

## Bezlotoxumab for Prevention of Recurrent *C. difficile* Infection in High-Risk Patients



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Recurrence of *Clostridioides difficile* infection (CDI) is a common occurrence and significantly increases hospitalizations, inpatient cost, morbidity, and mortality. While metronidazole, vancomycin, and fidaxomicin are approved for treatment, bezlotoxumab is the first drug approved by the FDA to prevent CDI recurrences. Results of phase 3 clinical trials from a pooled data set revealed that sustained cure from recurrence of CDI at 12 weeks was significantly higher in the bezlotoxumab group (63.5% [496/781]) in comparison to the placebo group (53.7% [415/773]). The number needed to treat in patients older than 65 years of age with recurrent CDI is six. Real-world data from a multicenter retrospective cohort study of 200 patients across 34 outpatient infusion centers in the United States revealed the overall CDI recurrence rate after a single infusion of bezlotoxumab was comparable to CDI recurrence reported for the overall population enrolled in the MODIFY I and II phase 3 clinical trials. Considering the high cost of bezlotoxumab, identifying a high-risk target population is essential to make this treatment cost-effective.

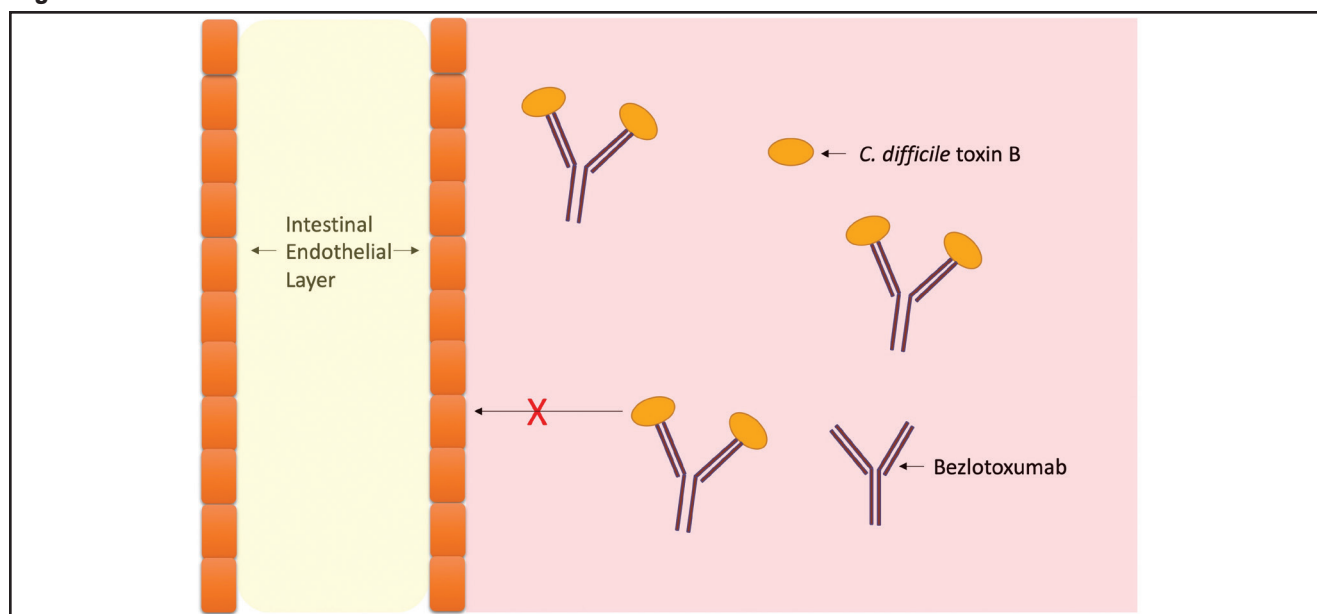
**C***lostridioides* (formerly *Clostridium*) *difficile* is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus which, in developed countries, is the leading cause of infectious diarrhea in hospitalized patients.<sup>1,2</sup> Disruption of healthy gastrointestinal tract flora by antibiotics leads to loss of colonization resistance and opportunistic infection with *C. difficile*.<sup>3</sup> Over the last decade, there has been a rise in *Clostridioides difficile* infection (CDI) related hospitalizations, healthcare costs, morbidity, and mortality; furthermore, approximately 30% of patients develop recurrent

