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Sustained Clinical Response as an Endpoint in Treatment Trials of *Clostridium difficile*-Associated Diarrhea

Stuart Johnson,[a] Dale N. Gerding,[a] Thomas J. Louie,[b] Nancy M. Ruiz,[c] and Sherwood L. Gorbach[c,d]

Research Service, Hines Veterans Affairs Hospital, and the Department of Medicine, Division of Infectious Diseases, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, USA[a]; University of Calgary, Calgary, Alberta, Canada[b]; Optimer Pharmaceuticals, Inc., San Diego, Californua, USA[c]; and Department of Medicine, Tufts Medical Center, Boston, Massachusetts, USA[d]

Recurrence of diarrhea following initially successful treatment is a major shortcoming in the treatment of *Clostridium difficile*-associated diarrhea (CDAD). Sustained response is a clinical endpoint proposed to account for differences among treatment agents with respect to a combination of initial response/cure and recurrence.

Until recently, vancomycin was the only FDA-approved treatment for *C. difficile* infection (CDI). Treatment guidelines have recommended metronidazole for a first occurrence of nonsevere CDI and for a first relapse or reinfection (2, 3, 4). Vancomycin and metronidazole are both effective in providing initial response, with ≥85% cure rates, but 20 to 40% of patients whose symptoms resolve have recurrent disease caused by relapse of the original infection or reinfection from external sources (2, 3, 4). In parallel with changes in strain prevalence and severity of disease, clinical response rates have changed with metronidazole during the last decade, with a reduced initial response, longer time to resolution of diarrhea, and an increased rate of recurrence (15, 17).

Most clinical trials for new agents to treat CDAD have used cure/resolution of diarrhea and/or time to resolution of diarrhea as the primary outcomes. In 2006, a trial of nitazoxanide versus metronidazole introduced sustained responses at 31 days after the first dose of treatment as an additional endpoint (16). Initial response was assessed within the span of days 11 to 13, allowing an additional 18 to 20 days for documenting recurrences. Recurrence generally occurs within 7 to 14 days after cessation of therapy with vancomycin or metronidazole (1, 7, 14). In one study, mean time to relapse with the same strain was reported as 14.5 days and mean time to reinfection with another strain was 42.5 days after the end of treatment for the preceding episode (9). Relapse and reinfection can be difficult to distinguish, since infection with more than one strain has been reported rarely (6, 22) and the same or a new strain may be acquired from the environment. In addition, recurrence with the same strain may be more common among patients infected with the epidemic BI/NAP1/027 strain (7, 10). Because of the high rate of recurrence, an agent that provides both initial clinical cure and a sustained response is desirable.

Fidaxomicin was recently approved for the treatment of CDAD on the basis of noninferiority to vancomycin for an initial cure at the end of therapy and superiority for a sustained response 25 days after therapy. This agent, which achieves high stool concentrations and which is highly active against clinical isolates of *C. difficile* (MIC_{90} of ~0.125 mg/ml), has a narrow spectrum of activity with minimal impact on bacterial species in the microbiome which are thought to provide colonization resistance in the colon (12, 20). Preservation of the commensal flora is thought to reduce the risk of relapse from persistent spores in the gut or reinfection from the environment.

In this paper, we contrast data from two phase 3 trials comparing fidaxomicin to vancomycin (5, 13) and from the first phase 3 trial comparing a toxin-binding polymer and metronidazole (11). These data are analyzed using the new endpoint, sustained clinical response, which may provide an additional, clinically meaningful benchmark for practitioners treating patients with CDAD.

Fidaxomicin clinical trials. Two phase 3 randomized, controlled, double-blind trials enrolled patients at multiple sites in the United States, Canada, and Europe and compared fidaxomicin (200 mg twice daily for 10 days) with vancomycin (125 mg four times daily for 10 days) (5, 13). Patients may have had no more than one prior episode of CDAD within the 3 months prior to randomization. The primary outcome was the clinical response (or cure) rate determined at the end of therapy and was based upon improvement in diarrhea or other symptoms such that, in the investigator's judgment, further CDAD treatment was not needed. The protocol-specified exploratory endpoint in study 003 and the secondary endpoint in study 004 was global cure, currently referred to as the sustained clinical response. Sustained clinical response was defined as the clinical response at the end of therapy followed by survival without proven or suspected CDAD recurrence through 25 days beyond the end of therapy.

