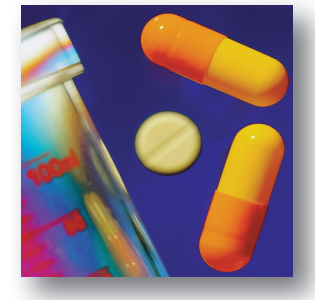

Bezlotoxumab (Zinplava) for *Clostridium Difficile* Infection

The First Monoclonal Antibody Approved to Prevent the Recurrence of a Bacterial Infection

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INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), *Clostridium difficile* (Figure 1) is the most common microbial cause of health care-associated infections in U.S. hospitals, costing up to $4.8 billion each year in excess health care costs for acute-care facilities alone. Older Americans are especially vulnerable to this potentially deadly diarrheal infection. The CDC has reported that two-thirds of health care-associated *C. difficile* infections (CDI) occur in patients 65 years of age or older.[1] CDI can also affect individuals in the community setting.[2,3] In addition to hospitalization and advanced age, risk factors for infection include antibiotic use, severe illness, and gastric acid suppression.[4,5]

Using data from 2011, the CDC estimated in 2015 that approximately 29,000 patients died within 30 days of the initial diagnosis of CDI. Of those deaths, approximately 15,000 were estimated to be directly attributable to CDI. More than 80% of the deaths associated with *C. difficile* occurred among patients 65 years of age or older.[1]

It has been estimated that 20% to 30% of patients with CDI develop recurrent disease.[6] Patients who have had more than two episodes of CDI have a 65% risk of experiencing additional episodes.[7]

Using an economic computer simulation model, McGlone and colleagues found that CDI is costly not only to hospitals, but to society as a whole. Costs were based on varying lengths of hospitalization, CDI-attributable length of stay, and the probability of initial and secondary recurrences. The computer model indicated that the median cost of a case of CDI ranged from $9,179 to $11,456 (in 2012 dollars) from the hospital perspective and from $13,310 to $16,464 from the societal perspective.[8]

The current antibiotic treatment options for CDI include metronidazole, oral vancomycin, fidaxomicin (Dificid, Merck), and rifaximin (Xifaxan, Salix Pharmaceuticals).[9] Although metronidazole is not FDA-approved for the treatment of patients with CDI, it has been used for that indication since 1994.[10] Treatment guidelines issued jointly by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America identify metronidazole as the treatment of choice for the initial episode of mild-to-moderate CDI, and vancomycin as the treatment of choice for the initial episode of severe CDI.[11] Metronidazole is not recommended beyond the first recurrence of mild disease because prolonged use may result in neurotoxicity.[11] For second recurrences, tapered vancomycin has been suggested.[12] Fidaxomicin, a macrolide antibiotic, may be considered as an adjunct to vancomycin for recurrent CDI.[13] Early trial data suggested that rifaximin may be useful in patients with mild-to-moderate CDI whose infections are resistant to metronidazole.[14] The drug was subsequently used successfully in patients with refractory or fulminant CDI as part of combination therapies.[15,16]

Because of the high rate of CDI recurrence, research interest has turned to finding alternatives to antibiotic therapies.

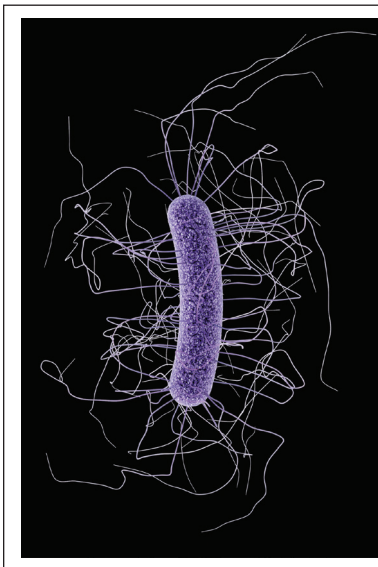

Figure 1 This 3D illustration depicts the ultrastructural morphology exhibited by a single gram-positive *Clostridium difficile* bacillus. (Credit: Centers for Disease Control and Prevention)

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One such approach involves the administration of monoclonal antibodies to neutralize *C. difficile* toxins and enhance the immune response.[9,17] *C. difficile* toxins A (an enterotoxin) and B (a cytotoxin) are responsible for the virulence of the disease and appear to play a major role in its recurrence.[18] Moreover, studies in human subjects found that circulating antibodies against toxins A and B were protective against both primary and recurrent CDI.[19,20]

Medarex, Inc. (now part of Bristol-Myers Squibb), in partnership with the University of Massachusetts Medical School, developed two monoclonal antibodies that specifically targeted *C. difficile* toxin A (actoxumab) or toxin B (bezlotoxumab) to help prevent the recurrence of CDI. The two antibodies were licensed to Merck for global development and commercialization as a combination treatment.[21]

In a phase 2, randomized, double-blind, placebo-controlled study conducted by Medarex, the addition of actoxumab and bezlotuxumab to antibiotic treatments significantly reduced the recurrence of CDI compared with placebo in 200 patients (7% versus 25%, respectively; $P < 0.001$). Actoxumab and bezlotuxumab were administered together as a single infusion.[22]

This study was followed by two pivotal, phase 3 trials (MODIFY I and II), which concluded that the addition of actoxumab to bezlotoxumab did not improve the latter's efficacy.[23] These studies are discussed later in the Pivotal Clinical Trials section.

