in the combined analysis (clinical success: 202/278 [72.7%] vs 210/259 [81.1%] for metronidazole and vancomycin, respectively; $P = .02$). TTROD and time to CDI recurrence were prolonged with tolevamer compared with metronidazole and vancomycin

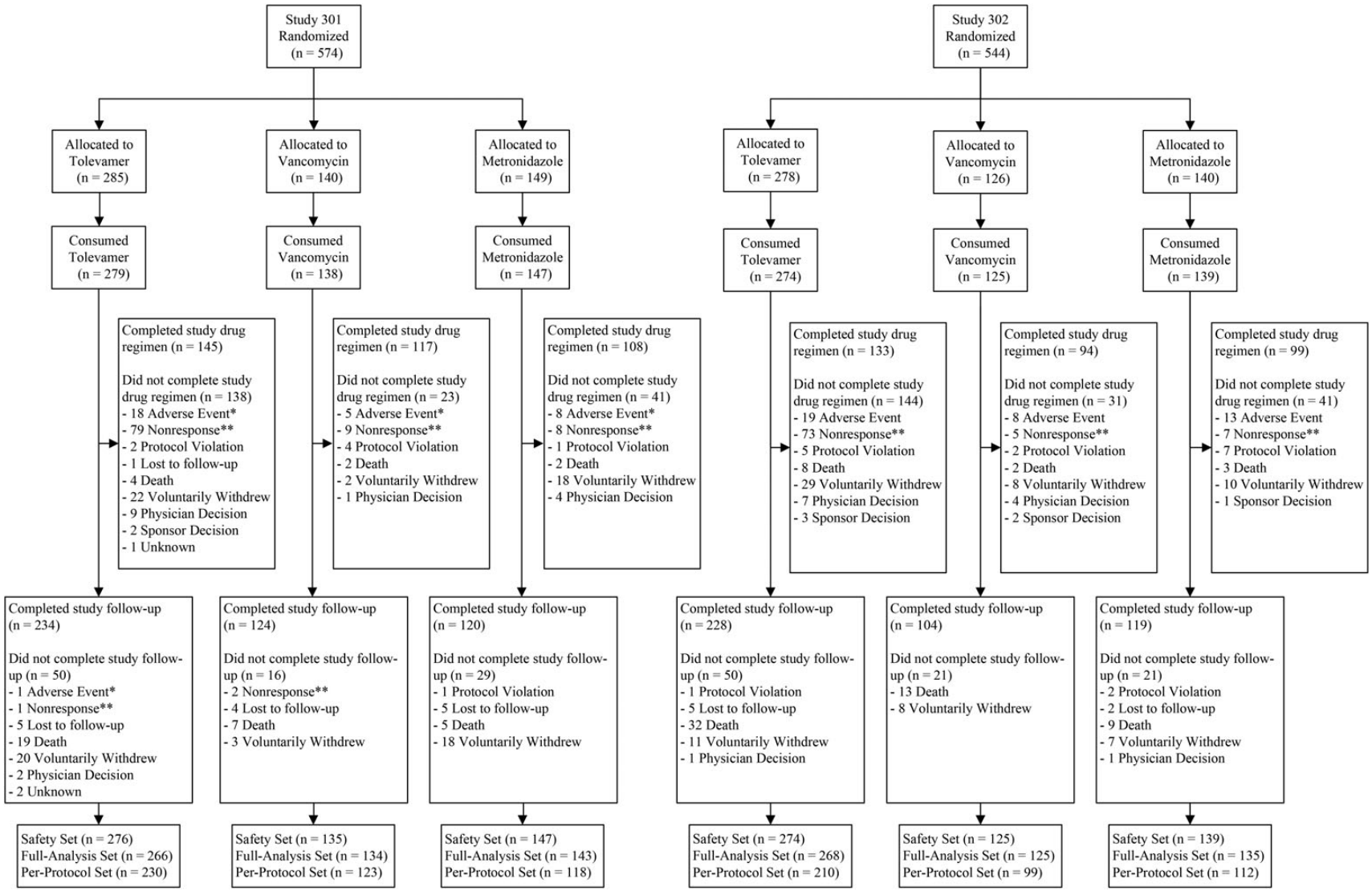

Figure 1. Patient disposition for study 301 and study 302. *, Adverse events could include recurrence of *Clostridium difficile* infection; **, patients may have had more than 1 indication of nonresponse.

