Real World Experience of Bezlotoxumab for Prevention of Recurrent *C. Difficile* Infection: A Single-Arm Multicenter Pilot Study in Office Infusion Centers

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BACKGROUND

- Bezlotoxumab (Zinplava™) is approved by the FDA to reduce recurrent *C. difficile* infection (rCDI) in adult patients receiving standard-of-care (SoC) antibiotics for CDI and who are at high risk for recurrence.[1]
- The MODIFY trials demonstrated that patients receiving bezlotoxumab plus SoC had significantly lower rates of rCDI compared to those with SoC alone.[2,3]
- Currently, there are no data about utilization practices and 3-month recurrence rates after using bezlotoxumab in the real-world setting.

OBJECTIVE

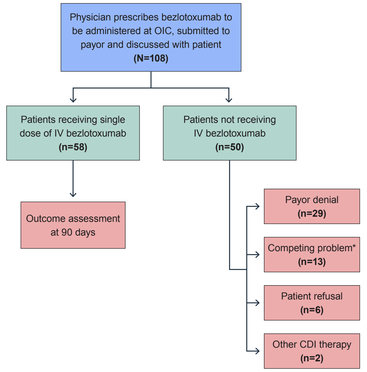
- To determine real-world patient and utilization characteristics of bezlotoxumab administered in outpatient office infusion centers (OICs) in the U.S.
- To report CDI recurrence rate assessed at 90-day follow-up in patients receiving a single dose of bezlotoxumab in OICs and determine risk factors associated with recurrence
- Hospitalizations due to rCDI were captured

METHODS

- **Study design**: retrospective multicenter single-arm study
- **Data source**: pharmacy and electronic health records from Mar 2017 through Nov 16, 2017
- **Index CDI definition**: episode of CDI (ICD-10 code: A04.7) that resulted in referral for bezlotoxumab
- **Patient population**: CDI patients ≥18 years from 22 OICs in the U.S.
- **Study parameters**: demographics, co-morbidities including Charlson score, number of past CDI episodes and rCDI risk factors. Utilization characteristics included time from laboratory diagnosis (positive *C. difficile* test) to initiation of bezlotoxumab, time from initiation of SoC antibiotic to bezlotoxumab, choice of SoC and laboratory test to confirm toxigenic *C. difficile*
- **Outcome assessment**: 90 days (12 weeks) post bezlotoxumab for rCDI by MD visit or phone call to patient assessing:
  - recurrence of diarrhea lasting ≥2 days and
  - medical intervention (SoC antibiotic, FMT) with or without positive stool test for toxigenic *C. difficile*
- **Statistical analysis**: continuous data are reported as mean or medians and interquartile ranges (IQRs), categorical data as counts and percentages. Risk factors for rCDI was assessed using Pearson Chi-Square test. Kaplan-Meier method was used to describe time to CDI recurrence stratified by previous number of CDI episodes and analyzed using the log-rank Chi-Square test. A p<0.05 was considered significant.

STUDY COHORT

Figure 1. Study Design Flow Diagram



*; Exacerbation or treatment of other disease (n=8), patient not discharged from hospital (n=3), transfer of care (n=2).

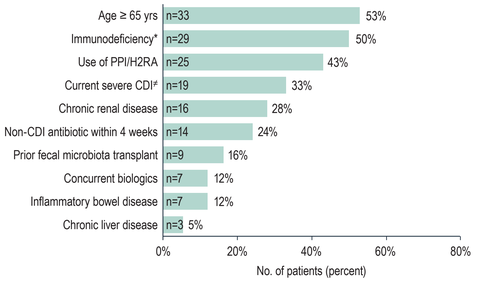
Table 1. Baseline Demographics and Clinical Characteristics

Characteristics	Results (N=58)
Age (mean years ± SD)	63±18
Gender female, n (%)	39 (67)
Weight (mean kg ± SD)	73±19
Charlson score (median, [IQR])	3.0 [1.3-6.0]
Hospitalization related to current CDI episode, n (%)	22 (38)
Length of hospitalization, days (mean ± SD)	6±4
Co-morbidities, n (%)	
Hypertension	27 (47)
Malignancy	17 (29)
Cardiovascular disease	16 (28)
Diabetes mellitus	11 (19)
Chronic kidney disease	10 (17)
Lyme disease	4 (7)
Number of prior CDI episodes [median, IQR]	2.0 [1.0-3.0]
Prior 6-month CDI episode, n (%)	45 (78)
Risk factors for CDI per patient* (mean, %)	4±1
2 or more, n (%)	55 (95)
3 or more, n (%)	46 (79)

*; Age ≥65 years, severe CDI presentation, prior 6-month CDI episode, use of proton-pump inhibitor (PPI) or H2-receptor antagonist (H2RA), use of non-CDI antibiotic(s) within 4 weeks, immunodeficiency, chronic renal disease, inflammatory bowel disease, concurrent biologics and prior fecal microbiota transplant

RESULTS

Figure 2. Distribution of Risk Factors Among Study Cohort



*; determined by medication use (steroid, PD-L1 inhibitor, chemotherapy) or condition (immune deficiency, transplant solid organ or HSCT/autologous or allogeneic, absolute neutrophil count <500 cells/μL).
#; defined by any of the following: albumin ≤3.0 g/dl, colectomy related to CDI, creatinine ≥1.5 x baseline, hypotension or shock, ICU stay related to CDI, toxic megacolon, WBC ≥15,000 cells/μL.