The primary analysis was based on the modified intention-to-treat (mITT) population, which included all patients who met inclusion criteria for diarrhea (>3 unformed bowel movements per 24 h and toxin A or B in stool) and who received at least one dose of the study drug. The mITT analysis included patients regardless of compliance in order to preserve randomization and prevent bias. A one-sided, lower, 97.5% confidence interval (CI) was used in the analysis of the rate of clinical cure (or clinical response at the end of therapy), with a noninferiority margin of −10%. Sustained clinical response was analyzed using two-sided tests of population proportions, with an α value of 0.05. Missing sustained clinical response outcomes were imputed by a multiple-imputation method, and 25 imputed data sets were averaged to estimate treatment effects (8, 18, 19, 21). A logistic model predicted the probability of a sustained clinical response for each patient using the following covariates: treatment assignment,

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Address correspondence to Stuart Johnson, stuart.johnson2@va.gov.

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TABLE 1 Clinical response rates at the end of therapy in the combined phase 3 fidaxomicin trials and the first phase 3 tolevamer trial[a]

Trial	No. cured/total no. in group (%)		Difference (%) (95% CI)
	Study drug	Comparator	
Fidaxomicin vs vancomycin	477/542 (88)	485/563 (86)	1.9 (−2.1 to 5.8)
Tolevamer vs metronidazole	124/266 (47)	103/143 (72)	−25.4 (−34.9 to −15.9)

[a] mITT (modified intent-to-treat analysis) was used for the fidaxomicin and vancomycin trials; FAS (full analysis set) was used for the tolevamer and metronidazole trial.

TABLE 2 Estimated sustained clinical response rates at 25 days after end of therapy in the combined fidaxomicin trials and the tolevamer trial[a]

Trial	Sustained response rate (%) (*n*)		Difference (%) (95% CI)
	Study drug	Comparator	
Fidaxomicin vs vancomycin	71 (542)	57 (563)	14.0 (8.4 to 19.6)
Tolevamer vs metronidazole	45 (266)	52 (143)	−6.6% (−16.8 to 3.5)

[a] mITT (modified intent-to-treat analysis) was used for the fidaxomicin and vancomycin trials; FAS (full analysis set) was used for the tolevamer and metronidazole trial.

study, study center, sex, race, age, weight, height, body mass index (BMI), subject status, prior CDAD episodes, daily number of bowel movements at baseline or baseline disease severity, diarrhea alone or with other symptoms, prior use of CDAD antibiotics, metronidazole failure, number of study days in the treatment phase, diarrhea at follow-up visits after cure, and serum albumin concentrations of <2.5 g/dl or ≥ 2.5 g/dl.

The mITT population of the combined fidaxomicin trials comprised 1,105 patients, with 542 treated with fidaxomicin (289 in study 003 and 253 in study 004) and 563 treated with vancomycin (307 in study 003 and 256 in study 004). The end-of-therapy clinical response rates for the combined trials were 88% (447/542) for fidaxomicin and 86% (485/563) for vancomycin (Table 1). There was no significant difference in initial response rates between the two treatments (1.9% difference; 95% CI, −2.1 to 5.8). Fidaxomicin response rates were 88% in study 003 and 88% in study 004, compared with 86% and 87%, respectively, for vancomycin.

Between the two trials, 962 of 1,105 patients were cured and 194 cured patients had a return of symptoms and a positive toxin test. Of the 768 remaining cured patients, 692 (90%) were followed for at least 25 days and were evaluable for sustained responses at day 25. Sustained response assessments were imputed for 64 patients who (i) died during the study, (ii) received concomitant medication to treat CDAD during treatment or follow-up, and/or (iii) had an end-of-study assessment earlier than day 25 of the follow-up. The sustained response rate for fidaxomicin in the combined studies (71%) was higher than the response rate for vancomycin (57%), a difference of 14.0% (95% CI, 8.4 to 19.6) (Table 2). These differences in sustained response were significant in both fidaxomicin studies. In study 003, the sustained response rate was 70% for the fidaxomicin treatment group, compared with 57% for the vancomycin group (95% CI, 4.4 to 20.9). Similarly, in study 004, sustained response rates were 72% following fidaxomicin treatment and 57% after vancomycin (95% CI, 5.8 to 23.3).