Table 1. Study Populations and Demographics (Full Analysis Set)

	Study 301				Study 302				301 vs 302
	Tolevamer (n = 266)	Metronidazole (n = 143)	Vancomycin (n = 134)	Total 301 (n = 543)	Tolevamer (n = 268)	Metronidazole (n = 135)	Vancomycin (n = 125)	Total 302 (n = 528)	*P* Value
Age, y	62 ± 17.9	62 ± 17.9	62 ± 17.1	62 ± 17.7	69 ± 16.4	67 ± 15.8	67 ± 16.9	68 ± 16.4	<.0001
Mean ± SD (range)	(19–99)	(18–95)	(19–96)	(18–99)	(19–97)	(18–95)	(20–92)	(18–97)	
Age group, N (%)									
≤65	143 (54)	75 (52)	73 (54)	291 (54)	102 (38)	55 (41)	48 (38)	205 (39)	.98
>65	123 (46)	68 (48)	61 (46)	252 (46)	166 (62)	80 (59)	77 (62)	323 (61)	
Gender, N (%)									
Male	126 (47)	63 (44)	69 (51)	258 (48)	118 (44)	60 (44)	66 (53)	244 (46)	.14
Female	140 (53)	80 (56)	65 (49)	285 (52)	150 (56)	75 (56)	59 (47)	284 (54)	
Body Weight, kg Mean ± SD	76 ± 24	76 ± 27	73 ± 19	75 ± 24	68 ± 16	69 ± 18	68 ± 16	68 ± 17	<.0001
Inpatient, N (%)	157 (59)	79 (55)	70 (52)	306 (56)	242 (90)	125 (93)	115 (92)	482 (91)	<.0001
Treatment naive									
No	140 (53)	78 (55)	64 (48)	282 (52)	115 (43)	61 (45)	59 (47)	235 (45)	.81
Yes	126 (47)	65 (45)	70 (52)	261 (48)	153 (57)	74 (55)	66 (53)	293 (55)	
CDI history, N (%)									
Primary	182 (68)	99 (69)	103 (77)	384 (71)	222 (83)	109 (81)	105 (84)	436 (83)	.22
First recurrence	54 (20)	25 (17)	16 (12)	95 (17)	28 (10)	12 (9)	14 (11)	54 (10)	
Multiple recurrence	29 (11)	19 (13)	15 (11)	63 (11)	17 (6)	14 (10)	5 (4)	36 (7)	
Missing	1			1	1		1	2	
CDI severity,[a] N (%)									
Mild	76 (29)	33 (23)	27 (20)	136 (25)	82 (31)	42 (31)	48 (38)	172 (33)	.34
Moderate	95 (36)	53 (37)	73 (54)	221 (41)	125 (47)	58 (43)	45 (36)	228 (43)	
Severe	95 (36)	57 (40)	33 (25)	185 (34)	61 (23)	35 (26)	32 (26)	128 (24)	
Missing			1	1					
Concomitant antibiotic use,[b] N (%)									
No	208 (78)	121 (85)	109 (81)	438 (81)	209 (78)	104 (77)	78 (62)	391 (74)	.044
Yes	58 (22)	22 (15)	25 (19)	105 (19)	59 (22)	31 (23)	47 (38)	137 (26)	
Antibiotic use during follow-up, N (%)									
No	116 (44)	62 (43)	63 (47)	241 (44)	95 (35)	63 (47)	53 (42)	211 (40)	.22
Yes	150 (56)	81 (57)	71 (53)	302 (56)	173 (65)	72 (53)	72 (58)	317 (60)	
CD strain, N (%)									
BI	69 (26)	36 (25)	31 (23)	136 (25)	22 (8)	11 (8)	7 (6)	40 (8)	.89
Non-BI	125 (47)	70 (49)	69 (51)	264 (49)	162 (60)	79 (59)	71 (57)	312 (59)	
Unknown	72 (27)	37 (26)	34 (25)	143 (26)	84 (31)	45 (33)	47 (38)	176 (33)	

Protocol 301 study sites were in Canada and United States, and protocol 302 study sites were in Australia, Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Ireland, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

Abbreviations: CDI, *Clostridium difficile* infection; SD, standard deviation.

