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Bezlotoxumab for prevention of *Clostridioides difficile* recurrence in patients with inflammatory bowel disease: a retrospective multicenter experience

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Abstract

Background Bezlotoxumab can reduce recurrent *Clostridioides difficile* infection (rCDI); however, data from patients with inflammatory bowel disease (IBD) are limited. Since rCDI is common in IBD, we assessed the efficacy of bezlotoxumab for rCDI prevention in patients with and without IBD.

Methods Adults who received bezlotoxumab for CDI were identified. Clinical variables and adverse events were collected during a minimum follow-up of 1 year. The primary outcome was rCDI, classified at 4 time intervals (30, 60, 90 days, and 1 year).

Results Of the 70 patients identified, 34 patients had IBD. Most patients (88.6%) had ≥2 prior CDI episodes (interquartile range [IQR] 1-4). Bezlotoxumab was commonly combined with vancomycin (61.4%) or fidaxomicin (42.9%), which did not differ between patients with and without IBD. Following bezlotoxumab, the 1-year rCDI rate was 28.6% (median 65 days, IQR 32.8-158.3), while the 30-, 60- and 90-day rCDI rates were 5.7%, 12.9% and 22.9%, respectively. Patients with IBD had comparable rCDI rates to non-IBD patients, including at 30 (5.9% vs. 5.6%, P>0.99), 60 (17.6% vs. 8.3%, P=0.30), and 90 days (20.6% vs. 13.9%, P=0.54), and 1 year (32.4% vs. 25.0%, P=0.60). A history of colorectal surgery or vancomycin exposure was more common among patients with IBD and rCDI. Adverse events occurred in 6 patients (8.6%), most commonly heart failure exacerbation.

Conclusions The rCDI rate following bezlotoxumab was similar in patients with and without IBD. In patients with IBD, a history of colorectal surgery or prior vancomycin exposure was more common among those who experienced rCDI.

Keywords Inflammatory bowel disease, bezlotoxumab, recurrent *Clostridioides difficile* infection

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Introduction

Clostridioides difficile infection (CDI) is a common infection with symptoms ranging from mild diarrhea to fulminant colitis [1]. Particularly problematic is the rate of recurrent CDI (rCDI), which is more common among patients who are older or immunocompromised, or have significant comorbid conditions [2,3]. Patients with inflammatory bowel disease (IBD) are at increased risk of CDI, CDI-related morbidity and rCDI compared to the general population [4-6].

Current recommendations for CDI and rCDI treatment focus on antimicrobial therapy and fecal microbiota transplantation (FMT), or other microbiome restoration therapies [7]. Additionally, for patients with prior rCDI, or patients considered to be at high risk of recurrence, guidelines recommend the use of the anti-toxin B monoclonal antibody bezlotoxumab to reduce the risk of recurrence [2,8]. Bezlotoxumab has been shown to reduce the rate of rCDI when used in conjunction with standard-of-care antimicrobials, potentially through neutralizing the effect of *Clostridioides*

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difficile toxin B and thus preventing toxin-mediated intestinal mucosal injury [9]. However, available data to guide clinicians in the use of bezlotoxumab for patients with IBD and CDI are limited to a *post hoc* analysis of the MODIFY I/II trial [10] and case studies [11].

Herein, we summarize our real-world experience using bezlotoxumab in high-risk patients with and without IBD for rCDI prevention across a tri-state medical network in the United States. Our main aim was to characterize the rate of rCDI in our patient population in hopes of informing future practice.

Patients and methods

Patient selection

We retrospectively identified adult patients with and without a history of IBD who received bezlotoxumab for CDI between November 1, 2016, and November, 2023 (Fig. 1). The selection of this time period was based on the initial United States Food and Drug Administration approval of bezlotoxumab in 2016. An initial cohort of 159 patients was identified using the ICD-10 codes for CDI (A04.7*) and a history of treatment with bezlotoxumab. Patients were then stratified into 2 groups by history of IBD, using ICD-10 codes (K50.*, K51.*). Verification of the IBD diagnosis (confirmed by biopsy or endoscopy), CDI diagnosis (confirmed by stool testing) and bezlotoxumab use (confirmed by infusion documentation) was performed manually. All patients received bezlotoxumab as a single 10 mg/kg intravenous infusion over 60 minutes. CDI was defined as: (a) presence of the toxigenic *C. difficile* bacterium by polymerase chain reaction and positive toxin enzyme immunoassay; or (b) presence of toxigenic *C. difficile* bacterium by polymerase chain reaction in patients with acute diarrheal illness (defined as ≥3 loose bowel movements/day for ≤2 weeks) [1,8]. In patients with IBD, diarrheal illness was defined as ≥3 loose bowel movements/day or change from baseline stool consistency or frequency.