CDI after completing initial antibiotic therapy. Those who have suffered a previous recurrence have an increased risk of further recurrences, up to 60% after a third CDI episode.<sup>4,5</sup> Other important risk factors for CDI recurrence are age > 65 years, immunosuppressive disease state or therapy, and antibiotic use.

Toxigenic strains of *C. difficile* produce two potent exotoxins: toxin A and toxin B, which are responsible for mucosal injury, acute inflammation (colitis), and diarrhea.<sup>5-7</sup> Toxin B is ten times more potent than toxin A and thus, strains that do not produce toxin A can be as virulent as strains producing both toxin A and B.<sup>8</sup> A “hypervirulent” strain, NAP1/BI/027, produces an additional binary AB toxin called CDT. CDT toxin results in the breakdown of gut wall promoting adherence of

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**Figure 1. Mechanism of Action of Bezlotoxumab**


bacteria and increased uptake of toxin A and toxin B. Additionally, loss of TcdC function in NAP1/B1/027 leads to hyperproduction of toxin A 16 times and toxin B 23 times by down-regulating feedback inhibitor associated with halting toxin A and B production.<sup>9</sup> Moreover, increased spread and survival of this strain have also been associated with increased sporulation, also called hypersporulation.<sup>10</sup> Thus this strain has been associated with severe disease requiring intensive care unit admissions, colectomy, and significantly higher mortality rates.<sup>5,6</sup>

Host immunity (passive or active) to *C. difficile* toxins may play an essential role in the severity of symptoms or risk of recurrence. Higher levels of anti-toxin A and anti-toxin B antibodies have been correlated with a protective effect against primary and recurrent *Clostridioides difficile* infection (rCDI).<sup>11-13</sup>

Multiple medications, including metronidazole, vancomycin, and fidaxomicin, are used to treat primary disease, but these do little to prevent CDI recurrence.<sup>14</sup> Fidaxomicin may result in a lower incidence of rCDI when used early in patients with a non-NAP1/B1/027 strain; however, when compared to oral vancomycin, it does not appear to be more effective for the treatment of mild to moderate CDI.<sup>15</sup> Fecal microbiota transplantation (FMT) has demonstrated high cure rates for rCDI, but regulatory questions, lack of long-term safety

data, and the absence of standardized techniques for delivery of fecal microbiota has limited widespread application of FMT.<sup>16,17</sup>

With this in mind, a human monoclonal antibody against *Clostridioides difficile* toxin A (actoxumab) and toxin B (bezlotoxumab), were pursued as therapeutic agents to prevent rCDI in addition to the antibiotic therapy.<sup>18</sup> After nine clinical trials, bezlotoxumab (BEZ; Zinplava), a novel agent, was approved by the FDA in 2016.<sup>7,12,19-24</sup>

## PHARMACOLOGY

Bezlotoxumab (BEZ) is an IgG1 immunoglobulin (human monoclonal antibody) that binds to toxin B and prevents it from entering the gastrointestinal cell layer preventing colonic cell damage (Figure 1).<sup>19,25,26</sup> Bezlotoxumab does not bind to toxin A of *Clostridioides difficile*. There is a low potential for drug-drug interaction as bezlotoxumab is eliminated by catabolism. The long plasma half-life of 19 days allows the single-dose administration of bezlotoxumab to prevent rCDI. Ethnicity, gender, race, age, and comorbid conditions did not affect bezlotoxumab exposure. No dose adjustment is required in patients with renal or hepatic impairment.

