EDITORIAL

Bezlotoxumab — A New Agent for *Clostridium difficile* Infection

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Clostridium difficile was identified in 1976 as the cause of "clindamycin colitis" in a study of the hamster model of the disease. That work led to the identification of toxin A ("cytotoxin") and toxin B ("enterotoxin"), oral vancomycin for treatment, and the problem of relapsing disease.[1]

C. difficile infection has subsequently become a major health problem in the United States and much of the world, fueled in part by the global epidemic of the NAP-1 strain (ribotype 027). However, the extensive use and abuse of antibiotics are also implicated, especially the often unnecessary use of fluoroquinolones and second-generation and third-generation cephalosporins, which are the major causes of *C. difficile* infection.[2] Data from the Centers for Disease Control and Prevention for 2011 showed an annual toll in U.S. health care facilities that was estimated to be 453,000 cases, 83,000 recurrences, and 15,000 deaths, with an annual cost of approximately $40 billion.[2,3]

Efforts to prevent *C. difficile* infection have been extensive and have included the introduction of fidaxomicin, which is associated with reduced rates of relapse,[4] as well as several new drugs that are currently being evaluated in trials, including ridinilazole, surotomycin, cadazolid, RBX2660, and SER-109. Also under evaluation is the oral administration of nontoxigenic *C. difficile* organisms to compete with toxigenic strains, as well as three vaccines (currently in clinical trials) consisting of formalin-inactivated toxins A and B, recombinant toxins A and B, and a genetically modified recombinant toxin protein.[5,6]

This issue of the *Journal* includes a report[7] of the results of two phase 3 trials, MODIFY I and MODIFY II, that were designed to evaluate bezlotoxumab (which provides passive immunity to toxin B), actoxumab (which provides passive immunity to toxin A), and the combination of these agents in comparison with placebo (the actoxumab-only regimen was discontinued after an interim analysis and was included only in MODIFY I). Bezlotoxumab has been shown by x-ray crystallography to neutralize toxin B by blocking its binding to host cells.[8] Actoxumab presumably blocks the activity of toxin A by the same mechanism. In both trials, the experimental treatment regimens were compared with placebo among participants who were receiving standard-of-care therapy with oral vancomycin, metronidazole, or fidaxomicin. The study was well designed, with a randomized, blinded trial format and a sample size of 2655 participants at 322 sites in 30 countries. The results showed that bezlotoxumab achieved a significant benefit over placebo; the rates of recurrent infection in MODIFY I were 17% versus 28%, favoring bezlotoxumab ($P<0.001$); in MODIFY II, the rates were 16% versus 26%, also favoring bezlotoxumab ($P<0.001$). Both the bezlotoxumab regimen and the actoxumab–bezlotoxumab regimen had good safety profiles without substantial adverse reactions; diarrhea and nausea were the most common adverse events (each occurred in 5.9% of the combined sample of participants from the actoxumab–bezlotoxumab, bezlotoxumab, and placebo groups).

Bezlotoxumab has now been approved by the Food and Drug Administration (FDA) and will be available to clinicians for the management of *C. difficile* infection. The benefit of bezlotoxumab treatment appears to be a risk of first post-treatment relapse that is nearly 40% lower than

that associated with standard treatment alone. Use of this agent will need to be viewed in comparison with alternative options, including the new drugs and vaccines that are currently being evaluated in trials for the treatment and prevention of *C. difficile* infection. There are several important issues that are unresolved and need to be addressed to place this drug in perspective. Particularly important will be relative risk stratification and product cost. It is unfortunate that the analysis did not define which patients benefited most; in addition, we do not fully understand the relative benefits and risks associated with each combination of standard antibiotic with bezlotoxumab. The assessment of bezlotoxumab combined with fidaxomicin is particularly important, since this agent has already been shown to have substantial clinical success and cost effectiveness for preventing relapses of *C. difficile* infection in patients with primary infection.[4] For patients with relapsing *C. difficile* infection, stool transplantation has also proved highly successful, but this treatment is generally reserved for patients who have had multiple relapses.[9]

The cost issue obviously looms large, given the realities of contemporary medical care and specifically the experience with fidaxomicin.[10] Thus, determining the cost-effectiveness of bezlotoxumab as compared with alternative treatment strategies will be important. This analysis must account for variations, particularly in certain subgroups of patients, such as those with a high risk of relapse because of age (older than 65 years), concurrent antacid treatment, severe *C. difficile* infection, renal failure, or a need for concurrent antibiotic treatment.[11] The results of some of these analyses may well be embedded in this very large trial and may become known after subsequent analyses. One possible advantage of bezlotoxumab treatment is that it provides passive immunity to a microbial product and therefore is not subjected to the risk of antibiotic resistance. Nevertheless, it is noteworthy that *C. difficile* resistance to standard antibiotic therapy has not been problematic, despite extensive use of these agents.

In conclusion, bezlotoxumab is a new, now-FDA-approved anti–*C. difficile* agent that has proved effective in reducing the rate of first post-treatment relapses of *C. difficile* infection; however, uptake by clinicians will vary on the basis of cost and assessments of relapse risk in association with this drug as compared with the alternative options.

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

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