Patients were excluded if the CDI diagnosis or bezlotoxumab therapy could not be verified. Only patients with a confirmed diagnosis of IBD were included in the IBD cohort. Patients with IBD who had received bezlotoxumab prior to their IBD diagnosis were excluded from both the IBD and non-IBD cohorts. Additionally, patients were excluded if they did not have a minimum of 1 year's follow-up data after bezlotoxumab therapy, defined as clinical encounters, or notes between the patient and a gastroenterologist or member of the gastroenterology team. Following manual verification and exclusion, a total of 70 patients were identified, of whom 34 had a history of IBD. Institutional Review Board approval was obtained for the study.

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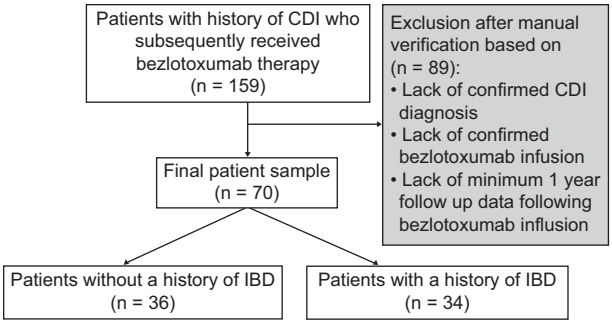

Figure 1 Patient selection diagram
CDI, Clostridioides difficile infection; IBD, inflammatory bowel disease

Data collection

Patient demographics, medical history and clinical data were collected. Demographic data included age at first CDI and sex. Clinical data included comorbid conditions, according to the Charlson Comorbidity Index (CCI), and history of organ or bone marrow transplantation. For patients with a history of IBD, clinical data included IBD subtype, Montreal classification and prior surgical history. The Montreal classification was recorded prior to the first CDI episode. The use of either IBD or non-IBD directed immunomodulatory medications (IMM) at the time of bezlotoxumab administration was recorded, with patients categorized by number and subtype of IMM. IMMs were defined as systemic glucocorticoids (doses equivalent to ≥20 mg/day prednisone), tumor necrosis factor inhibitors, integrin inhibitors, interleukin inhibitors, Janus kinase inhibitors, thiopurines and calcineurin inhibitors. Topical corticosteroids and budesonide were not included among IMMs, given their lack of significant systemic absorption.

In terms of CDI-related clinical variables, data was collected for both prior episodes of CDI and the CDI episode for which bezlotoxumab therapy was applied (henceforth referred to as "bezlotoxumab-targeted CDI" [BZ-CDI]). Prior CDI history included the number of CDI episodes and prior CDI-directed therapy. For the BZ-CDI episode, data collected included CDI classification (initial, first recurrence, or second recurrence and beyond), severity, time between BZ-CDI diagnosis and bezlotoxumab infusion, age at bezlotoxumab infusion, and concomitant CDI-directed therapy (vancomycin, fidaxomicin, FMT). No patients received non-FMT fecal microbiota-based therapy (live-jslm/Rebyota, live-brpk/Vowst); thus, this was not included in the analysis. Bezlotoxumab-related adverse effects were also collected.

The primary outcome of interest was rCDI following bezlotoxumab therapy, defined as symptom recurrence and positive confirmatory testing following resolution of the BZ-CDI episode [1]. Recurrence was classified within 4 timeframes (30, 60 and 90 days, and 1 year) following bezlotoxumab therapy. To differentiate rCDI from unresolved CDI, rCDI was only counted if it occurred after CDI resolution (defined as resolution of diarrhea, return to baseline bowel habits in patients with IBD, and/or negative stool testing for CDI). Additionally, recurrence of diarrheal symptoms in patients

with or without IBD where testing was negative for CDI (or no CDI testing was performed) was not counted as an rCDI episode.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics as medians with interquartile ranges (IQR) for continuous variables, and proportions for categorical variables. Wilcoxon rank sum (for continuous variables) and Fisher exact tests (for categorical variables) were performed to compare baseline characteristics between patients with and without IBD. Additional analysis was performed to compare patients with IBD who experienced rCDI with those who did not. All tests were 2-sided, with the alpha level set at 0.05 for statistical significance. Analysis was performed using SPSS statistical software (version 25, IBM SPSS).