There are no contraindications to bezlotoxumab, but caution is advised for use in patients with a history of congestive heart failure (CHF).<sup>27,28</sup> Per phase 3 clinical trials during the 12-week study

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period, a group of patients with a history of CHF treated with bezlotoxumab had a higher incidence of worsening CHF and adverse outcomes than the group of patients with a history of CHF treated with placebo.<sup>12</sup> Based on these studies, it is not clear whether congestive heart failure was well controlled in these patients before administering bezlotoxumab or not.

**CLINICAL TRIALS**

**Phase 1 and 2**

After five, phase 1 trials evaluated the safety and efficacy of bezlotoxumab, a single dose of 10 mg/kg to be administered intravenously over 60 mins were recommended.<sup>21,22,29</sup>

The first phase 2 trial was terminated early as animal data revealed that a combination of bezlotoxumab and actoxumab, a human monoclonal antibody that binds to toxin A, was more effective. Another phase 2, multicenter, randomized, double-blind, placebo-controlled clinical trial with 200 patients, revealed lower recurrence rate and relative risk of recurrence of CDI associated with significantly longer time to CDI recurrence in the bezlotoxumab and actoxumab group compared to the placebo group.<sup>20</sup> Data from the placebo-treated group showed no relationship between plasma anti-toxin A antibodies and rCDI, whereas plasma anti-toxin B antibodies were found to be protective against rCDI.

**CLINICAL TRIALS**

**Phase 3 (MODIFY I and MODIFY II)**

Two independent, multicenter, 12-week, double-blind, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 patients (>= 18 years of age) evaluated the safety and efficacy of bezlotoxumab in patients receiving standard-of-care antibiotics for primary or recurrent *Clostridioides difficile*.<sup>12</sup> Efficacy was assessed in a modified intention-to-treat (mITT) group.

While both trials randomized patients to single-dose administration of bezlotoxumab alone, bezlotoxumab and actoxumab or placebo along with standard-of-care antibiotics; MODIFY I initially also included an actoxumab alone arm which was terminated early after being associated with significantly increased rates of death caused

by sepsis and lack of efficacy compared to bezlotoxumab and actoxumab arm (p=0.02).<sup>12,30</sup> Randomization was stratified based on the oral standard-of-care antibiotic and the location of the patient (inpatient vs. outpatient).

*Clostridioides difficile* infection (CDI) was confirmed by a positive stool test and >= 3 loose stools in >=24 hours. Standard-of-care antibiotics included oral metronidazole, vancomycin, or fidaxomicin. Patients on oral vancomycin or fidaxomicin could receive intravenous metronidazole. The choice of standard-of-care antibiotic therapy and the day of administration of the study infusion was the health care provider's preference. In most patients (94%), bezlotoxumab was administered within the first six days of standard-of-care antibiotics, with day 3 being the median administration day.<sup>12</sup>

The primary endpoint was defined as a new episode of CDI recurrence after initial clinical cure during the 12 weeks of follow up period. The initial clinical cure was defined as no loose stools for two consecutive days after completing standard-of-care antibiotic therapy for <=16 days. A secondary endpoint, also called global cure or sustained clinical response, was the sustained cure rate, which meant initial clinical cure as defined above and no recurrence of CDI through 12 weeks.

**Results of MODIFY I and MODIFY II**

In the pooled data set from the MODIFY I and MODIFY II trials, the initial clinical cure rate was similar in the bezlotoxumab group (80% [625/781]) and the placebo group (80.3% [621/773]). However, sustained cure at 12 weeks was significantly higher in the bezlotoxumab group (63.5% [496/781]) in comparison to the placebo group (53.7% [415/773]).<sup>12</sup> For sustained cure, the adjusted difference between bezlotoxumab and placebo group was 9.7 percentage points (95% CI 4.8 to 14.5; p<0.0001), and the pooled data set results were mostly driven by MODIFY II trial.<sup>12</sup> Approximately 71% of recurrences of CDI occurred within the four weeks of study infusion.

