Comparing the Effectiveness of IV Bezlotoxumab Versus Placebo in Decreasing Morbidity and Mortality in Patients With Fulminant C. Diff Requiring Surgery

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Objectives/Aims

Aim 1: To prospectively evaluate Bezlotoxumab as an adjuvant treatment for fulminant *C. difficile* colitis with current surgical intervention and antibiotic therapy for a decrease in mortality.

Aim 2: To prospectively evaluate Bezlotoxumab as an adjuvant treatment for fulminant *C. difficile* colitis with current surgical intervention and antibiotic therapy for a decrease in morbidity.

Aim 2a: To evaluate for a decrease in multi-system organ failure by monitoring for ventilator free days, need for dialysis, and development of liver or cardiac failure.

Aim 2b: To further evaluate for decrease in morbidity based on both length of stay in the intensive care unit and total inpatient length of stay.

Aim 2c: To evaluate sequential organ failure assessment score (SOFA) throughout intensive care length of stay.

Hypothesis

It is hypothesized that Bezlotoxumab will result in a decrease in 30-day mortality in patients with fulminant *C. difficile* colitis requiring surgical intervention compared to the placebo and current standard of care cohort.
Bezlotoxumab treatment with surgical intervention will also result in a decrease in morbidity associated with fulminant *C. difficile* colitis including end-organ failure, length of stay in the ICU, total inpatient hospitalization, and improved SOFA scores.

Background

Clostridioides difficile (*C. difficile*) is a gram-positive, anaerobic, and toxin-producing bacillus. *C. difficile* infection is the leading cause of nosocomial diarrhea and ranges in clinical severity from asymptomatic carriers to fulminant *C. difficile* colitis with sepsis and multi-system organ failure. Even with initial treatment, the recurrence rate of infection remains high, up to 20%. The risk of recurrent infection increases exponentially after the initial episode and with each subsequent infection, both the risk of mortality and readmission rates rise. Fulminant *C. difficile* colitis is defined as patients with a demonstration of *C. difficile* infection with abdominal pain, pyrexia, leukocytosis or leukopenia, hemodynamic instability, or need for the intensive care unit admission for organ failure. These patients are monitored closely within the intensive care setting and surgical teams are consulted for consideration for surgical management consisting of a colectomy with end ileostomy and continuation of antibiotic therapy. Lack of prompt response to maximum medical therapy is often the indication for surgical management, along with peritonitis at time of evaluation or evidence of perforation on imaging studies. The mortality rate for fulminant *C. difficile* colitis has been reported as high as 80%, in some studies, and increases further with any delay in surgical intervention. Even with surgical intervention, the morbidity and mortality rates remain as high as 60%. Surgery addresses the majority of the colon, but does not address the rectum as a source of toxin-production and can continue to be a cause of persistent toxemia. Often, Vancomycin rectal enemas will be continued in this particular patient population, but the efficacy of this treatment modality continues to be evaluated for efficacy and is an area of ongoing study. In our particular post-operative cohort at our institution, it has been observed that patients will continue to experience end-organ failure despite surgical removal of their colon. In fact, several patients continue to require long-term dialysis due to not obtaining renal recovery post-operatively and some continue to require respiratory support.

The virulence factors of *C. difficile* are products of the bacterium and not the bacterium itself. The main virulence factors are the clostridial toxins: toxin A and toxin B. Both toxins bind the colonic epithelium, undergo endocytosis, and form pores within the epithelial cells. They also inactivate intracellular Rho proteins, which are responsible for maintaining the integrity of the host cellular structure. Both mechanisms result in mucosal damage and a pro-inflammatory state producing colitis and severe infection. Tropism has also been demonstrated for the toxins to extra-intestinal tissue, resulting in toxin-mediated neurotoxicity, cardiotoxicity, and nephrotoxicity. This same tropism has been demonstrated in human bodily fluids during fulminant *C. difficile* infection and continues to be an area of high interest and evaluation. Several animal

studies have demonstrated that of the toxins, toxin B appears to be more virulent and independently pathogenic from toxin A.