Results

Demographics

Of the 70 patients who received bezlotoxumab for rCDI prevention and had a minimum of 1 year's follow-up data, 34 patients had IBD. Patient demographics and characteristics are detailed in Table 1. Of the patients with IBD, 47.1% had Crohn's disease (CD) and 52.9% had ulcerative colitis (UC). In terms of IBD classification (Table 2), most patients with UC had left-sided (50%) or extensive disease (38.9%) with severe symptoms (50%).

Table 1 Comparison of baseline characteristics, comorbidities, and CDI recurrence

Variable	Median (IQR) or number (%)			
	All Patients N=70	IBD Patients N=34	Non-IBD Patients N=36	P-value
	Demographics			
Age at first CDI (years)	60.6 (35.6-71.9)	45.0 (29.6-61.3)	68.2 (53.9-75.7)	<0.001
Male	33 (47.1%)	17 (50.0%)	16 (44.4%)	0.811
Caucasian	64 (91.4%)	31 (91.2%)	33 (91.7%)	0.900
	Comorbidities			
IBD				
Crohn's disease	16 (22.9%)	16 (47.1%)	NA	NA
Ulcerative colitis	18 (25.7%)	18 (52.9%)	NA	NA
Heart failure	10 (14.3%)	2 (5.9%)	8 (22.2%)	0.085
Diabetes mellitus	20 (28.6%)	3 (8.8%)	17 (47.2%)	<0.001
Chronic obstructive pulmonary disease	4 (5.7%)	1 (2.9%)	3 (8.3%)	0.615
Chronic kidney disease	21 (30.0%)	4 (11.8%)	17 (47.2%)	0.002
Liver cirrhosis	6 (8.6%)	2 (5.9%)	4 (11.1%)	0.674
Leukemia or lymphoma	7 (10.0%)	0 (0.0%)	7 (19.4%)	0.011
Cancer (any)	19 (21.1%)	4 (11.8%)	15 (41.7%)	0.007
Transplant (any)	13 (18.6%)	2 (5.9%)	11 (30.6%)	0.012
Autoimmune disease (any)	3 (4.3%)	0 (0.0%)	3 (8.3%)	0.240
Charlson Comorbidity Index	4.0 (1.0.-9.0)	1.5 (0.0-4.0)	8.0 (4.0-10.0)	<0.001
	CDI history			
Prior CDI episodes	2.0 (1.0-4.0)	3.0 (2.0-4.0)	2.0 (1.0-3.0)	0.122
Prior CDI treatment (not mutually exclusive)				
Vancomycin	57 (81.4%)	27 (79.4%)	30 (83.3%)	0.763
Fidaxomicin	23 (32.9%)	15 (44.1%)	8 (22.2%)	0.075
Fecal microbiota transplant	14 (20%)	10 (29.4%)	4 (11.1%)	0.075

(*Contd...*)

Table 1 (*Continued*)