[a] CDI disease severity was categorized as mild (3–5 bowel movements [BM]/day; white blood cell counts [WBC] ≤ 15 000/mm^3; mild or absent abdominal pain due to CDI), moderate (6–9 BM/day; WBC, 15 001–20 000/mm^3; mild, moderate, or absent abdominal pain due to CDI); or severe (10 or more BM/day; WBC ≥ 20 001/mm^3; severe abdominal pain due to CDI). Any one of the defining characteristics could have been used to assign a severity category, and the more severe category was used when characteristics overlapped.

[b] Patients who received antibiotics other than vancomycin or metronidazole during the treatment period.

(Figure 3*A* and 3*B*). CDI recurrence patterns were similar to those observed in the individual studies (Figure 2*C*).

Clinical success and recurrence were also analyzed with respect to the following subgroups: age (≤ or >65 years), disease severity at screening, CDI history (primary CDI, first recurrence, or multiple recurrence), concomitant antibiotic use, antibiotic use during follow-up, and *C. difficile* strain (BI or non-BI; Supplementary Table 3). Disease severity was inversely

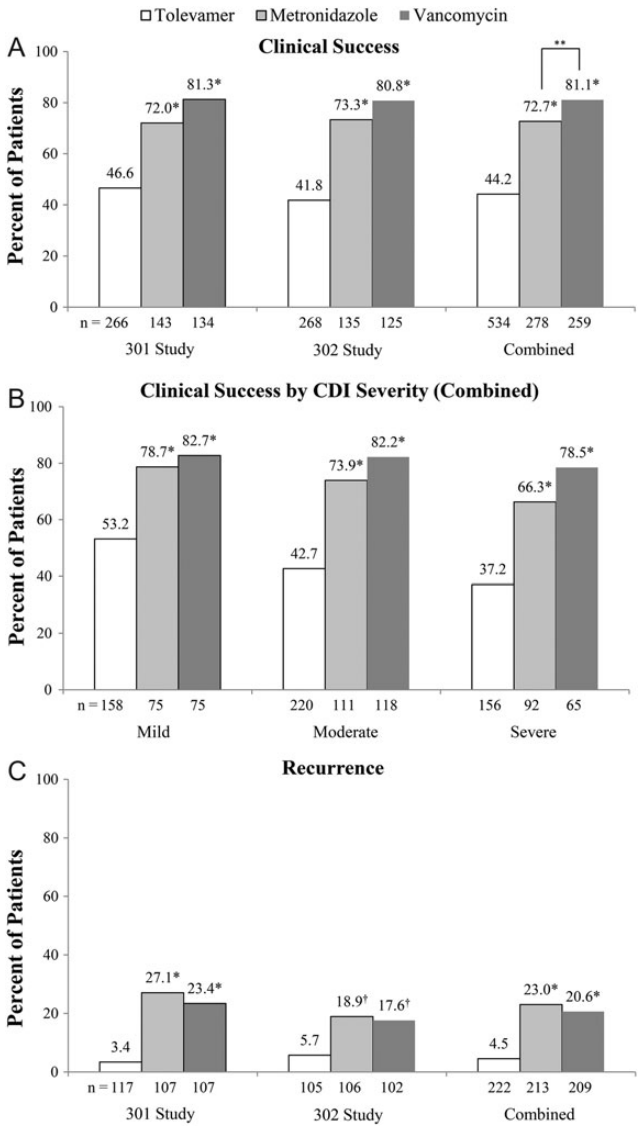

Figure 2. Clinical success in the 301, 302, and combined studies (A); clinical success by *Clostridium difficile* infection (CDI) severity in the combined studies (B); and recurrence in the 301, 302, and combined studies (C). All graphs present data from the full analysis set. CDI disease severity was categorized as mild (3–5 bowel movements [BM]/day; white blood cell counts [WBC] ≤15 000/mm^3; mild or absent abdominal pain due to CDI), moderate (6–9 BM/day; WBC, 15 001–20 000/mm^3; mild, moderate, or absent abdominal pain due to CDI); or severe (10 or more BM/day; WBC ≥20 001/mm^3; severe abdominal pain due to CDI). Any one of the defining characteristics could have been used to assign a severity category, and the more severe category was used when characteristics overlapped. *P < .001 for comparisons between tolevamer and metronidazole and between tolevamer and vancomycin. **P = .020 for comparison between metronidazole and vancomycin. †P < .05 for comparisons between tolevamer and metronidazole and between tolevamer and vancomycin.

