NCT04626947

Title: Prevention of Recurrent Clostridium Difficile Infection (CDI) in Patients With Inflammatory Bowel Disease (IBD)

Protocol: Version 1. 10/25/2019

Study Title: Prevention of recurrent Clostridium difficile infection (CDI) in patients with inflammatory bowel disease (IBD)

Institution Name: University of Pittsburgh School of Medicine

Principal Investigator: David G. Binion, MD, AGAF, FACG
Professor of Medicine, Clinical and Translational Science
Co-Director, UPMC Inflammatory Bowel Disease Center
Director, Translational Inflammatory Bowel Disease Research
Director, Nutrition Support Service
Division of Gastroenterology, Hepatology and Nutrition
Department of Medicine. University of Pittsburgh School of Medicine

Investigator Contact Information: *BST WR 11 - 200 Lothrop Street. Pittsburgh, PA 15213*
412-647-7827 binion@pitt.edu

---

1. Objectives & Hypotheses

a. Primary objective: Compare the short term tolerability and effectiveness of enhanced CDI therapy with Bezlotuxumab in patients with IBD after CDI. Special attention will be paid to rates of recurrent CDI, healthcare utilization, quality of life and disease activity.

b. Secondary objective:
Evaluate the long term clinical outcomes of enhanced CDI therapy with Bezlotuxumab in patients with IBD. 90 days, 1 year and 2 year patterns of recurrent CDI, healthcare utilization, quality of life and disease activity will be assessed. We will use our published control population as well as patients who agree to be monitored but do not receive enhanced therapy as the control population.

Hypothesis: Administration of a human monoclonal antibody that binds to Clostridium difficile toxin B (Bezlotoxumab) in IBD patients with documented CDI will safely and effectively improved long-term clinical outcomes assessed by reduced rates of recurrent CDI, healthcare utilization, quality of life and disease activity and reduced overall charges associated with two year patterns of care.

2. Background & Rationale, Significance of Selected Topic & Preliminary Data

Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis are lifelong chronic inflammatory conditions characterized by multiple remitting and relapsing events. During their lifetime, patients will experience multiple hospitalizations and surgical interventions as a part of the natural course of their disease. IBD patients frequently require corticosteroids, immunomodulators and biologic agents to induce and

maintain remission, which may pose a risk for infectious complications. In addition to this iatrogenic risk from immunosuppression, IBD patients have frequent contact with the healthcare environment (hospitalization, emergency department and clinic) which can further increase their risk for infection, including enteric infection with Clostridium difficile (C difficile)(1)(2). New evidence suggests that the gut microbiome in patients with IBD is dysbiotic, with a reduced diversity of microflora, which may predispose these patients to develop enteric infectious complications, including C difficile infection (CDI).(3) Epidemiologic evidence and single center studies have demonstrated that IBD patients are at increased risk of developing C difficile infection (CDI) and recurrent CDI, likely due to an underlying dysbiosis in their enteric flora as well as their impaired ability to mount an immune response to C difficile toxin, which may be linked to iatrogenic side effects of immunosuppression with systemic corticosteroids, immunomodulators and biologic agents(4).

Our group has previously demonstrated that IBD patients are at increased susceptibility for developing CDI and clinical outcomes of CDI in the IBD patient population are overall worse, with increased morbidity and mortality(5)(6). This work was performed prior to the advent of enhanced immunotherapeutics targeting C difficile toxins (i.e. bezlotuximab) (7). Due to the need for uniformity in the short term clinical response to anti-C difficile therapy, and a clinical read out emphasizing diarrhea resolution, IBD patients were excluded from many of the pivotal trials on new agents for the treatment and prevention of CDI over the past decade. This was necessary as CDI will frequently trigger a “flare” of underlying IBD related inflammation, which will make interpretation of C. difficile treatment too difficult. As a result of this pragmatic trial necessity, there is very limited data regarding the effectiveness, tolerability and long-term impact of these newer agents on a high risk population of patients, who would theoretically have the most benefit from improved CDI treatment. This lack of evidence has unfortunately been used as a barrier, preventing IBD patients from gaining access to enhanced CDI treatment. Thus a “Catch-22” scenario has emerged, where IBD patients, who suffer from complex and severe CDI which frequently precipitates flare of their underlying IBD, where excluded from the pivotal trials (out of necessity), but the resulting lack of evidence now functions as a barrier to their ability to receive these more effective, albeit more costly upfront treatments.
This proposal seeks to address this knowledge gap by specifically treating IBD patients with C difficile antibody approaches to demonstrate effectiveness as well as improved long-term outcomes and overall cost-effectiveness.