Variable	Median (IQR) or number (%)			
	All Patients N=70	IBD Patients N=34	Non-IBD Patients N=36	P-value
CDI history				
CDI classification for which bezlotoxumab received				
Episode				
Initial	8 (11.4%)	3 (8.8%)	5 (13.9%)	>0.99
1st recurrence	13 (18.6%)	4 (11.8%)	9 (25.0%)	0.112
2nd recurrence and beyond	49 (70.0%)	27 (79.4%)	22 (61.1%)	0.121
Severity				
Non-severe	30 (42.9%)	20 (58.8%)	10 (27.9%)	0.015
Severe	31 (44.3%)	10 (29.4%)	21 (58,3%)	0.018
Fulminant	9 (12.9%)	4 (11.8%)	5 (13.9%)	>0.99
Time from CDI to bezlotoxumab (days)	24.5 (13.0-40.5)	25.5 (14.0-40.8)	19.5 (9.5-41.0)	0.781
Age at bezlotoxumab infusion (years)	61.0 (41.6-73.2)	48.5 (33.4-62.0)	69.7 (55.0-78.0)	<0.001
Concomitant antibiotic therapy with bezlotoxumab (not mutually exclusive)	70 (100%)	34 (100%)	36 (100%)	>0.99
Vancomycin	43 (61.4%)	21 (61.8%)	22 (61.1%)	>0.99
Fidaxomicin	30 (42.9%)	15 (44.1%)	15 (41.7%)	>0.99
Fecal microbiota transplant	6 (8.6%)	3 (8.8%)	3 (8.3%)	>0.99
Post-bezlotoxumab outcomes				
CDI recurrence				
30-day	4 (5.7%)	2 (5.9%)	2 (5.6%)	>0.99
60-day	9 (12.9%)	6 (17.6%)	3 (8.3%)	0.300
90-day	12 (17.1%)	7 (20.6%)	5 (13.9%)	0.535
1 year	20 (28.6%)	11 (32.4%)	9 (25.0%)	0.599
Time to CDI recurrence	65.00 (32.8- 158.3)	49.0 (32.0-132.0)	69.0 (35.0-219.0)	0.395
Adverse events (any)	6 (8.57%)	0 (0.0%)	6 (16.7%)	0.025
Heart failure exacerbation	4 (5.71%)	0 (0.0%)	4 (11.11%)	0.115
Nausea	1 (1.43%)	0 (0.0%)	1 (2.78%)	>0.99
Transfusion reaction	1 (1.43%)	0 (0.0%)	1 (2.78%)	>0.99
Immunomodulatory medication use (at time of bezlotoxumab administration)				
No immunosuppressant	33 (41.1%)	10 (29.4%)	23 (63.9%)	0.005
1 immunosuppressant	23 (32.9%)	17 (50.0%)	6 (16.7%)	0.005
2 or more immunosuppressants	14 (20.0%)	7 (20.6%)	7 (19.4%)	>0.99
TNF inhibitors (infliximab, adalimumab)	8 (11.4%)	8 (23.5%)	0 (0.0%)	0.002
Integrin inhibitors (vedolizumab)	3 (4.3%)	3 (8.8%)	0 (0.0%)	0.109
Interleukin inhibitors (ustekinumab)	9 (12.9%)	9 (26.5%)	0 (0.0%)	<0.001
JAK inhibitor (tofacitinib)	1 (1.4%)	1 (2.9%)	0 (0.0%)	0.486
Corticosteroids (>20mg prednisone equivalent)	8 (11.4%)	6 (17.6%)	2 (5.6%)	0.145
Thiopurines (6-MP, AZA)	5 (7.1%)	3 (8.8%)	2 (5.6%)	0.669
Calcineurin inhibitors (tacrolimus, cyclosporin)	13 (18.6%)	2 (5.9%)	11 (30.6%)	0.012

CDI, Clostridioides difficile infection; IQR, interquartile range; IBD, inflammatory bowel disease; JAK, Janus kinase; TNF, tumor necrosis factor

For CD, most had ileocolonic disease (68.8%) and non-stricturing/non-penetrating (37.5%) or penetrating/fistulizing (43.8%) type.

Compared to patients without IBD, patients with IBD were younger at first CDI (45.0 vs. 68.2 years, P<0.001) and had fewer comorbid conditions (CCI 1.5 vs. 8.0, P<0.001), including a significantly lower prevalence of diabetes (8.8% vs. 47.2%), chronic kidney disease (11.8% vs. 47.2%), malignancy (11.8% vs. 41.7%), and history of transplant (5.9% vs. 30.6%).