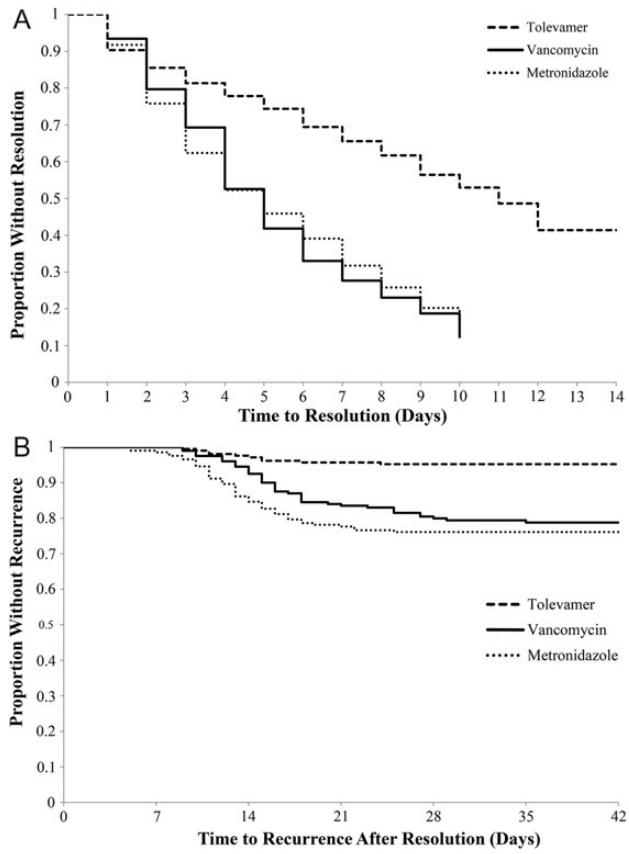

Figure 3. Kaplan–Meier graphs of time to resolution of diarrhea (A) and time to recurrence after resolution of *Clostridium difficile* infection (B) in the combined studies (full analysis set). Only patients with diarrhea resolution were included in these analyses. Patients whose diarrhea did not resolve at the end of treatment were censored at the end of the prescribed treatment period. Patients were followed for 28 days after treatment completion regardless of when diarrhea resolved. Therefore, the time to recurrence observation period could have been up to 42 days.

associated with clinical success in patients who received tolevamer (clinical success for mild, 53.2%; moderate, 42.7%; and severe disease, 37.2%; P = .015; Figure 2*B*; Supplementary Table 3). This association was not observed in those who received metronidazole or vancomycin, although the percentages for metronidazole were 78.7%, 73.9%, and 66.3% for mild, moderate, and severe disease, respectively (P = .19). Among patients with severe disease, 78.5% in the vancomycin group achieved clinical success compared with 66.3% in the metronidazole group (P = .059), both of which were greater than the rate in the tolevamer group (37.2%; P < .001 for both comparisons).

Among patients who were taking other antibiotics during the follow-up period, 13.0% in the tolevamer group, 46.2% in the metronidazole group, and 38.7% in the vancomycin group had recurrences of CDI, which was significantly greater than those who did not receive other antibiotics (P < .001 for all 3 treatment groups; Supplementary Table 3). Within each treatment group, there were no statistically significant differences

in the clinical success or recurrence of patients in subgroups of CDI history (primary, first recurrence, or multiple recurrences), concomitant antibiotic use during the treatment period, or *C. difficile* strain (BI or non-BI), except for the recurrence rate of subgroups of CDI history in the metronidazole group (Supplementary Table 3). The recurrence rates for primary CDI were 19% for both metronidazole (32 of 167 patients) and vancomycin (33 of 171 patients). The recurrence rates for the first recurrence and multiple recurrences were in the range of 25%–38%, but the differences between the subgroups were only statistically significant for metronidazole (primary CDI, 32 of 167 patients [19.2%]; first recurrence, 9 of 25 patients [36%]; multiple recurrences, 8 of 21 [38.1%]; $P = .040$; Supplementary Table 3).

