Bezlotoxumab to Prevent Recurrent *Clostridium difficile* Infection

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Introduction

The Gram-positive bacteria *Clostridium difficile* is a common cause of antibiotic-associated diarrhea. *Clostridium difficile* infection (CDI) may also result in pseudomembranous colitis, toxic megacolon, colon perforation, sepsis, or death.1

Risk factors for CDI are presented in the Box to the right; a number of these are commonly seen in the long-term care setting. Elderly patients are disproportionately affected by CDI, with higher rates of infection, greater severity of disease, and an increased risk of mortality.2

In October 2016, the U.S. Food and Drug Administration approved the first monoclonal antibody for the prevention of recurrent infections of *Clostridium difficile*. Bezlotoxumab (marketed as Zinplava™) is indicated to reduce recurrence of CDI in adult patients who are being treated for CDI with antibacterial drugs and are at high risk of recurrence of CDI.3 Although high risk is not explicitly defined as part of the drug’s indication, in clinical trials of bezlotoxumab this included elderly patients, individuals who were immunocompromised, patients with a history of CDI, and those with clinically severe infection or infected with the BI/NAP1/027 bacterial strain.

Bezlotoxumab is not an antibacterial agent and should not be used as monotherapy for the treatment of CDI.3 *Clostridium difficile* produces two exotoxins that cause inflammation and mucosal damage, leading to colitis: toxin A and toxin B.3 Bezlotoxumab binds to and neutralizes toxin B, which is thought to prevent disease recurrence and may offer an antibiotic-sparing therapy option. Bezlotoxumab does not impact *C. difficile* toxin A.3,4

The following article will evaluate the efficacy of bezlotoxumab for the prevention of recurrent CDI.

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**Box. Risk factors for *C. difficile* Infection**

<table>
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<tr>
<th>Risk Factor</th>
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<tr>
<td>Advanced age</td>
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<td>Antibiotic exposure</td>
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<td>Chemotherapy</td>
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<td>Gastrointestinal surgery</td>
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<td>Immunocompromised state</td>
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<td>Long length of stay</td>
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<tr>
<td>Nasogastric tube use</td>
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<td>Proton pump inhibitor use</td>
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<td>Serious underlying illness</td>
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Clinical Trials of Bezlotoxumab

Bezlotoxumab was approved on the basis of two phase III clinical trials which included more than 2,600 patients receiving standard of care antibiotic therapy in either the outpatient or inpatient setting (see the Table on pages 3-4). Bezlotoxumab was administered as a single intravenous infusion of 10mg/kg. A second investigational monoclonal antibody, actoxumab, which was targeted at neutralizing C. difficile toxin A, was also studied as monotherapy and in combination with bezlotoxumab. However, a planned interim analysis did not show efficacy of actoxumab, and additional study was not pursued.7

Although bezlotoxumab had no significant impact on initial clinical cure of CDI, data pooled from both studies showed significantly reduced rates of recurrent infection when compared to placebo (17% vs. 27%; p≤0.0003). These outcomes indicate that for every 10 patients treated with adjunctive bezlotoxumab in addition to standard antibiotic therapy, compared to placebo, one additional case of recurrent CDI will be prevented. The combination of the two monoclonal antibodies did not show additional benefit over bezlotoxumab alone.5,6

Data in abstract form suggests that bezlotoxumab is also associated with significant reductions in readmission rates secondary to CDI for inpatients ≥65 years of age, those with a history of previous CDI, and in CDI cases considered clinically severe.8 However, this data has not yet been published and is not available for review.

In general, the safety profile of bezlotoxumab was similar to that of placebo. Common adverse reactions were seen at similar rates in each treatment group, and included nausea, diarrhea, pyrexia, and urinary tract infections. Infusion-related reactions were mild, occurring in 9% of patients who received bezlotoxumab and 8% of patients who received placebo.5,6

However, the serious adverse reaction of heart failure was reported more commonly in bezlotoxumab recipients than those receiving placebo (2.3% vs. 1%). When only those patients with a history of underlying congestive heart failure (CHF) were analyzed, the rate of heart failure was 12.7% in the bezlotoxumab group, compared to 4.8% in the placebo group. Furthermore, in patients with a history of CHF, the mortality rate during the study period was 19.5% in the bezlotoxumab-treated group versus 12.5% in the placebo-treated group. Etiology of these deaths was variable, and included heart failure, infectious processes and respiratory failure. Although the significance of this data is unclear, use of bezlotoxumab should be used with extreme caution in patients with a history of CHF.9
<table>
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<tr>
<th>Ref</th>
<th>Drug Regimens &amp; Patient Population</th>
<th>Duration &amp; Design*</th>
<th>Primary Endpoints</th>
<th>Results/Comments</th>
<th>LOE†</th>
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<td>5</td>
<td>Bezlotoxumab (B) vs. Bezlotoxumab + actoxumab (B+A) vs. Actoxumab (A) vs. Placebo (P)</td>
<td>12 weeks MC, PC, DB, RCT MODIFY I Study</td>
<td>Recurrent CDI during 12 weeks of follow up, defined as a new episode of CDI after initial clinical cure of baseline episode</td>
<td>Recurrent CDI: B = 17%; treatment difference vs. P = -10.1, p&lt;0.001, NNT = 9 B+A = 16%; treatment difference vs. P = -11.6, p&lt;0.001, NNT = 8 A = 26% P = 28%</td>
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All participants received a single 60 minute intravenous infusion of the study drug while receiving standard-of-care antibiotic therapy.