Table 2 Inflammatory bowel disease classification

Montreal classification			
Ulcerative colitis	All patients N=18	Recurrent CDI N=5	No recurrent CDI N=13
Extent			
E1: Ulcerative proctitis	2 (11.1%)	0	2 (15.4%)
E2: Left sided	9 (50.0%)	3 (60.0%)	6 (46.2%)
E3: Extensive	7 (38.9%)	2 (40.0%)	5 (38.5%)
Severity			
S0: Clinical remission	3 (16.7%)	0	3 (23.1%)
S1: Mild	3 (16.7%)	1 (20.0%)	2 (15.4%)
S2: Moderate	3 (16.7%)	1 (20.0%	2 (15.4%)
S3: Severe	9 (50.0%)	3 (60.0%)	6 (46.2%)
Crohn's disease	All patients N=16	Recurrent CDI N=6	No recurrent CDI N=10
Age of onset			
A1: ≤16 years	2 (12.5%)	1 (16.7%)	1 (10.0%)
A2: 17-39 years	12 (75.0%)	3 (50.0%)	9 (90.0%)
A3: ≥40 years	2 (12.5%)	2 (33.4%)	0
Disease location			
L1: Ileal	2 (12.5%)	2 (33.4%)	0
L2: Colonic	3 (18.8%)	0	3 (30.0%)
L3: Ileocolonic	11 (68.8%)	4 (66.7%)	7 (70.0%)
L4: Isolated upper	0	0	0
Disease phenotype			
B1: Non-stricturing, non-penetrating	6 (37.5%)	2 (33.4%)	4 (40.0%)
B2: Stricturing	3 (18.8%)	2 (33.4%)	1 (10.0%)
B3: Penetrating/ fistulizing	7 (43.8%)	2 (33.4%)	5 (50.0%)
p: Perianal disease	4 (25.0%)	3 (50.0%)	1 (10.0%)

CDI, Clostridioides difficile infection

CDI history

Prior CDI episodes

Most patients (62, 88.6%) had ≥1 prior episodes of CDI (median 2, IQR 1-4, range 1-10). In terms of previously received CDI therapy, 81.4% of patients had received vancomycin, 32.9% had received fidaxomicin, and 20% had undergone FMT prior to bezlotoxumab. No significant differences in CDI history were noted between patients with or without IBD (Table 1).

BZ-CDI episode

Bezlotoxumab was most commonly given following the second occurrence of CDI (70%), with severity classified as non-severe in 42.9%, severe in 44.3% and fulminant in 12.9%. The median time from BZ-CDI to bezlotoxumab administration was 24.5 days (IQR 13.0-40.5). Bezlotoxumab was given along with antimicrobial therapy in all patients, with vancomycin (61.4%) and fidaxomicin (42.9%) being the most common. Concomitant IMMs were used in 58.9% of patients, with 20% receiving 2 or more IMMs (Table 1).

Patients with IBD were significantly younger at the time of bezlotoxumab administration (48.5 vs. 69.7 years), receiving bezlotoxumab more commonly during a non-severe CDI episode (58.8% vs. 27.9%). A non-significant trend towards receiving bezlotoxumab earlier was also noted in patients with IBD, who frequently received bezlotoxumab during an initial CDI or first recurrence. No difference was noted in terms of time from BZ-CDI to bezlotoxumab or concomitant antimicrobial therapy, although a greater proportion of patients with IBD were receiving IMMs (70.6% vs. 36.1%).

Recurrent CDI following bezlotoxumab

The rate of rCDI at 1 year following bezlotoxumab was 28.6% (median 65 days, IQR 32.8-158.3). The 30-, 60- and 90-day rCDI rates were 5.7%, 12.9% and 17.1%, respectively (Table 1). The rate of rCDI did not differ significantly between patients with and without IBD (overall rate 32.4% vs. 25.0%, P=0.60; 30-day rate 5.9% vs. 5.6%, P>0.99; 60-day rate 17.6% vs. 8.3%, P=0.30; and 90-day rate 20.6% vs. 13.9%, P=0.54; Table 1). Adverse reactions to bezlotoxumab occurred in 6 (8.57%) patients, all without IBD. The most common adverse reaction was heart failure exacerbation.