Importantly, the subgroup analysis of the pooled data set, recurrent CDI rates were statistically significantly lower in the bezlotoxumab group in comparison to the placebo group for patients >=65 years of age, those suffering a recurrent episode of

CDI, immunocompromised patients and in severe CDI,<sup>12</sup> defined as a Zar score of 2 or higher.<sup>31</sup> The determination of immunocompromised patients was based on medical history or the use of immunosuppressive therapy. The number needed to treat to prevent one episode of recurrent CDI with bezlotoxumab was ten; however, that number decreased to six for patients with age  $\geq 65$  and previous CDI in the past six months.<sup>12</sup>

The initial cure rate for patients receiving actoxumab-bezlotoxumab was 73% (568/773) in the pooled data set. The rate of recurrent CDI was also similar in the actoxumab-bezlotoxumab group compared to the bezlotoxumab group, suggesting that the neutralization of toxin B by bezlotoxumab is adequate to reduce the risk of recurrent CDI.<sup>29</sup> Interestingly, the rate of CDI recurrence was significantly lower for hypervirulent strain (NAP1/BI/027) for patients who received a combination of actoxumab-bezlotoxumab (11.8% [9/76]) in comparison to bezlotoxumab alone (23.6% [21/89]) and the placebo group (34% [34/100]).<sup>12</sup> This information suggests that the combination of actoxumab and bezlotoxumab might provide better results for the hypervirulent strain (NAP1/BI/027); however, more future studies are required to confirm this.

## REAL-WORLD DATA

A retrospective study of 46 patients was done in five university hospitals in Finland (in Helsinki, Kuopio, Oulu, Tampere, and Turku).<sup>32</sup> These patients were the first 46 patients to receive bezlotoxumab in Finland in April – December 2017. Polymerase chain reaction (PCR) was the only test used to diagnose CDI. Patients received bezlotoxumab on 0 – 7 days after the initiation of the standard-of-care antibiotics. Vancomycin was used alone or along with another antibiotic in 80% (37 of 46) of patients as a standard-of-care. Eighteen patients received metronidazole, fidaxomicin, and tigecycline. Patients had a mean age of 66 years, out of which 24 were men and 22 were women. 29 of the 46 patients received bezlotoxumab in inpatient and the other 17 in an outpatient setting. Twenty-eight patients were immunocompromised due to immunosuppressive treatment or other medical comorbidities. 78% (36/46) of patients had three or more known risk factors for CDI's recurrence.

Results revealed that 73% (32/44) patients did not have rCDI in 3 months of bezlotoxumab treatment.<sup>32</sup> 71% (20/28) of immunocompromised patients and 63% (10/16) of patients with severe CDI based on the Zar score did not have rCDI in the three months.<sup>32</sup> Two severely ill patients died within three months of bezlotoxumab infusion at Turku University Hospital. One patient died five days after bezlotoxumab infusion due to end-stage cardiac disease, and the other died approximately 45 days after bezlotoxumab infusion due to graft-versus-host disease.

Another study using whole-genome sequencing calculated the difference in the same-strain relapse versus new-strain reinfection in MODIFY I/II trials.<sup>33</sup> Two hundred fifty-nine patients were evaluated for rCDI, out of which 76% (198/259) of the patients in the study experienced relapse with the same strain, whereas only 19% (50/259) had reinfection with a new strain. Ribotype 027 was associated with higher proportions of relapses as compared to other ribotypes. This study also revealed that a cumulative incidence of CDI relapse with the same strain in high-risk patients was significantly lower for patients treated with bezlotoxumab than patients not treated with bezlotoxumab ( $p < 0.0001$ ).<sup>33</sup>