Bezlotoxumab is a novel, therapeutic agent recently approved by the United States Food and Drug Administration for treatment in refractory, recurrent *C. difficile* infection with current standard of care antibiotics. It is a fully humanized monoclonal antibody that binds the N-terminal domains of toxin B with its Fab fragments resulting in complete neutralization of toxin B and prevents its adherence to the colonic mucosal cells. In the phase three clinical trial demonstrating its effectiveness in preventing recurrent *C. difficile*, Bezlotoxumab was administered intravenously in a ten milligram per kilogram dosing over sixty minutes. Dosing adjustments were not needed in patients with concurrent hepatic or renal dysfunction as the drug is metabolized via protein catabolism into smaller peptides and amino acids. The half-life of the drug was demonstrated to be approximately nineteen days. The benefit as a one-time dose administration that allows for restoration of the gut microbiome, with minimal serious adverse events, and no appreciated drug-drug interactions, make this a medication that is safe to use in a large patient population. Of note, there was demonstration of worsening of heart failure in patients previously diagnosed with heart failure, but this was not found to be statistically significant and it is recommended to be used with caution, if the risks outweigh the benefits.

Innovation/Significance of Research

This trial is innovative in the use of Bezlotoxumab. This novel monoclonal antibody has been proven effective in reducing recurrent *C. difficile* infection, but it has not been evaluated in studies to assess its efficacy as adjuvant therapy in patients requiring surgical intervention. In fulminant *C. difficile* colitis, toxemia is the result of toxins traversing the damaged colonic barrier resulting in systemic toxemia. Several novel studies have now shown this toxemia is causing extra-intestinal damage and contributing to the concomitant end-organ failure. The use of surgical intervention removes most of the organisms responsible for the production of the toxin and provides partial source-control, but it does not address the toxin already in circulation or address the rectum as a potential source of toxin production, as this is not resected in the operation. Using Bezlotoxumab as adjuvant therapy, the antibody can bind and inhibit toxin B in systemic circulation to potentially decrease the acute and chronic organ failure experienced in this patient population and provide further inhibition of the toxin within the rectum to result in a decrease in morbidity and mortality.

Procedures

Research Design

This will be an interventional prospective, randomized, double-blinded controlled trial performed at a single center. Prospective data will be collected of all consenting patients with a diagnosis of either initial or recurrent fulminant *C. difficile* colitis requiring surgical intervention. The data to be collected includes standard-of-care blood draws; no extra lab draws are planned for this trial. In the event labs are not drawn, we will plan to obtain serum creatinine, total bilirubin, and platelet counts to continue SOFA score evaluations while the patient is in the surgical ICU. Consent will be obtained either from the patient or their legally authorized representative. Inclusion criteria will be all patients over the age of eighteen with diagnosed fulminant *C. difficile* colitis requiring surgical colectomy with end ileostomy. Surgical intervention will be determined by the operating surgeon at time of initial consult assessment and during the follow-up assessments while the patient is hospitalized. Patients may be excluded on the account they are pregnant, prisoners/ incarcerated, have a previous administration of IVIG within 30-days of being randomized, or have a history of congestive heart failure.

Randomization will be performed through OSU's REDCap system with a computer generated randomization process and hospital investigational pharmacy blinding processes into both a therapeutic arm (Bezlotoxumab) and a placebo (normal saline) arm of the study. All current standards of care will continue to be administered in these patients, regardless of their respective study arm. To control for the antibiotics administered, the patients will need to be stratified according to the standard-of-care antibiotics and balanced in regards to this variable. Current standard of care therapy at our institution for fulminant *C. difficile* colitis includes Vancomycin (both oral and rectal, if needed) and intravenous Metronidazole. At this time, Bezlotoxumab is not standard of care, as it has not been studied in this patient population. Thus, there

are no known risks to patients not receiving Bezlotoxumab with the current standard of care regimen. Fulminant *C. difficile* colitis is defined, per our guidelines, as proven infection with hypotension/ shock, ileus, or megacolon.

Upon conclusion of the surgical intervention, the Anesthesia or nursing team will administer the trial medication, Bezlotoxumab, or the placebo, normal saline. Dosing is planned to be ten milligrams per kilogram, which is standard dosing for therapeutic Bezlotoxumab approved for use by the U.S. Food and Drug Administration. This dose will be administered as a one-time single-infusion dose administered over the span of one hour. The placebo administration of normal saline will be at the same dosing with a single-infusion over one hour. The patient will receive standard of care post-operative management and the information obtained from standard-of-care lab draws will be assessed throughout their hospital stay. The patient will be seen and evaluated in clinic in the post-operative period at the one month follow-up and either in clinic or via telephone at their three month and six month follow-up.

Sample Size

Based upon a sample size of n=50 patients per group, this study has 80% power to detect a 45% difference between groups in mortality; this calculation is based on a published mortality rate of 60%.