Comparing patients with IBD who experienced rCDI following bezlotoxumab therapy with those who did not, no difference was noted in the demographic, comorbid or CDI-related variables (Table 3). This included no significant difference in the number of prior CDI episodes, BZ-CDI classification, severity, time from BZ-CDI to bezlotoxumab infusion, concomitant antimicrobial therapy, or concomitant IMM. In terms of IBD classification, for patients with UC there was no difference in rCDI between patients with extensive versus non-extensive disease (28.0% vs. 27.0%, P>0.99) or severe versus non-severe disease (33.3% vs. 22.2%, P>0.99). For CD, rCDI was not significantly different between patients with ileal versus colonic/ileocolonic disease (100% vs. 28.6%, P=0.13), or between patients with non-stricturing/non-penetrating versus stricturing or penetrating disease (33.3% vs. 30%, P>0.99). In terms of surgical resection, rCDI was more common among patients with IBD who had prior colorectal surgery (81.8% vs. 21.7%, odds ratio [OR] 16.2, 95% CI 2.61-100.48; P=0.002), including patients with an ileal pouch (45.5% vs. 4.3%, OR 18.3, 95% CI 1.79-188.13; P=0.008). Additionally, exposure to vancomycin prior to the BZ-CDI episode was more common among patients with IBD who experienced rCDI, although no significant difference was noted for prior fidaxomicin or FMT exposure.

Table 3 Comparison of baseline characteristics, comorbidities and CDI recurrence in patients with IBD

Variable	Median (IQR) or Fraction (%)			
	All IBD Patients N=34	Recurrent CDI N=11	No recurrent CDI N=23	P value
Demographics				
Age at first CDI (years)	45.0 (29.6-61.3)	44.3 (32.5-60.9)	47.3 (26.7-62.7)	0.419
Male	17 (50.0%)	5 (45.5%)	12 (52.2%)	>0.99
Caucasian	31 (91.2%)	11 (100.0%)	20 (87.0%)	0.455
Comorbidities				
IBD				
Crohn's disease	16 (47.1%)	6 (54.5%)	10 (43.5%)	0.717
Ulcerative colitis	18 (52.9%)	5 (45.5%)	13 (56.5%)	
Heart failure	2 (5.9%)	0 (0.0%)	2 (8.7%)	>0.99
Diabetes mellitus	3 (8.8%)	0 (0.0%)	3 (13.0%)	0.535
Chronic obstructive pulmonary disease	1 (2.9%)	0 (0.0%)	1 (4.3%)	>0.99
Chronic kidney disease	4 (11.8%)	1 (9.1%)	3 (13.0%)	>0.99
Liver cirrhosis	2 (5.9%)	0 (0.0%)	2 (8.7%)	>0.99
Leukemia or lymphoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Cancer (any)	4 (11.8%)	2 (18.2%)	2 (8.7%)	0.580
Transplant (any)	2 (5.9%)	0 (0.0%)	2 (8.7%)	>0.99
Autoimmune disease (any)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Charlson Comorbidity Index	1.5 (0.0-4.0)	2.0 (1.0-3.0)	1.0 (0.0-5.0)	0.814
IBD surgical history				
Prior IBD-directed surgery (not mutually exclusive)	14 (41.2%)	9 (81.8%)	5 (21.7%)	0.002
Stricturoplasty	2 (5.9%)	0 (0.0%)	2 (8.7%)	>0.99
Small bowel resection	2 (5.9%)	2 (18.2%)	0 (0.0%)	0.098
Large bowel resection	13 (38.2%)	8 (72.7%)	5 (21.7%)	0.008
Presence of stoma (ileostomy and colostomy)	3 (8.8%)	1 (9.1%)	2 (8.7%)	>0.99
Presence of ileal pouch (ileal pouch-anal anastomosis)	6 (17.6%)	5 (45.5%)	1 (4.3%)	0.008
CDI history				
Prior CDI episodes	3.0 (2.0-4.0)	2.0 (2.0-5.0)	3.0 (2.0-4.0)	0.141
Prior CDI treatment (not mutually exclusive)				
Vancomycin	27 (79.4%)	11 (100%)	16 (69.6%)	0.046
Fidaxomicin	15 (44.1%)	4 (36.4%)	11 (47.8%)	0.715
Fecal microbiota transplant	10 (29.4%)	5 (45.5%)	5 (21.7%)	0.232
CDI classification for which bezlotoxumab received				
Episode				
Initial	3 (8.8%)	0 (0.0%)	4 (17.4%)	0.280
1st recurrence	4 (11.8%)	2 (18.2%)	1 (4.3%)	0.239
2nd recurrence and beyond	27 (79.4%)	9 (81.8%)	18 (78.3%)	>0.99
Severity				
Non-severe	20 (58.8%)	7 (63.6%)	13 (56.5%)	0.729
Severe	10 (29.4%)	3 (27.3%)	7 (30.4%)	>0.99
Fulminant	4 (11.8%)	1 (9.1%)	3 (13.0%)	>0.99
Time from CDI to bezlotoxumab (days)	25.5 (14.0-40.8)	21.0 (13.0-26.0)	27.0 (14.0-43.0)	0.402
Age at bezlotoxumab infusion (years)	48.5 (33.4-62.0)	49.3 (33.5-61.1)	47.6 (29.9-62.9)	0.481