One of the most extensive multicenter retrospective cohort study of 200 patients between April 2017 and December 2018 across 34 outpatient infusion centers in the United States was published recently.<sup>34</sup> *C. difficile* was diagnosed using PCR (76.5%) and enzyme immunoassay (EIA) (23.5%). Patients received vancomycin (68.5%), fidaxomicin (30%), and metronidazole (1.5%) as a standard-of-care antibiotics. The median time interval for bezlotoxumab infusion was 11 days from initiation of the standard-of-care antibiotics. Three patients were lost in follow up, and two chronically ill patients with multiple medical comorbidities died 40 days and 75 days post bezlotoxumab infusion. 86% of patients enrolled in the study had at least one CDI recurrence before bezlotoxumab infusion. 80% of patients had  $\geq 2$  risk factors for rCDI, most frequently age  $\geq 65$  years (67.7%), and  $\geq 1$  CDI episode in the past six months (61.5%). The study results revealed that the overall CDI recurrence rate after a single infusion of bezlotoxumab was 15.9%, which translates into 84.1% successful

prevention of CDI recurrence in patients enrolled in the study.<sup>34</sup> These results are comparable to 16.5% of CDI recurrence reported for the overall population enrolled in the MODIFY I and II phase 3 clinical trials.<sup>12</sup>

### DISCUSSION

Data from MODIFY I and II phase 3 trials suggest that bezlotoxumab (15.7% [107/679]) decreases the recurrence rate of CDI when compared to placebo (25.6% [169/658]) in non-hypervirulent strains.<sup>12</sup> The only possible severe side-effect of bezlotoxumab infusion is worsening congestive heart failure in patients with a history of heart failure. It will be pertinent to develop cost-effective guidelines for targeting high-risk elderly patients, considering the high cost (approximately \$4000 for a 1000mg/40ml vial) of bezlotoxumab.<sup>35</sup>

FMT has also been effective for rCDI.<sup>36,37</sup> It is vital to recognize that it is typically administered after a course of antibiotic therapy rather than as a primary treatment modality; bezlotoxumab is also a preventive agent used in association with a standard-of-care treatment. Large head-to-head clinical trials will be required to determine the efficacy of FMT compared to bezlotoxumab to prevent a recurrence. It is crucial to keep in mind that neither fidaxomicin nor bezlotoxumab has shown significant efficacy in preventing recurrent CDI in patients infected with the hypervirulent strain (NAP1/BI/027).

A post hoc pooled analysis revealed that the CDI recurrence rate was further lower for the bezlotoxumab group when the diagnosis was made using toxin EIA 14.5% (54/372) compared to PCR 19.6% (70/357); while rates were similar for the placebo group.<sup>38,39</sup> Nucleic acid amplification tests (PCR) only identify the toxigenic DNA sequences but not the toxin protein, hence also detecting asymptomatic carriers of toxigenic strains of *C. difficile*. EIAs, which test directly for toxins A/B produced by the organism, are specific for active infection and predictive of poor outcomes compared to more sensitive nucleic acid amplification tests (NAAT), which detect toxigenic strains but not toxin protein.<sup>40</sup> Thus, the number needed to treat (NNT) could be even lower for populations if EIA is used for diagnosis.<sup>39</sup>

Currently, there is no data for the use of bezlotoxumab in the pediatric population or pregnant and lactating patients. Phase 4 clinical trials will provide further insight into the role of bezlotoxumab in these population subtypes.

### CONCLUSION

The future for the treatment of recurrent CDI appears promising. While participants with  $\geq$ three risk factors had the most significant reduction of CDI recurrence with bezlotoxumab, those with 1 or 2 risk factors also significantly benefited. We recommend that bezlotoxumab be considered in treating high-risk patients,  $\geq$  65 years of age, with more than one risk factor to prevent further CDI recurrence. Patients with concomitant antibiotics use, inflammatory bowel disease, and those not responding to FMT may also benefit from bezlotoxumab treatment. As bezlotoxumab may be administered to patients at any point during a course of CDI treatment, outpatient infusion would avoid unnecessary inpatient cost and is an economical option. It will be intriguing to see more clinical trials to assess the combined effect of bezlotoxumab and FMT or bezlotoxumab and fidaxomicin for the treatment of recurrent *C. difficile* infection. ■

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Answers to this month's crossword puzzle:

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