In October 2016, the FDA approved bezlotoxumab (Zinplava, Merck) to reduce the recurrence of CDI in adults.[24] It is the first human monoclonal antibody approved to reduce the recurrence of a bacterial infection.[25]

DESCRIPTION[26]

Bezlotoxumab is an IgG_1 immunoglobulin with an approximate molecular weight of 148.2 kDa. Bezlotoxumab injection is a sterile, preservative-free, clear to moderately opalescent, colorless to pale yellow solution that requires dilution for intravenous (IV) infusion. It is provided in a 50-mL vial that contains 1,000 mg of bezlotoxumab in 40 mL of solution.

INDICATION[26]

Bezlotoxumab is indicated to reduce the recurrence of CDI in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence. Bezlotoxumab is not indicated for the treatment of CDI and is not an antibacterial drug.

MECHANISM OF ACTION[26]

Bezlotoxumab binds to *C. difficile* toxin B and neutralizes its effects on mammalian cells. Bezlotoxumab does not bind to *C. difficile* toxin A.

CLINICAL PHARMACOLOGY[26]

Pharmacokinetics

The pharmacokinetic (PK) characteristics of bezlotoxumab were studied in 1,515 patients with CDI in two phase 3 trials. Based on a population PK analysis, the geometric mean clearance of bezlotoxumab was 0.317 L/day, with a mean volume of distribution of 7.33 L and an elimination half-life of approximately 19 days. After a single IV dose of 10 mg/kg, the geometric mean area under the curve and maximal serum concentration were 53,000 mcg•h/mL and 185 mcg/mL, respectively. The clearance of bezlotoxumab increased with increasing body weight. Bezlotoxumab is eliminated via catabolism.

Specific Populations

Gender, race, ethnicity, and the presence of comorbid conditions have no clinically meaningful effects on the exposure of bezlotoxumab. In addition, no clinically meaningful differences in the exposure of bezlotoxumab were found between patients with renal impairment and patients with normal renal function; between patients with hepatic impairment and those with normal hepatic function; or between patients 65 years of age and older and patients younger than 65 years of age. Bezlotoxumab has not been studied in pediatric patients.

Drug–Drug Interactions

Because bezlotoxumab is eliminated via catabolism, no metabolic drug–drug interactions are expected.

PIVOTAL CLINICAL TRIALS[26]

The safety and efficacy of bezlotoxumab were investigated in two phase 3, randomized, double-blind, placebo-controlled, multicenter studies in patients receiving standard of care (SoC) antibacterial drugs for the treatment of CDI. Randomization was stratified by SoC (metronidazole, vancomycin, or fidaxomicin) and hospitalization status (inpatient versus outpatient) at the time of study entry. Enrolled patients were 18 years of age or older and had a confirmed diagnosis of CDI. Patients were excluded from the trials if surgery for CDI was planned, or if they had uncontrolled chronic diarrheal illness.

The patients received a 10- to 14-day course of oral SoC, and a single infusion of bezlotoxumab or placebo was administered during the course of SoC. Patients treated with oral vancomycin or oral fidaxomicin could also receive IV metronidazole.

In the first study, 403 patients were randomly assigned to receive bezlotoxumab, and 404 patients received placebo. In the two treatment groups, 386 and 395 patients, respectively, were evaluable for efficacy. In the second study, the two treatment groups consisted of 407 and 399 patients, respectively. The numbers of patients evaluable for efficacy totaled 395 and 378, respectively. The patients' median age was 65 years; 85% were white; 57% were women; and 68% were inpatients. A similar proportion of patients received oral metronidazole (48%) or oral vancomycin (48%), and 4% of the patients received oral fidaxomicin as their SoC.

In the first study after 12 weeks of treatment, 60.1% of the patients receiving bezlotoxumab plus SoC achieved a sustained clinical response compared with 55.2% of those in the group that received placebo plus SoC. In the second trial, the corresponding findings were 66.8% and 52.1% (Table 1).