(*Contd...*)

Table 3 (*Continued*)

Variable	Median (IQR) or Fraction (%)			
	All IBD Patients N=34	Recurrent CDI N=11	No recurrent CDI N=23	P value
CDI history				
Concomitant CDI therapy with bezlotoxumab (not mutually exclusive)	34 (100%)	11 (100%)	23 (100%)	>0.99
Vancomycin	21 (61.8%)	7 (63.6%)	14 (60.9%)	>0.99
Fidaxomicin	15 (44.1%)	4 (36.4%)	11 (47.8%)	0.715
Fecal microbiota transplant	3 (8.8%)	0 (0.0%)	3 (13.0%)	0.535
Immunomodulatory medication use (at time of bezlotoxumab administration)				
No immunosuppressant	10 (29.4%)	4 (36.4%)	6 (26.1%)	0.692
1 immunosuppressant	17 (50.0%)	5 (45.5%)	12 (52.2%)	>0.99
2 or more immunosuppressants	7 (20.6%)	2 (18.2%)	5 (21.7%)	>0.99
TNF inhibitors (infliximab, adalimumab)	8 (23.5%)	2 (18.2%)	6 (26.1%)	>0.99
Integrin inhibitors (vedolizumab)	3 (8.8%)	1 (9.1%)	2 (8.7%)	>0.99
Interleukin inhibitors (ustekinumab)	9 (26.5%)	4 (36.4%)	5 (21.7%)	0.425
JAK inhibitor (tofacitinib)	1 (2.9%)	0 (0.0%)	1 (4.3%)	>0.99
Corticosteroids (>20mg prednisone equivalent)	6 (17.6%)	2 (18.2%)	4 (17.4%)	>0.99
Thiopurines (6-MP, AZA)	3 (8.8%)	1 (9.1%)	2 (8.7%)	>0.99
Calcineurin inhibitors (tacrolimus, cyclosporin)	2 (5.9%)	0 (0.0%)	2 (8.7%)	>0.99

CDI, Clostridioides difficile infection; IBD, inflammatory bowel disease; IQR, interquartile range; JAK, Janus kinase; TNF, tumor necrosis factor; 6-MP, 6-mercaptopurine; AZA, azathioprine

Discussion

In this retrospective multicenter study of patients with CDI who received bezlotoxumab, the overall rate of rCDI at 1 year was 28.6%. Although the overall rate of rCDI was numerically higher in patients with IBD than those without IBD, the difference did not reach statistical significance. Furthermore, no significant difference was noted in the rate of rCDI at 30, 60, or 90 days following bezlotoxumab therapy between patients with or without IBD. In this real-world study, bezlotoxumab was noted to be relatively safe, with few adverse events, although heart failure exacerbation did occur in a subset of patients without IBD, probably reflecting the higher proportion of patients with underlying heart failure in this group.

Comparing patients with IBD who experienced rCDI after bezlotoxumab therapy with those who did not, no significant differences were noted in the demographic, comorbid or CDI-related variables. This included no significant differences in BZ-CDI classification or severity, concomitant antimicrobial use, IBD classification or IMM use. Nevertheless, exposure to vancomycin during prior episodes of CDI, and a history of IBD-related surgery, were more common among patients who experienced rCDI. A possible hypothesis may be that greater prior exposure to vancomycin, and its resultant alterations to the microbiome, may in turn increase the risk of rCDI [12]. Furthermore, although it remains unknown by which mechanism intestinal resection might increase the risk of rCDI, possible hypotheses may include a more severe disease phenotype, postoperative alterations to the microbiome, and increased fecal stasis [13,14].