Screening/Consent

- Screening assessments will take place within 24 hours prior to surgical colectomy. This will be performed at the time of inpatient consult evaluation by a surgical resident and Attending Board-Certified Surgeon, who will assist in ensuring the Clinical Trial team is further notified.
- Patients will be screened for inclusion/exclusion criteria and consented per good clinical practice (GCP) and IRB guidelines. When consented, all patients will be assigned a unique number for identification purposes and, under no circumstances will a patient be assigned more than one allocation number.
- The Clinic Trial team will meet with all patients or their legal decision maker to discuss trial enrollment.

Randomization/Dosing

- Study team will generate a blinded randomization via computerized randomization.
- Investigational pharmacy will prepare the investigational product according to GCP guidelines and hospital pharmacy blinding processes.
- The two options for randomization consist of a placebo arm and a treatment arm. The placebo arm will receive a one-time single-infusion of normal saline dosed at 10mg/kg and have all standard-of-care (SOC) continued. Treatment arm will also continue with standard of care treatment with the addition of a one-time single-infusion of Bezlotoxumab dosed at 10mg/kg. The admission weight will be obtained for each candidate and this will be used to dose both the placebo and the treatment.
- If screening and randomization/dosing occur on the same calendar day, redundant assessments/labs will not be repeated.

Laboratory Assessments

- Standard-of-care labs will often be sufficient to evaluate SOFA scores
- If SOC labs are not obtained, the labs we will require for assessments of SOFA scores will be obtained by the Clinical Trial team and include: serum creatinine, total bilirubin, and platelet count

- If not already obtained prior to imaging or treatment at our institution, a serum or urine pregnancy test (if applicable) will be obtained to determine trial eligibility.

Data to be collected

Data will be collected and stored in OSU's REDCap database.

To control for the antibiotics administered, the patients will be stratified according to the standard-of-care antibiotics and balanced in regards to this variable.

Mortality will be analyzed based on 30-day survival and assessed using a Kaplan-Meier curve. Survival assessments will be performed for the second and third follow-up appointments as well, but the main point of interest in regards to mortality will be the 30-day mortality from operation.

Organ function, via SOFA score will be evaluated throughout the patient's hospitalization in the ICU. The ventilator free days, need for dialysis, evaluation for liver failure, and cardiac failure will also be monitored while the patient is hospitalized. This information will be obtained directly from information in the patient's chart. Daily lab draws will be able to assist in determining organ failure. This data will be analyzed using an analysis of variance (ANOVA) and paired t-test, as appropriate.

The length of ICU stay and total inpatient hospitalization will be recorded for the patient's initial presentation and immediately post-operatively. This will be analyzed via mean (average) calculations with standard deviations.

Specific Drug Requirements

The investigational pharmacy will need to purchase the drug and supplies locally as a marketed product to be used in our clinical trial. We plan on ordering 70 vials of Bezlotoxumab to account for patients that may require more than one vial based on their admission weight. The investigational drug will be prepared and diluted in solution by the investigational drug services (IDS) team.
The investigator and delegated research team members from IDS will be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, will meet all the qualifications specified by the applicable regulatory and sponsor requirements, and will provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.

The investigator and delegated research team from IDS members will:
• Ensure that the investigational product is used in accordance with the IRB approved protocol.
• Have continuous documented training on handling and dispensing of investigational products.
• Explain the correct use of the investigational product to each subject and will check, at intervals appropriate for the clinical research study, that each subject is following the instructions properly.
• In a randomized, double-blinded clinical research study, follow the study's randomization procedures, and ensure that the randomization assignment is broken only in accordance with the protocol. (If the clinical research study is double-blinded, the investigator will promptly document and explain to the sponsor any premature unblinding of the investigational product such as accidental unblinding or unblinding due to a serious adverse event.)
• If emergency breaking of the study drug blind is medically necessary, the delegated research team member will document the reasons for breaking the blind and contact the study sponsor and other required regulatory authorities immediately.

Receipt and Inventory

Upon receipt of study drugs, a delegated research team member will review the shipment to ensure the information on the packing slips matches exactly what has been received at the site. This includes verifying the content, amount of study drug, lot numbers, expiration dates, supplies required for blinding the drug and that randomization assignment have been received. All information is to be tracked on a Master Drug Accountability Log by IDS.

Safe Handling and Compounding

Study drug will be handled per the package insert and the Investigational Drug Service (IDS) guidelines. It will be prepared and diluted using sterile technique by the IDS.