Clinical Success Analysis of Vancomycin vs Metronidazole

While the studies were designed to draw inferences regarding tolevamer's efficacy, the resulting database also provides comprehensive information on the efficacy profile of metronidazole and vancomycin. In order to determine factors associated with clinical success among patients who received vancomycin or metronidazole, a post hoc logistic regression model was developed using 12 candidate variables (Figure 4*A*). The results showed that vancomycin treatment ($P = .013$), treatment naive status ($P = .0043$), primary CDI disease ($P = .039$), and mild or moderate CDI severity ($P = .045$) were significantly associated with clinical success. These 4 factors were included in a final model, which is illustrated in Figure 4*B*. The results showed that vancomycin treatment ($P = .034$), treatment naive status ($P = .0051$), and mild or moderate CDI severity ($P = .036$) were significantly associated with clinical success (Figure 4*B*).

Safety

The incidences of adverse events and serious adverse events were generally similar between the treatment groups (Table 2). The percentage of patients who discontinued study medication because of an adverse event was greater in the tolevamer group (25.5%) than in the metronidazole (11.2%) or vancomycin (6.5%) groups. Overall, 90 patients died during the study. All but 2 of these deaths, both in the tolevamer group, were considered by the investigators to be unrelated to study medication (Supplementary material). Twenty-two patients (4.0%) in the tolevamer group, 3 (1.0%) in the metronidazole group, and 12 (4.6%) in the vancomycin group had adverse events that could be indicative of nephrotoxicity, including renal failure, renal impairment, or increases in blood creatinine and urea levels.

DISCUSSION

Metronidazole and vancomycin have been the mainstays of antibiotic treatment for CDI over the last 30 years. Although a new antibacterial agent, fidaxomicin, was recently approved for this indication [18, 19], it is ironic that treatment of CDI continues to rely on antibiotics when this condition most commonly occurs as a result of the disruptive effect of antibiotics on the indigenous colonic microbiota. We report the results of 2 large, multicenter, randomized trials of a nonantibiotic, toxin-binding agent, tolevamer, compared with metronidazole and vancomycin.

Tolevamer was consistently inferior to both metronidazole and vancomycin for clinical success at the end of treatment. These results were apparent in both trials and in all secondary analyses, including analysis by disease severity, primary vs recurrent CDI, with or without concomitant antibiotic use, and infection with the epidemic BI strain. In addition, the TTROD was more than twice as long for tolevamer as for either of the antibiotic treatments. However, for the patients who did respond to tolevamer, the rate of recurrent CDI over the next 30 days was low (4.5%) and significantly lower than recurrence rates for either metronidazole (23.0%) or vancomycin (20.6%). These results suggest the possibility that treatment of CDI with an agent that is less likely to disrupt the gut microflora may result in a decreased rate of CDI recurrence. However, this conclusion must be tempered by the potential for selection bias, given the relatively small proportion of patients in the tolevamer group who achieved success and were evaluable for recurrence. These patients were also more likely to have mild disease than those in the other groups. In a previous study, the recurrence rates for metronidazole and vancomycin were also low (8% and 5%, respectively) in patients with mild disease [8]. Tolevamer showed insufficient benefit to be considered a viable treatment option. Disease severity clearly affected clinical response to tolevamer (Figure 2*B*). Indeed, in the phase 2 study [17], tolevamer (6 g daily) was noninferior to vancomycin, but this study population only included patients with mild or moderate disease.

The 2 trials were conducted using identical protocols but in different geographic locations, resulting in study population differences. Patients in the 301 trial, conducted exclusively in North America, were more likely to have had previous CDI episodes, severe CDI, and infection with the BI strain [20]. These data reflect the epidemiology of the BI/027/NAP1 strain, which is more widespread in North America [16, 21, 22] than in Europe [23, 24] where the 302 trial was primarily conducted. One finding in the 301 trial was that patients with severe CDI who were treated with vancomycin were more likely to have clinical success than those treated with metronidazole. This difference was not seen in the 302 trial, but the efficacy of vancomycin over metronidazole for severe CDI has also been described in a smaller randomized trial in the United States using a somewhat different definition for severity [8].