Although the current study adds to the limited available literature on bezlotoxumab use in patients with IBD, several limitations should be noted when interpreting the results. Firstly, owing to the use of bezlotoxumab for patients at increased risk of rCDI (of which a history of IBD is merely one), our study is limited by the differences in age and comorbid conditions between patients with and without IBD. Since IBD itself is considered a risk factor for rCDI, and thus may prompt clinicians to use bezlotoxumab, patients without IBD who received bezlotoxumab, as would be expected, were often characterized by other risk factors for rCDI potentially not present in the IBD patients (such as older age, significant comorbid conditions, or an immunocompromised state). Although this limited our ability to compare the rates of rCDI between the IBD and non-IBD groups, it is consistent with prior literature noting that patients with IBD who received bezlotoxumab were younger and had fewer comorbid conditions [10]. Furthermore, despite its multicenter design, our study was limited by low patient numbers. This reflects both our stringent patient inclusion criteria, and the limited

availability and clinical use of bezlotoxumab in our patient population. Although it was important for our study to have longitudinal follow-up data available after bezlotoxumab use to determine the rCDI rate, it should be noted that this may have reduced patient numbers and thus limited conclusions regarding low-incidence events, such as bezlotoxumab-induced adverse reactions. Additionally, it should be noted that our study was retrospective in design, which may have introduced selection bias in our patient population.

Nevertheless, despite these limitations, our study significantly adds to the limited available literature regarding the use of bezlotoxumab and CDI-directed monoclonal antibody therapy in patients with IBD, by providing real-world experience of efficacy and safety. Additionally, despite the use of monoclonal antibody therapy such as bezlotoxumab in a population at high risk of recurrence, our study highlights a near 29% rCDI rate, and thus a continued unmet need for further therapeutic options in this patient population. Our results are consistent with prior literature noting higher rates of rCDI in patients with IBD [6], although the difference we found did not reach significance, probably because of our highly comorbid comparator group. It is thought that IBD-associated intestinal inflammation and dysbiosis explain in part the high rCDI rate observed, via disruption of the normal gut microbiota and impaired resistance to *C. difficile* colonization [15,16]. Given the morbidity related to CDI and rCDI, particularly in patients with IBD—where CDI may result in infection-related complications or trigger IBD-related disease destabilization and complications—there remains a need for more effective strategies and therapeutics for CDI prevention, treatment and reduction of recurrence. This is particularly important, as a limited number of antimicrobials have remained the mainstay of CDI treatment, with some evidence noting an increased pattern of resistance to vancomycin [17-19], which has been associated with lower odds of clinical cure and higher odds of rCDI [20]. Although fidaxomicin is associated with lower rCDI rates, and recent research reports that the use of FMT at initial CDI is effective, with low rCDI rates [21], treatment options remain limited for patients with or at risk of multiple rCDI episodes. Although some data suggest that the addition of bezlotoxumab to rescue FMT after FMT failure is effective [22], the overall benefit of using bezlotoxumab with FMT in patients with IBD is unclear [23]. It should be noted that, at the time of writing, bezlotoxumab has been discontinued in certain markets; this limits its therapeutic use, as well as further investigation into bezlotoxumab and the utility of CDI-directed monoclonal antibody therapeutics in preventing rCDI, either alone or in combination.

In conclusion, in our retrospective multicenter study of patients with CDI who received bezlotoxumab, the rate of rCDI was similar in patients with and without a history of IBD, although IBD patients were younger and had fewer comorbid conditions. While the utility of bezlotoxumab in patients with IBD for prevention of rCDI is difficult to determine, bezlotoxumab may be a potential viable and safe alternative in patients with IBD who are deemed to have a high risk of recurrence.

Summary Box

What is already known:

- Bezlotoxumab is an anti-toxin B monoclonal antibody that has been shown to reduce the risk of recurrent *Clostridioides difficile* infection (rCDI)
- For patients at high risk of rCDI, guidelines recommend the use of bezlotoxumab to reduce the risk of recurrent infection
- While patients with inflammatory bowel disease (IBD) are at high risk of rCDI, data and clinical experience for the use of bezlotoxumab is limited and the rate of rCDI is unknown

What the new findings are:

- The overall rCDI rate was found to be 28.6%, with most patients experiencing recurrence within 90 days
- The rate of rCDI was found to be similar in patients with and without IBD
- The rate of adverse events was not greater in patients with IBD who used bezlotoxumab
- In patients with IBD, a history of prior vancomycin exposure or colorectal surgery was associated with rCDI

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