Storage

The study drug will be stored in a secure environment that is lockable, separate from routine drug stock, with limited access for only the IDS. The site will ensure that the study drugs are stored according to the storage requirements detailed in the protocol or supplied by the sponsor. This includes ensuring the study drug is stored at the appropriate temperature and a temperature log will be maintained.
All refrigerators used for study drug storage will be plugged into outlets with back-up power where available. No food, drink, or specimens will be stored in the same location as study drug.

Dispensing of Study Drug

Prior to dispensing study drug, the delegated research team members from IDS will ensure that study drug supplies are adequate and within an appropriate expiration date. If additional supplies are needed, the monitor or study sponsor will be contacted to request additional study drug. The Master Drug Accountability Log will be updated any time study drug inventory changes. Documentation will include:

- Amount dispensed
- Lot number
- Name of individual dispensing study drug
- Subject's number
- Subject's initials
- Date (and time) of dispensing
- Date (and time) and amount of study drug returned

The delegated research team members from IDS will ensure that the correct study drug is used from the appropriate study supply and documented on the appropriate study drug accountability form.
Discrepancies in the amount dispensed to the subject, used by the subject, or amount expected to be returned by the subject will be documented along with the reason for the discrepancies.

Labeling of Study Drugs

All investigational drugs dispensed shall bear on the label "Investigational Drug: Limited by Federal Law to Investigational Use." Additional labeling information to be included: MRN, date, study number, study drug name, directions for use, quantity, and name of investigator and initials of dispensing staff.

Return/Destruction of Study Drug

At the conclusion of the study, the delegated research team member from IDS will ensure that all documentation regarding receipt, storage, dispensing, and return of used containers and unused study drug is complete, accurate, and ready for review for the termination visit.

Delegated research team members may appropriately destroy study drug at the site with written authorization and approval from the sponsor to do so. Destruction of study drug must follow institutional policies and procedures required by OSHA and biohazard materials policies. IDS will assist with study drug destruction, as needed.

Adverse Experience Reporting

All adverse events will be assessed for clinical significant by the investigator or designated sub-investigator, and documented if clinically significant. Any adverse events determined to be potentially related to study procedures or investigational product will be reported to the institutional review board.

Study Flowchart (see next page)

Procedures	**Screening** [a]	**Randomization/Dosing**	**Hospital Stay** [b]	**1st Outpatient FU (1 month ± 2 weeks)**	**2nd Outpatient FU (3 months post dc ± 2 weeks)** [c]	**3rd Outpatient FU (6 months post dc ± 2 weeks)** [c]
Informed Consent	X					
Demographics	X					
Past Medical History	X					
Inclusion/Exclusion	X					
Randomization		X				
Study Drug Infusion [d]		X				
Laboratory Assessments [e]	X	X	X			
Physical Exam (SOC)	X	X	X	X		
Symptom Assessment [f]	X	X	X	X		
Vital Signs (SOC)	X	X	X	X	X	X
SOFA Score [g, h]	X	X	X			
Concomitant Meds [i]	---------->					
Adverse Events [j]	---------->					
Pregnancy Test [k]	X					
Survival Assessment			X	X	X	X
Ventilator Assessment	X	X	X	X	X	X
Dialysis Assessment	X	X	X	X	X	X

a. If screening and randomization/dosing occur on the same calendar day, assessments do not need to be repeated
b. All procedures done daily during hospital stay unless otherwise noted
c. 2nd and 3rd outpatient follow-ups can be done by phone call if patient is unavailable to return to clinic
d. Study drug will be infused at the end of the surgical colectomy related to C. difficile colitis over one hour through intravenous infusion
e. All laboratory testing will be done per standard of care, with the exception of any labs not done per SOC that are needed to calculate a SOFA score (i.e. total bilirubin, serum creatinine, and platelet count).
f. Assessment will include monitoring for hepatic or cardiac failure, need for dialysis, and signs and symptoms related to C. difficile infection
g. SOFA scores will be calculated daily during ICU admission and as available per standard of care once patient has been stepped down from ICU level care.
h. Please see Appendix for oxygenation estimates and conversions.
i. Only concomitant medications relevant to diagnosis and treatment under study will be collected (i.e. antibiotics, steroids, etc.)
j. Only clinically significant adverse events will be recorded – adverse events will be assessed by the PI or designated Sub-Is

k. Pregnancy test for women of childbearing potential may be urine or serum, and if not done per standard of care will be done by research personnel.

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