Despite these differences between the 2 trials, the 3 treatment arms were well matched in both studies, allowing us to combine the data into 1 analysis set with more than 250 patients in each treatment arm. Overall, the results demonstrated that

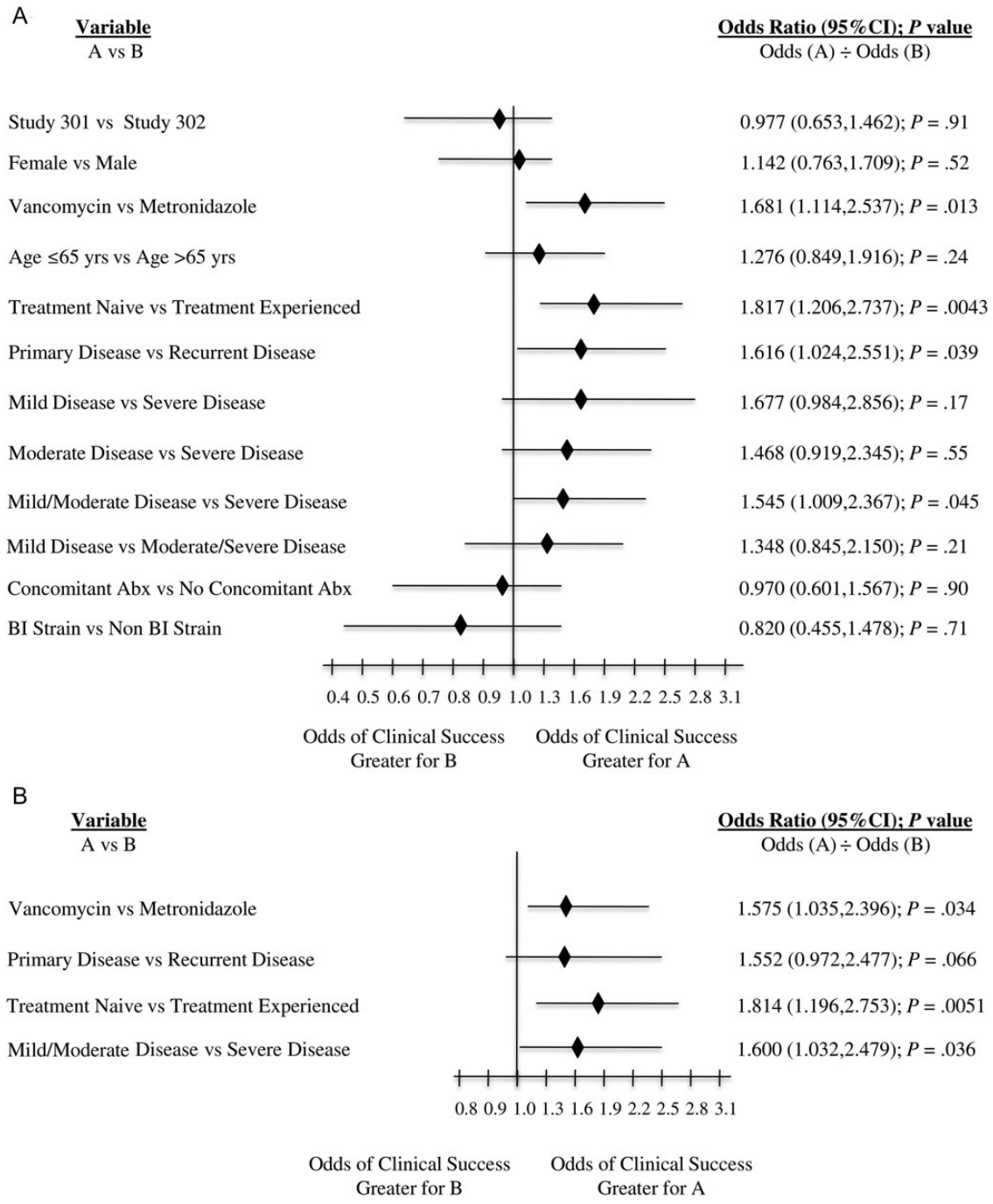

Figure 4. Univariate (A) and multivariate (B) logistic regression analysis of factors associated with clinical success for patients in the vancomycin and metronidazole groups (combined studies, full analysis set). Abbreviations: Abx, antibiotics; CI, confidence interval.

metronidazole was inferior to vancomycin for clinical success. In addition, clinical success in patients with severe disease was higher in those treated with vancomycin; however, this difference did not reach statistical significance ($P = .059$; Figure 2*B*). Although metronidazole is typically administered 3 times daily, it was administered 4 times daily in this study in order to maintain the blind. However, the total daily dose was consistent with that recommended in the guidelines [6]. Recurrence rates for metronidazole and vancomycin were similar and consistent with previous experience [4, 5]. Among the other secondary analyses, concomitant antibiotic use in the treatment period did not have an effect on clinical success or recurrence, but additional antibiotic use during the follow-up period was highly associated with CDI recurrence in all 3 treatment arms, highlighting the importance of antibiotic use in