In order to demonstrate an improved long-term natural history following enhanced C difficile therapy in IBD, our group had to first demonstrate the natural, multiyear history of CDI on patients with IBD using existing treatment modalities. Our recently published manuscript characterizing the long-term natural history of IBD following CDI clearly demonstrates that the underlying IBD accelerates in many of the patients experiencing this infection. This project, performed with the support of an investigator initiated study (IIS) from Merck, used a propensity score matching strategy to determine an appropriate IBD control population to assess the impact of CDI over the year of infection and the year following infection. This work led to important insights regarding CDI in IBD(5). The propensity score matching was performed in the year preceding the CDI, and the matching was carried out for 24 criteria known to be relevant for the development of CDI. IBD patients at risk for CDI were in general sicker than the average patient, with higher rates of steroid exposure, hospitalization and antibiotic exposure, compared with the

average patient in the clinic. As expected, C difficile exerted a negative effect on the natural history of IBD and is associated with an increase in IBD severity and healthcare utilization. During the year of CDI, IBD patients had an increased objective evidence of inflammation, increased disease activity scores and lower quality of life scores when compared to those who did not have CDI. Most importantly, we demonstrated that within this vulnerable population, CDI has a long lasting, negative effect on patient clinical trajectories, which was clearly evident in the year after infection. IBD patients with CDI continued to require antibiotics and demonstrated a 6 fold increase in healthcare charges compared with matched individuals who did not experience CDI. IBD patients with CDI generated mean healthcare charges (irrespective of pharmacy charges) of $48,000 annually, compared with an expected median charge of $7,000 in the matched control population.
Thus, we proposed to prospectively assess the short and long-term impact of enhanced CDI therapy in the IBD patient population with Bezlotuxumab. Having defined the natural history of CDI over a 2 year time period, we will use an identical structure to determine if there is an improvement in clinical trajectory with enhanced CDI therapy the year after infection.

3. Study Design:

This is a prospective, single center, non-randomized, observational, open label study to compare tolerability, efficacy, and short and long term clinical outcomes of Bezlotuxumab in CDI IBD patients.
A total number of 50 patients will be enrolled. Patients who agreed to receive Bezlotuxumab will be compared to our recently published historical controls as well as IBD registry patients who do not elect to receive enhanced C difficile therapy.

Patient population will include any patient who receives care at the Digestive Disorder Center at UPMC Presbyterian Hospital.

Inclusion criteria: >18 years old, diagnosis of IBD and CDI.
Exclusion criteria: <18 years old, no IBD, no CDI, history of colectomy.

4. Study Flowchart

Data collection:

Visit 1 (Enrollment)

a. Demographic information
b. type of IBD
c. disease duration
d. history of bowel resection
e. current medications
f. inflammatory markers: CRP, ESR, Albumin
g. CBC
h. quantitative immunoglobulins
i. Vitamin levels (Vit D and Vit B)
j. Disease related quality of life (SIBDQ)
k. Disease activity scores (HBI-UCAI)
l. Dietary intake (sugar and fat intake)

m. Stool sample

Visit 2 (90 days after enrollment)
Clinic visit or Telephone call
a. inflammatory markers: CRP, ESR, Albumin (if available as a standard of care)
b. CBC (if available as a standard of care)
c. Disease related quality of life (SIBDQ)
d. Disease activity scores (HBI-UCAI)
e. ED visits
f. Hospital admissions