SAFETY PROFILE[26]

Warnings and Precautions

In the pivotal phase 3 studies of bezlotoxumab, heart failure was reported more often with active treatment than with placebo. These adverse events occurred primarily in patients with underlying congestive heart failure (CHF). In the subgroup with a history of CHF, 12.7% (15 of 118) of bezlotoxumab-treated patients and 4.8% (five of 104) of placebo-treated patients experienced heart failure during the 12-week studies. In addition, in patients with a history of CHF, more deaths occurred among bezlotoxumab-treated patients (23 of 118 [19.5%]) than among placebo-treated patients (13 of 104

Table 1 Efficacy Results Through 12 Weeks After Infusion in Pivotal Trials of Bezlotoxomab[26]

	Bezlotoxomab With SoC n (%)	Placebo With SoC n (%)	Adjusted Difference (95% CI)
Trial 1	**(N = 386)**	**(N = 395)**	
Sustained clinical response	232 (60.1)	218 (55.2)	4.8 (–2.1 to 11.7)
Clinical failure	87 (22.5)	68 (17.2)	—
Recurrence	67 (17.4)	109 (27.6)	—
Trial 2	**(N = 395)**	**(N = 378)**	
Sustained clinical response	262 (66.8)	197 (52.1)	14.6 (7.7 to 21.4)
Clinical failure	69 (17.5)	84 (22.2)	—
Recurrence	62 (15.7)	97 (25.7)	—

CI = confidence interval; SoC = standard of care (metronidazole, vancomycin, or fidaxomicin).

[12.5%]) during the 12-week studies. The causes of death included cardiac failure, infections, and respiratory failure.

In patients with a history of CHF, bezlotoxumab should be reserved for use when the benefits outweigh the risk.

Adverse Events

In the two pivotal trials, adverse events reported during the first four weeks after bezlotoxumab administration were pooled for the total study population of 786 patients. The median age of the patients receiving bezlotoxumab was 65 years (range, 18–100 years); 50% were 65 years of age or older; 56% were women; and 83% were white. The most common adverse events associated with bezlotoxumab during the first four weeks after infusion included nausea (7%), pyrexia (5%), and headache (7%).

Serious adverse events occurring within 12 weeks after infusion were reported in 29% of the bezlotoxumab-treated patients and in 33% of the placebo-treated group.

DOSAGE AND ADMINISTRATION[26]

Bezlotoxumab is administered during antibacterial drug treatment in patients with CDI. The recommended dose is 10 mg/kg administered as a single IV infusion over 60 minutes. The safety and efficacy of repeat administration of bezlotoxumab in patients with CDI have not been studied.

Bezlotoxumab should be used only in conjunction with the antibacterial drug treatment of CDI.

COST CONSIDERATIONS

Bezlotoxumab is available at an average wholesale price (AWP) of $4,560 per vial.[27]

A study published in 2016 investigated the cost-effectiveness of bezlotoxumab plus SoC versus placebo plus SoC for the prevention of recurrent CDI in the U.S.[28] The investigators used a computer-based health-state transition model to simulate the natural history of CDI. In this model, the researchers followed patients with recurrent CDI from infection until death and evaluated the costs and efficacy of bezlotoxumab plus SoC compared with that of placebo plus SoC using a third-party payer perspective. The patients included two subgroups at increased risk of recurrent CDI: those 65 years of age and older (subgroup 1) and those with a history of CDI (subgroup 2). Recurrence rates after infusion for bezlotoxumab and placebo were obtained from pooled MODIFY I and MODIFY II data. The investigators projected threshold prices at which bezlotoxumab would be cost-effective at the $100,000/quality-adjusted life-years [QALY] threshold.

The model predicted that treating patients with bezlotoxumab plus SoC would reduce the combined incidence of first, second, and third CDI recurrences after infusion by 16% and 39% in subgroup 1 and subgroup 2, respectively. In addition, the model indicated that the threshold prices at which bezlotoxumab would be cost-effective at the $100,000/QALY threshold were $17,188 and $30,118 for the two subgroups, respectively. The investigators concluded that bezlotoxumab has the potential to reduce the disease burden associated with CDI in a cost-effective manner by reducing the incidence of recurrent CDI.[28]

An editorial in the *New England Journal of Medicine* pointed out, however, that the next question that needs to be asked is how bezlotoxumab compares, in terms of relative relapse risk and cost, with other treatments for recurrent CDI.[29] One of those treatments is fidaxomicin, which is also associated with lower relapse rates.[30] Fidaxomicin is the only other treatment that reduces recurrences after the first CDI better than metronidazole and vancomycin.[31] Fidaxomicin is administered as one 200-mg tablet twice daily for 10 days.[32] The AWP for a 20-tablet package is $4,418.[27] Therefore, when compared with its main competitor, bezlotoxumab appears to offer a clear advantage in terms of convenience (one-time IV administration versus an oral twice-daily 10-day regimen) at a comparable price.

CONCLUSION

Bezlotoxumab is the first human monoclonal antibody approved to reduce the recurrence of a bacterial infection (CDI in adults).[24,25] Bezlotoxomab is not an antibacterial drug, and it is not indicated for the treatment of CDI.[26]

The recommended dose of bezlotoxumab is 10 mg/kg administered as a single IV infusion over 60 minutes during antibacterial drug treatment. It is supplied in a carton containing one single-dose vial of 1,000 mg/40 mL (25 mg/mL)[26] at an AWP of $4,560.[27]

Bezlotoxumab was associated with an increased risk of heart failure in pivotal clinical trials. In patients with a history of CHF, it should be reserved for use when the benefits outweigh the risk.[26]

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