Table 2. Summary of Adverse Events (Safety Analysis Set)

Adverse Event	Tolevamer, n = 550 (%)	Metronidazole, n = 286 (%)	Vancomycin, n = 260 (%)
Number of patients with 1 or more adverse event	487 (88.5)	249 (87.1)	226 (86.9)
Number of patients with 1 or more adverse event related to study medication	214 (38.9)	101 (35.3)	81 (31.2)
Number of patients who died	51 (9.3)	16 (5.6)	23 (8.8)
Number of patients who died because of an adverse event related to study medication	2 (0.4)	0	0
Number of patients with 1 or more serious adverse event	131 (23.8)	63 (22.0)	68 (26.2)
Number of patients with 1 or more serious adverse event related to study medication	16 (2.9)	3 (1.0)	3 (1.2)
Number of patients who discontinued study medication because of an adverse event	140 (25.5)*	32 (11.2)**	17 (6.5)***
Number of patients who discontinued study medication because of an adverse event related to study medication	67 (12.2)*	18 (6.3)**	7 (2.7)****

* $P < .001$ for comparisons of tolevamer vs vancomycin.

** $P < .01$ for comparisons of tolevamer vs metronidazole.

*** $P = .058$ for comparison of metronidazole vs vancomycin.

**** $P = .044$ for comparison of metronidazole vs vancomycin.

the recurrence of CDI, as has been shown in other clinical trials of CDI treatment [25].

Because tolevamer failed to meet the primary clinical endpoint, clinical success at day 10, in comparison with either comparator arm, we performed an additional post hoc analysis of the factors that contributed to clinical success in the vancomycin and metronidazole treatment arms. In a logistic regression analysis of 12 variables that might affect or confound the outcome of clinical success, 3 were identified to be significantly associated with clinical success. These include treatment with vancomycin, treatment naive status (no treatment prior to starting study drug), and mild or moderate CDI severity at study entry.

In summary, the nonantibiotic, toxin-binding agent tolevamer was not effective in treatment of CDI when compared with the antibiotic treatment arms. It is possible that this agent could be studied as an adjunctive treatment following standard antibiotic treatment for CDI, but these data do not support a luminal toxin-binding approach with tolevamer as monotherapy for CDI. These were the largest randomized, controlled trials of vancomycin and metronidazole, and the results are consistent with other data [8, 11–13] showing the lower efficacy of metronidazole compared with vancomycin in the treatment of CDI. This difference in efficacy was most evident in the subset of severe CDI patients (Figure 2*B*) and supports the most recent recommendations in the United States [6, 7] and Europe [26] to use vancomycin as first-line therapy for severe CDI.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. S. J., T. J. L., D. M. D., D. N. G., O. A. C., and S. C.-T. contributed to the study conception and design. As study investigators, S. J., T. J. L., D. N. G., and O. A. C. were involved with data acquisition. S. C.-T. and D. F. conducted the data analysis. All authors contributed substantially to data interpretation, participated in the drafting of the article, and approved the final version before submission.

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Potential conflicts of interest. S. J., T. J. L., D. N. G., and O. A. C. were investigators in the studies and their institutions received funding from Genzyme to conduct the studies. D. N. G. holds patents for the treatment and prevention of CDI licensed to ViroPharma and has received consulting fees from ViroPharma. O. A. C. was supported by the German Federal Ministry of Research and Education (BMBF grant 01KN1106) and has received research grants from, is an advisor to, or received lecture fees from 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cubist, F2G, Genzyme, Gilead, GlaxoSmithKline, Merck/MSD, Miltenyi, Optimer, Pfizer, Quintiles, Sanofi Pasteur, and ViroPharma. D. M. D. and S. C.-T. were Genzyme employees at the time the studies were conducted and owned Genzyme stock and/or stock options. The current affiliation of D. M. D. is bluebird bio in Cambridge, MA. The current affiliation for S. C.-T. is the Dartmouth Institute for Health Policy and Clinical Practice, Hanover, NH. D. F., S. P. G., and C. B. are

employees of ViroPharma Incorporated and own ViroPharma stock and/or stock options.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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