Visit 3 (1 year after enrollment)
Clinic visit or Telephone call
a. inflammatory markers: CRP, ESR, Albumin (if available as a standard of care)
b. CBC (if available as a standard of care)
c. Disease related quality of life (SIBDQ)
d. Disease activity scores (HBI-UCAI)
e. ED visits
f. Hospital admissions

Visit 4 (24 months after enrollment)
Clinic visit or Telephone call
a. inflammatory markers: CRP, ESR, Albumin (if available as a standard of care)
b. CBC (if available as a standard of care)
c. Disease related quality of life (SIBDQ)
d. Disease activity scores (HBI-UCAI)
e. ED visits
f. Hospital admissions
g. Total charges associated with cost of care

5. Study Procedures:

This is a prospective observational study comparing the effectiveness of Bezlotuxumab to reduce rates of CDI in patients with IBD. We will evaluate short and long-term clinical outcomes after treatment with Bezlotuxumab.

Patients who are part of the IBD Registry and have a defined IBD diagnosis and CDI will be approached to be consented for this study. Randomly the study treatment will be offered to 50 patients.
Diagnosis of CDI will be accomplished using the standard CLIA certified strategies employed in our microbiology/virology clinical laboratories, which include PCR amplification, two step GDH /gene amplification of liquid/unformed stool samples.
Patients will be divided into 2 groups of treatment and followed in a parallel fashion for the next 2 years: 1. Those who agree to receive Bezlotuxumab (Case) and 2. Those who do not agree to received Bezlotuxumab (controls).

6. Study Duration:

Total duration time: 5 years. 36 months enrollment and 24 months follow up.

7. Statistical Analysis and Sample Size Justification:

Sample size: 50 (Based on the prevalence of CDI within our patient population)

Descriptive statistics of baseline characteristics will be used to characterize the 50 IBD CDI patients who agree to receive Bezlotuxumab. The baseline characteristics under consideration include demographic data, type of IBD, duration of IBD, current medications, inflammatory markers, SIBDQ, HBI-UCAI and others collected at the time of enrollment. Mean, standard deviation, median and interquartile range will be reported on continuous variables and proportions reported on discrete variables.
Similar baseline characteristics will be collected at enrollment among historical controls and IBD registry patients who do not elect/ not offered to receive enhanced C difficile therapy. Similar descriptive statistics will be used to characterize these controls. A logistic regression model will be developed to predict the status of receiving Bezlotuxumab from the extensive list of baseline characteristics. Subsequently each study participant, including both the 50 patients who receive Bezlotuxumab and the controls, will be assigned a predicted probability of treatment based on this propensity score model. The inverse probability weighting method will be used to compare the Bezlotuxumab-treated IBD CDI patients and the controls in baseline characteristics to demonstrate balanced baseline characteristics between the two groups after inverse probability weighting (8).

In the primary analysis, we will compare the risk of recurrent CDI between the 50 treated and 118 controls at 90 days after enrollment. The inverse propensity score-weighted method will be used to estimate the proportion of recurrence CDI at 90 days under Bezlotuxumab among IBD CDI patients seen in the clinics and compared with that for IBD CDI patients without Bezlotuxumab. Other long-term outcomes for comparison include, number of healthcare utilization (emergency room visits and hospitalization), overall charges during the second year after the study enrollment; inflammatory markers and CBC (in continuum and binary: abnormal vs normal), SIBDQ, HBI-UCAI, dietary intake at the 90 days, 12-month and 24-month visits. The inverse probability-weighted method will be used to compare these outcomes between Bezlotuxumab-treated and controls with IBD CDI. Cardiac failure will be closely monitored throughout this study and the proportions of cardiac failure among the 50-treated patients by the first 90 days, 12 months and 24 months will be estimated. The paired t-test or the nonparametric signed-rank test will be used to test the change baseline to the 24-month visit in continuous outcomes and the McNemar test will be used to for discrete outcomes.(9)

Using data from the 50 IBD CDI patients, linear-mixed models and generalized linear-mixed models will be used to explore the longitudinal change in the repeatedly measured assessments of disease activity and quality of life, including current medications, inflammatory markers, annual overall financial charges, annual use of healthcare facilities (such as emergency room visit and number of hospitalizations) SIBDQ, and HBI-UCAI. Trajectory analyses on these multiple longitudinal patient outcomes will be used to identify IBD CDI patients who have responded to the treatment and who have not. Subsequently we will compare the baseline patient characteristics between the treatment responders and non-responders and the results will be invaluable in guiding future management of IBD CDI patients.