Tolevamer clinical trial. Results of the first randomized phase 3 trial of the toxin-binding polymer tolevamer have been presented in abstract form (11) and are included here to illustrate results or outcomes using the endpoint of a sustained response when comparing two agents that are not equivalent in clinical cure at the end of treatment. Like the fidaxomicin trials, tolevamer was studied in large, phase 3, industry-sponsored trials. In these studies, patients were randomized to a 2-week treatment period of tolevamer (9-g loading dose, followed by 3 g three times daily for 14 days), vancomycin (125 mg four times daily for 10 days), or metronidazole (375 mg four times daily for 10 days) and followed for 4 weeks after treatment completion. Although the study design was similar to that of the fidaxomicin trials, patients with more than one CDAD recurrence were allowed in the tolevamer trials. We include only the results of the tolevamer and metronidazole arms for the full analysis set (FAS) defined as all randomized patients who received at least one dose of study medication and had any postdosing investigator evaluation data. Sustained clinical response was reported using the same analysis that was used for global cure in the first phase 3 study of fidaxomicin (13) but without the multiple-imputation method used in the fidaxomicin trial analysis.

In contrast to the fidaxomicin/vancomycin trials, the clinical response at the end of therapy in the FAS population from the tolevamer trial showed that tolevamer was inferior to metronidazole. The cure rate for tolevamer was only 47% (124/266), compared to an initial cure rate of 72% (103/143) for metronidazole (−25.4% difference; 95% CI, −34.9 to −15.9) (Table 1). However, the calculated sustained response in the tolevamer trial showed no significant difference between tolevamer and metronidazole despite the inferior cure rate for tolevamer at the end of treatment; the sustained response rates 4 weeks after treatment completion were 45% for tolevamer and 52% for metronidazole (−6.6% difference; 95% CI, −16.8 to 3.5) (Table 2).

Summary. Based on the results of the 003 and 004 phase 3 trials, fidaxomicin was approved by the U.S. Food and Drug Administration (FDA) for the treatment of CDAD in patients at least 18 years of age. The results first support the noninferiority of fidaxomicin to vancomycin for the initial clinical response but also support superiority for a secondary endpoint of sustained clinical response at 25 days after completion of therapy. Sustained clinical response after completion of therapy both is practical for clinical trial design and can be clinically meaningful for patients and physicians. Sustained clinical response is a combination of the initial response rate or cure rate with treatment, with subtraction of the recurrence rate in the initial weeks following treatment, the period of highest risk for recurrence. For the evaluation of clinical trial results, the sustained response rate endpoint maintains the initial randomization of the trial, whereas the population evaluated only for recurrence is no longer randomized, i.e., patients who did not achieve an initial cure are no longer included in the recurrence analysis.

The FDA approval process for fidaxomicin involved additional analysis of the sustained response endpoint to account for patient dropout or "missing data." In these studies, among patients who achieved the primary outcome of clinical response at the end of therapy without the need for further CDAD treatment for the remainder of the study period, 90% were evaluable for sustained

responses at 25 days after completing the study drug treatment. However, patients who received treatment for CDAD during follow-up without CDAD recurrence confirmed, who died during the study, or whose last study assessment was before day 25 of follow-up were considered to be "missing" for this endpoint. Responses for this group of 6% (64/1,105) of patients in the mITT population were determined by a multiple-imputation method, with the average of 25 iterations of imputed and confirmed responses as the sustained clinical response rate.

For agents such as vancomycin and fidaxomicin, which have similar initial response rates (86% and 88%), the higher sustained response rate is reflected by the lower recurrence rate with fidaxomicin. However, if two agents differ in both initial response and recurrence rates, they could have a similar sustained response rate but be quite different. For example, in the first phase 3 trial comparing a toxin-binding polymer (tolevamer) with standard therapy for CDAD, the clinical success rate at the end of treatment for tolevamer was clearly inferior to those of both metronidazole and vancomycin (11). However, the recurrence rate for patients who responded to tolevamer was much lower than the recurrence rate for either of the standard treatment agents. Analyzing the available data on tolevamer and metronidazole in this study and making similar assumptions for a sustained response rate, the outcomes for tolevamer and metronidazole were not significantly different (Table 2). This example supports the importance of knowing both the cure rate and the recurrence rate when interpreting sustained response rates in the evaluation of future trials of therapeutic agents for CDAD.

In conclusion, treatment with fidaxomicin instead of vancomycin in two clinical trials resulted in 12.7% and 14.6% absolute increases (22.8% and 26.3% relative increases, respectively) (P value of <0.001 for comparing the two drugs in both trials) in sustained clinical responses at 25 days after completing therapy in patients with CDAD in North America and Europe. Sustained clinical response is a useful measure of CDAD treatment outcome when comparing agents for which the initial clinical responses are similar. Caution is required in comparing agents with dissimilar initial response rates and dissimilar recurrence rates, since they may have similar sustained response rates but differ markedly in clinical interpretation.

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