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The Rising Incidence of *C. difficile* and Bezlotoxumab: The Targeting of Toxin B

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Abstract

Clostridium difficile (*C. difficile*) infection has become a growing issue facing hospitals in North America and Europe. Each case of *C. difficile* infection is now being shown to add $7,200 to the cost of a patient's stay. These growing incidents and costs have spurred research in new treatments of this infection. Metronidazole and oral vancomycin continue to be the preferred first-line drugs with the macrocyclic agent, fidaxomicin, a possible option for some patients. From a more procedural route, fecal microbiota transplants are seeing an increase in use due to their high success rate.

Bezlotoxumab (Zinplava), a monoclonal antibody approaches *C. difficile* treatment from a different angle. When used with a *C. difficile* targeting antibiotic, bezlotoxumab binds to Toxin B, a sizable and destructive toxin released by the *C. difficile* bacterium. By binding to this toxin, bezlotoxumab gives the gastrointestinal mucosa time to heal and time for the normal flora to grow. Bezlotoxumab is not a replacement for antibiotics.

The MODIFY I and MODIFY II trials were the largest conducted trials to date for *C. difficile* treatment. These trials studied nearly 2,700 patients worldwide and compared bezlotoxumab to placebo and actoxumab, a monoclonal antibody that instead targeted Toxin A. Actoxumab was found to be ineffective, however, the completion of both trials showed bezlotoxumab to be superior to placebo and to significantly reduce the *C. difficile* recurrence rates (p=0.0003).

Since murumonab-CD3 was approved for use in 1986, monoclonal antibodies have become preferred drugs for a wide variety of disease states. Orthoclone OKT3 (muromonab-CD3) was approved for the prevention of kidney transplant rejection through its targeting of the antigen CD-3. While side effects and advancements in transplant therapy have caused its withdrawal from the United States market, it is considered a landmark in antibody therapy and was the impetus to a new age of medicine.[1]

Monoclonal antibodies have been shown to effectively treat several forms of cancer, Alzheimer's disease and numerous autoimmune diseases such as ulcerative colitis, rheumatoid arthritis and Crohn's disease. Debilitating and incurable diseases have become manageable through breakthroughs that are becoming increasingly common. The next target for monoclonal antibodies? Infections.[1]

Clostridium difficile (*C. difficile*) is the leading cause of hospital-acquired diarrhea in North America and Europe.[2] Recent antibiotic exposure and gastric acid suppressants (PPIs/H2RAs) have been shown to predispose patients to a greater risk of contracting this infection.[2] This antibiotic-associated diarrhea emerges through a competition mechanism of *C. difficile* versus the depleted normal GI flora.[3] However, patients once thought to be at low-risk are being infected at increasing rates as the spread of this bacterium continues. It is estimated that each case of *C. difficile* increases hospital costs by $7,200, amounting to more than $5 billion in the United States each year.[4] The CDC has noted a 20-fold increase in mortality, resulting in 29,000 deaths in 2011.[2]

C. difficile is spread through an oral-fecal route and is non-invasive in nature, however, it is most lethal because of two toxins that are released: toxin A (TcdA) and toxin B (TcdB).[5,6] These two toxins, each about 300 kilodaltons (kDa), are two of the largest bacterial toxins known. It is speculated that of the two toxins, TcdB poses the chief threat as it is estimated to cause ten times greater damage to epithelial tissue of the colon than toxin TcdA.[6,7] Once this epithelial barrier is disrupted, this toxin begins to target and break down underlying cells, colonocytes, enterocytes and enteric neurons.[5] This breakdown of epithelial tissue can lead to bloating, hematochezia, toxic megacolon, colon perforation, sepsis and eventually death if not properly treated.[5]

Aptly named because of its difficulty to treat and eradicate, *C. difficile* is resistant to most antibiotics. Discontinuation of the causative antibiotic is widely recommended as necessary for effective treatment. However, the real challenge is preventing and effectively treating recurrent infections. Repeat regimens of metronidazole and/or vancomycin are recommended and vancomycin may be administered as a tapered regimen at some point.[8] Current guidelines according to the American College of Gastroenterology for the treatment of *C. difficile* infection recommend metronidazole (500mg TID for 10 days) for patients with mild to moderate cases and vancomycin (125 mg QID for 10 days) for patients with severe or complicated cases.[8] Fidaxomicin 200 mg daily for 10 days is also an option for treating recurrent infections.[9]

In the last five years, increasing virulence and incidence has led to a need for additional options to prevent recurrences. Fidaxomicin is a narrow-spectrum macrocyclic antibiotic which selectively targets *C. difficile* while preserving the normal GI flora.[10] While vancomycin has shown to be equally effective to fidaxomicin in the first treatment, the difference in recurrence rate showed fidaxomicin to have a statistically significant edge in preventing recurrence in patients not infected with the hypervirulent strain. Although it is quite expensive, at a cost of $3,360 for a 10-day treatment compared to $700 for vancomycin capsules, $25 for oral vancomycin compounded from intravenous vancomycin and $35 for metronidazole, its clinical application can be effective in patients with unbearable, chronic *C. difficile* infection.[11] Fecal microbiota transplant is another form of alternative therapy that is growing in usage. Fecal donors free of infectious diseases such as HIV, hepatitis C and other qualifications provide a stool sample that is mixed with saline and then placed into a patient through the route of colonoscopy, nasogastric tube or enema.[12] Fecal transplants have demonstrated great success in preventing recurrence of *C. difficile* infection with cure rates as high as 91%.[12] The ingestion or infusion of bacteria from a healthy donor passes through the GI system and competes with the *C. difficile* bacteria for resources, therefore restoring the normal gut flora of the patient.[12]