1,396 subjects analyzed (B = 386; B+A = 383; A = 232; P = 395)

Adult patients presenting with a primary or secondary *C. difficile* infection currently receiving standard of care antibiotic therapy for 10 to 14 days were included in this study. Patients with active chronic diarrheal disease or imminent (within 24 hours) planned surgery for CDI were excluded.

Mean age of participants was 66 years (range 18 to 100 years). Participants were largely white (86%) and female (56%).

Standard antibiotic therapy consisted of metronidazole (47% of patients), vancomycin (48%), and fidaxomicin (4%).
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<td>6</td>
<td>Bezlotoxumab (B) vs. Bezlotoxumab + actoxumab (B+A) vs. Placebo (P)</td>
<td>12 weeks MC, PC, DB, RCT MODIFY II Study</td>
<td>Recurrent CDI during 12 weeks of follow up, defined as a new episode of CDI after initial clinical cure of baseline episode</td>
<td>Recurrent CDI: B = 16%; treatment difference vs. P = -9.9, p&lt;0.001, NNT = 10 B+A = 15%; treatment difference vs. P = -10.7, p&lt;0.001, NNT = 9 P = 26%</td>
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All participants received a single 60 minute intravenous infusion while receiving standard-of-care antibiotic therapy.

1,163 subjects analyzed (B=395; B+A=390; P=378)

Adult patients presenting with a primary or secondary *C. difficile* infection currently receiving standard of care antibiotic therapy for 10 to 14 days were included in this study. Patients with active chronic diarrheal disease or imminent (within 24 hours) planned surgery for CDI were excluded.

Mean age of participants was 66 years (range 18 to 100 years). Participants were largely white (86%) and female (56%).

Standard antibiotic therapy consisted of metronidazole (49% of patients), vancomycin (48%), and fidaxomicin (3%).

Key secondary outcomes included recurrent infection and adverse outcomes in patients aged 65 years or older.

No significant differences in recurrence between patients ≥65 years and other subgroups were identified.

Safety data were reported as pooled rates combining both MODIFY I and II outcomes. Rates of adverse effects were similar across all groups and included nausea, vomiting, abdominal pain and diarrhea. Infusion-related reactions were reported by 9% of patients.

Patients taking bezlotoxumab more frequently reported the serious adverse effect of heart failure than those taking placebo (2.3% vs. 1%). This occurred more frequently in patients with a history of congestive heart failure (CHF).

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*Study design abbreviations: DB=double blind; RCT=randomized trial; PC=placebo-controlled; OL=open-label; PG=parallel group; XO=crossover; MC=multicenter

†Level of evidence: Grade 1=RCT; Grade 2=nonrandomized concurrent studies; Grade 3=historical cohort & case-control studies; Grade 4=case series; Grade 5=expert opinion
Conclusion

Bezlotoxumab is the first monoclonal antibody approved to reduce recurrence of *Clostridium difficile* in high risk adult patients who are receiving standard of care antibiotics. Currently available clinical practice guidelines from the American College of Gastroenterology, Infectious Diseases Society of America (IDSA), and American Medical Directors Association do not address bezlotoxumab or the use of adjunctive monoclonal antibody therapy.\(^{10-13}\) However, an update to the IDSA guidelines for CDI is underway, with publication expected in summer of 2017.\(^{14}\)

Administration of bezlotoxumab significantly reduced the risk of CDI recurrence when compared to placebo in phase III trials. These premarketing studies enrolled patients with primary or secondary CDI; however, it may be prudent to reserve bezlotoxumab for use in secondary infection, as it is difficult to predict which patients will experience recurrence. Bezlotoxumab is administered as a single intravenous infusion, and the safety or efficacy of repeat doses has not been studied. Treatment with bezlotoxumab increased the risk of heart failure and death in individuals with a history of CHF; therefore, extreme caution should be used when initiating treatment in these patients.

References

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