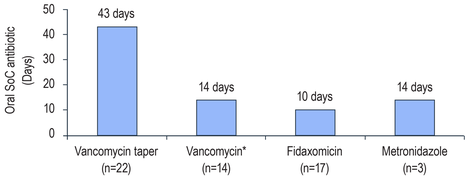
- Of the study population, the majority of patients (79%) had ≥3 risk factors, 5% had a single risk factor and none of the patients had zero CDI risk factor

Table 2. Outpatient Utilization Characteristics of Bezlotoxumab

Utilization Parameter	Results (N=58)
Time from laboratory diagnosis to bezlotoxumab infusion	
Days (mean ± SD)	25±21
Days (median, [IQR])	15.5 [22.5]
Time from initiation of SoC to bezlotoxumab infusion	
Days (mean ± SD)	22±25
Days (median, [IQR])	13.0 [18.5]
Oral SoC antibiotic at time of bezlotoxumab, n (%)	
Vancomycin taper	22 (38)
Vancomycin*	14 (24)
Fidaxomicin	17 (29)
Metronidazole	3 (5)
Vancomycin & fidaxomicin	1 (2)
Vancomycin & metronidazole	1 (2)
Laboratory test for *C. difficile* confirmation*, n (%)	
PCR for toxigenic genes	45 (78)
EIA for toxins A, B	6 (10)
EIA for toxins A, B and GDH antigen	5 (9)
PCR and toxigenic stool culture	2 (3)

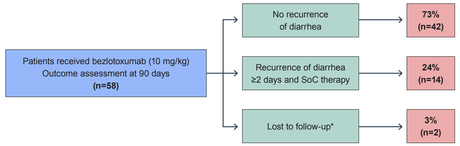
Abbreviations: EIA; enzyme immunoassay, GDH; glutamate dehydrogenase, IQR; interquartile range, PCR; polymerase chain reaction, SD; standard deviation, SoC; standard-of-care
*; Fixed doses of vancomycin included 125 mg (n=8) and 250 mg (n=6)

Figure 3. Median Duration of SoC Antibiotic Treatment



*; Fixed doses of vancomycin included 125 mg (n=8) and 250 mg (n=6).

Figure 4. CDI Recurrence Rate in Patients Receiving Bezlotoxumab



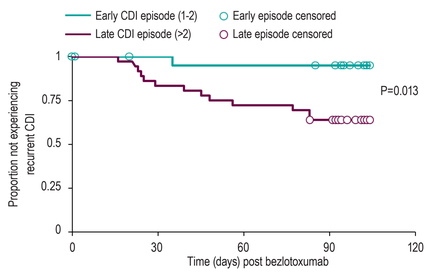
- Hospitalizations due to rCDI occurred in 6 of 14 patients
- 2 of 14 recurrent patients had a fecal microbiota transplant within 90 days follow-up

Table 3. Risk Factor Analysis of CDI Recurrence vs. No Recurrence

Risk factor for CDI (n=56)	N	No CDI Recurrence (n=42)	CDI Recurrence (n=14)	P-value
Age ≥65 years	30	22 (52%)	8 (57%)	0.76
Immunodeficiency*	27	20 (48%)	7 (50%)	0.88
Current severe CDI#	17	12 (29%)	5 (36%)	0.61
Prior 6-month CDI episode	44	32 (76%)	12 (86%)	0.86
Use of antacids (PPI or H2RA)	25	19 (45%)	6 (43%)	0.88
Other non-CDI antibiotics	12	10 (24%)	2 (14%)	0.45
Prior fecal microbiota transplant	8	6 (14%)	2 (14%)	0.99
Chronic renal disease	14	10 (24%)	4 (29%)	0.71
Inflammatory bowel disease	7	5 (12%)	2 (14%)	0.81
Concurrent biologics	7	5 (12%)	2 (14%)	0.82
>2 CDI episodes (incl. current)	35	22 (52%)	13 (93%)	0.013
2 or more risk factors	53	39 (93%)	14 (100%)	0.32
3 or more risk factors	44	32 (76%)	12 (86%)	0.43

*; determined by medication use (steroid, PD-L1 inhibitor, chemotherapy) or condition (immune deficiency, transplant solid organ or HSCT/autologous or allogeneic, absolute neutrophil count <500 cells/μL)
#; defined by any of the following: albumin ≤3.0 g/dl, colectomy related to CDI, creatinine ≥1.5 x baseline, hypotension or shock, ICU stay related to CDI, toxic megacolon, WBC ≥15,000 cells/μL

Figure 5. Kaplan Meier Plot of rCDI in Patients Given Bezlotoxumab



- Median and mean time to recurrence was 21 days (15 to 80) and 38±20 days, respectively as reflected from the survival plot

CONCLUSIONS

- **This study provides details on the targeted patient population and utilization practices of bezlotoxumab in the outpatient setting:**
  - time from laboratory diagnosis to bezlotoxumab infusion was longer than reported in clinical trials[2]
  - the majority of patients received vancomycin long term taper as SoC antibiotic
- **Patients given bezlotoxumab during early CDI episodes (episode 1 or 2) had significantly less recurrence than patients given bezlotoxumab for later episodes (p=0.013).**
- **This real world evidence study of bezlotoxumab administered in an outpatient setting demonstrated efficacy in the prevention of rCDI at 90 days.**
- **Results were comparable with data reported for MODIFY trials[2,3], despite having a highly co-morbid patient population with a high number of CDI risk factors and multiple episodes of rCDI.**

Disclosures

- This study was sponsored by Merck & Co., Inc., Rahway, NJ, USA

References

1. Wilcox MH, Gerding DN, Poxton IR et al. Bezlotoxumab for prevention of Clostridium difficile infection, N Engl J Med 376:305-17, 2017
2. Gene KM, Colleen MB et al. Increasing incidence of multiply recurrent Clostridium difficile infection in the United States. Ann Intern Med 167:152-58, 2017
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