

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

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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 $\geq 85\%$ 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* (MIC₉₀ 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,

Published ahead of print 21 May 2012

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doi:10.1128/AAC.00605-12

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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.

ACKNOWLEDGMENTS

Statistical assistance was provided by Yin Kean and writing assistance was provided by Sharon Dana, both employees of Optimer Pharmaceuticals, Inc.

The studies were funded by Optimer Pharmaceuticals, Inc. S.J. and D.N.G. receive support from the U.S. Department of Veterans Affairs Research Service.

S.J. is a consultant for ViroPharma, Optimer, Astellas, Pfizer, Cubist, and Bio-K+. D.N.G. holds patents for the treatment and prevention of CDI that are licensed to ViroPharma, is a consultant for ViroPharma, Optimer, Cubist, Merck, Pfizer, TheraDoc, Astellas, Novartis, BioRelix, and Actelion, and holds research grants from Actelion, GOJO, Merck, Optimer, Sanofi Pasteur, Eurofins Medinet, and ViroPharma. T.J.L. has received honoraria/consultancy support from Optimer, Merck, Cubist, Viropharma, Cembra, and Iroko. N.M.R. is an employee of Optimer Pharmaceuticals, Inc. S.L.G. is an employee of Optimer Pharmaceuticals, Inc., and a consultant for Cembra Pharmaceuticals, Inc.

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