Based on data from 28 IBD CDI patients, it was reported that the proportion of IBD patients with recurrent CDI within 12 weeks of follow-up was 26.7% among Bezlotuxumab-treated and 53.8% among those without Bezlotoxumab (10-11). With 118 controls and 50 Bezlotuxumab-treated patients, we will have 88% power to detect the same difference by using the Fisher's Exact test with a 2-sided alpha level at 0.05.

8. Specific Drug Supply Requirements:

Bezlotuxumab: single 10-mg/kg dose administered as an IV infusion over 60 minutes. Commercial product open label of Bezlotuxumab will be required from MSD. (for 55 patients)

9. Adverse Experience Reporting:

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of the causality to the study drug will be reported to the Principal Investigator and also to the University of Pittsburgh IRB. All SAEs and UPs must be reported Within 24 hours of first awareness of the event.

10. References:

1. *Sokol H, Lalande V, Landman C, Bourrier A, Nion-Larmurier I, Rajca S, et al. Clostridium difficile infection in acute flares of inflammatory bowel disease: A prospective study. Dig Liver Dis. 2017 Jan 30;*
2. *Stoica O, Trifan A, Cojocariu C, Gîrleanu I, Maxim R, Stanciu MC. Incidence and risk factors of Clostridium difficile infection in patients with inflammatory bowel disease. Rev Med Chir Soc Med Nat Iasi. 2015 Mar;119(1):81–86.*
3. *Bien J, Palagani V, Bozko P. The intestinal microbiota dysbiosis and Clostridium difficile infection: is there a relationship with inflammatory bowel disease? Therap Adv Gastroenterol. 2013 Jan;6(1):53–68.*
4. *Maharshak N, Barzilay I, Zinger H, Hod K, Dotan I. Clostridium difficile infection in hospitalized patients with inflammatory bowel disease: Prevalence, risk factors, and prognosis. Medicine. 2018 Feb;97(5):e9772.*
5. *Anderson A, Click B, Ramos-Rivers C, Cheng D, Babichenko D, Koutroubakis IE, et al. Lasting Impact of Clostridium difficile Infection in Inflammatory Bowel Disease: A Propensity Score Matched Analysis. Inflamm Bowel Dis. 2017;23(12):2180–2188.*
6. *Anderson AJ, Click B, Ramos-Rivers C, Babichenko D, Koutroubakis IE, Hartman DJ, et al. Development of an Inflammatory Bowel Disease Research Registry Derived from Observational Electronic Health Record Data for Comprehensive Clinical Phenotyping. Dig Dis Sci. 2016 Sep 12;61(11):3236–3245.*
7. *Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. N Engl J Med. 2017 Jan 26;376(4):305–317.*
8. *Robins, JM; Rotnitzky, A; Zhao, LP (1994). "Estimation of regression coefficients when some regressors are not always observed". Journal of the American Statistical Association. 89 (427): 846–866. doi:10.1080/01621459.1994.10476818.)*
9. *Agresti, Alan (2002). Categorical Data Analysis. Hooken, New Jersey: John Wiley & Sons, Inc.) To adjust for multiple testings, the Hochberg's step-up procedure will be used to control the familywise error rate at 0.05. (Reference: Hochberg, Yosef (1988). "A Sharper Bonferroni Procedure for Multiple Tests of Significance". Biometrika. 75 (4): 800–802.*

10. Wilcox MH, et al. N Engl J Med 2017;376:305–317.
11. Kelly CP et al, Gastroentoroloty, 2018, 155: 1270-1271).