Bezlotoxumab (Zinplava) approaches *C. difficile* treatment from a different angle. One of the first drugs of its kind, bezlotoxumab is a monoclonal antibody that binds to the receptor binding domain of toxin B which prevents Toxin B from binding to human cells.[13] Bezlotoxumab is not indicated for the treatment of *C. difficile* infection by itself.[14] Patients must be on standard antibiotic therapy of vancomycin/metronidazole to treat the infection and then are given one intravenous infusion of bezlotoxumab 10mg/kg over 60 minutes.[15] When a patient is prescribed vancomycin or metronidazole, the gut flora of good and bad microbes may be wiped out. After antimicrobial therapy, patients are at their highest risk of recurrence of infection caused by the remaining toxins in the GI tract.

Bezlotoxumab crosses the gut wall to the site of infection via toxin-mediated disruption of the epithelium.[13] Bezlotoxumab provides passive immunity towards toxin B produced by persistent or newly acquired *C. difficile* bacterium.[13] This allows the body's normal microbiota to recolonize the gut once antibiotics have been stopped.[13] The growth of normal bacteria in the body will reestablish the body's normal check against *C. difficile* growth by ways of competition for nutrients thus lowering the risk of recurrent infection. However, bezlotoxumab is not to be used in place of antibiotic therapy.[13]

In a study conducted by Merck, bezlotoxumab was evaluated on its own and in combination with another Merck monoclonal antibody, actoxumab. Actoxumab differs from bezlotoxumab in that it targets the less harmful toxin TcdA.

Bezlotoxumab was studied in two main phase 3 trials named Modify I and II. These are the largest *C. difficile* treatment trials to date and assessed nearly 2,700 patients across 300 sites, 30 countries and

six continents.[13] The Modify I trial contained four arms for comparison: bezlotoxumab, actoxumab, both together and then placebo; the Modify II trial contained three arms in bezlotoxumab, both bezlotoxumab and actoxumab together, and placebo. Patients were randomly assigned oral vancomycin, metronidazole or fidaxomicin treatment and then randomly stratified into one arm of the trial.[13] Four hundred patients were studied in each arm of each trial, leading to 1,600 patients for Modify I and 1,200 patients for Modify II. Actoxumab alone was discontinued in the second trial due to minimal efficacy in the treatment of recurrence.[16] Each trial contained a power of 95% or higher. The completion of both trials showed bezlotoxumab to be superior to placebo and to significantly reduce the *C. difficile* recurrence rates (p=0.0003).[13] This came to a 10% absolute risk reduction and a relative risk reduction of 40% of *C. difficile* recurrence for each trial.[13] From this the number needed to treat with bezlotoxumab to prevent a recurrence of infection was ten patients. In addition, actoxumab did not show a difference in recurrence rates when combined with bezlotoxumab.[13]

Bezlotoxumab has a half-life of about 19 days and is eliminated mostly by protein catabolism.[13] There is no hepatic metabolism nor renal elimination.[13] Because of the process by which bezlotoxumab is eliminated, organ dysfunction and age are not anticipated to affect the exposure of bezlotoxumab.[13] However, the clearance of bezlotoxumab has shown to increase in patients with greater body weight.[13] No other dose adjustment factor was seen during clinical trials including demographically different patients, elderly patients, patients with multiple disease states, hepatic impairment, or renal impairment.[13] Bezlotoxumab has low potential to be involved in a drug interaction with another drug.[13] As with many monoclonal antibodies, side effects and cost are concerns. When bezlotoxumab is given with standard of care antibacterial drugs for *C. difficile,* the most common adverse effects seen in clinical trials include nausea, pyrexia, and headache.[15] There is no established information regarding the safety or efficacy of bezlotoxumab in pregnant women, lactating women, or pediatric use. A more serious side effect that became apparent in the Modify trials was the potential for worsening of heart failure.[15] Patients with a history of congestive heart failure are more susceptible to this risk and should only take bezlotoxumab if the benefit outweighs this risk.[15]

The recent approval of bezlotoxumab has the potential to have a large impact on the standard treatment of *C. difficile* infection. Recurrent *C. difficile* infection has been greatly associated with normal treatment and has continually been a problem, but until high costs of monoclonal antibodies begin to decrease, bezlotoxumab can be reserved as an effective therapy for patients in dire need of an end to recurrent *C. difficile* infection.[7] Bezlotoxumab treatment in combination with standard of care medication can reduce the rate of recurrent infection and in turn decrease the length of hospital stays and hospital readmittance. Reducing the length of hospital stays and readmissions can help improve the quality of care for patients.

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