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Bezlotoxumab for *Clostridium difficile* Infection Complicating Inflammatory Bowel Disease

Ciarán P. Kelly,[1] Mark H. Wilcox,[2] Henning Glerup,[3] Nazimuddin Aboo,[4] Misoo C. Ellison,[5] Karen Eves,[5] Mary Beth Dorr[5]

[1]BIDMC and Harvard Medical School, Boston, MA, USA; [2]Leeds Teaching Hospitals and University of Leeds, Leeds, UK; [3]Regionshospitalet, Silkeborg, Denmark; [4]Parklands Medical Centre, Overport, Durban, South Africa; [5]Merck & Co., Inc., Kenilworth, NJ, USA

Corresponding author: Ciarán P. Kelly; BIDMC, 330 Brookline Avenue, Dana/601, Boston, MA 02215; email: ckelly2@bidmc.harvard.edu; phone: 617-667-1272; fax: 617-667-8144

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Individuals with inflammatory bowel disease (IBD) experience higher rates of *Clostridium difficile* infection (CDI) compared with the overall population, often lack typical CDI risk factors, and frequently experience recurrent episodes.[1] Despite this, evidence-based management approaches for CDI complicating IBD are lacking.

Bezlotoxumab (MK-6072), a fully human monoclonal antibody that binds to *C. difficile* toxin B, is indicated to prevent recurrent CDI (rCDI) in at-risk adults.[2]

In the MODIFY I/II (NCT01241552/NCT01513239) Phase 3 trials, bezlotoxumab resulted in a significantly lower rate of rCDI compared with placebo.[3] Unlike other Phase 3 CDI trials, individuals with IBD were eligible to participate.

Using pooled data from MODIFY I/II, this post-hoc analysis explored CDI-related outcomes in participants with IBD and CDI; initial clinical cure (ICC) and rCDI (defined in Table).[3]

There were 2559 participants in the modified intent-to-treat population. In total, 44 participants had IBD: 23 (52.3%) had ulcerative colitis, 18 (40.9%) Crohn's disease, and three (6.8%) non-characterized IBD. As the overall rCDI results were not different for the bezlotoxumab and the actoxumab + bezlotoxumab groups, these were pooled ("bezlotoxumab" group); similarly, the actoxumab and placebo groups were pooled ("no bezlotoxumab" group).

Of the 1554 participants randomized to the bezlotoxumab group, 28 had IBD and all completed the study. The 1005 remaining participants did not receive bezlotoxumab; 16 had IBD and 14 completed the study. The two remaining participants died (one due to stroke and the other due to septic shock).

Baseline participant characteristics showed that compared with those without IBD, participants with IBD were younger (mean age: 63.5 vs 50.3 years, respectively), more frequently outpatients (32.0% vs 54.5%), more often immunocompromised (21.1% vs 40.9%), and less likely to have received a prior systemic antibiotic (55.2% vs 40.9%).

There was a trend for a reduced rate of ICC in IBD participants in the bezlotoxumab group versus the no bezlotoxumab group (53.6% vs 81.3%, respectively; Table).

During the 12-week follow-up period, there was a trend for rCDI to occur less frequently in the bezlotoxumab group (26.7% vs 53.8%), representing a 27.2% absolute reduction (95% confidence interval [CI] -57.9–9.6) in the incidence of rCDI in IBD participants. A similar trend was observed in a sensitivity analysis using an expanded definition of ICC[3] (Table).

This is the first prospective evaluation of bezlotoxumab in patients with IBD complicated by CDI. Consistent with prior reports,[4,5] MODIFY participants with IBD were more likely to be younger, outpatients, immunocompromised, and not have received prior antibiotics; this contrasts with several traditional risk factors for CDI.[1,6] Also consistent with the literature, IBD participants who did not receive bezlotoxumab displayed a higher rCDI incidence compared with those without IBD.[7]

Here, bezlotoxumab was associated with a trend for a 50% relative reduction in the incidence of rCDI (Table). This can be linked to bezlotoxumab's ability to neutralize *C. difficile* toxin B, protecting against the damaging effects of toxin production during the high-risk period for rCDI. Reducing the incidence of clinical relapse may decrease the need for a new course of antibiotic treatment. This allows restoration of the gut microbiota,[8] which is considered an essential natural defense to prevent *C. difficile* colonization.[5]

Although these are promising results, study limitations included the use of a post-hoc analysis, small sample sizes in the IBD subgroups, and that the study was not powered to show statistical significance between cohorts. We note that the 95% CIs of the difference between groups included

zero, meaning that the results should not be considered conclusive. Therefore, further research is required to evaluate if bezlotoxumab is effective in preventing rCDI in individuals with IBD.

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Table. Proportion of IBD Participants that Experienced ICC and rCDI

	Bez[a] n/m[c] (%)	No bez[b] n/m[c] (%)	Difference % (95% CI)
ICC[d,e]	15/28 (53.6)	13/16 (81.3)	-27.2 (-51.1, 2.3)
rCDI			
Primary analysis[f]	4/15 (26.7)	7/13 (53.8)	-27.2 (-57.9, 9.6)
Sensitivity analysis[g]	7/27 (25.9)	7/15 (46.7)	-20.7 (-48.9, 8.9)

Bez, bezlotoxumab; CDI, *Clostridium difficile* infection; CI, confidence interval; IBD, inflammatory bowel disease; ICC, initial clinical cure; mITT, modified intent-to-treat.

[a]Includes participants receiving bezlotoxumab or bezlotoxumab + actoxumab.

[b]Includes participants receiving actoxumab or placebo.

[c]n, number of participants in the IBD subgroup analysis population meeting the endpoint criteria; m, total number of participants within the subgroup.

[d]mITT population; all randomized participants who received study infusion, had a positive baseline stool test for toxigenic *C. difficile* and received antibacterial drug treatment for CDI.

[e]ICC; no diarrhea during the 2 consecutive days following completion of ≤16 calendar days of antibacterial drug treatment for CDI.

[f]rCDI; a new episode of diarrhea with a positive stool test for toxigenic *C. difficile*, in participants that achieved ICC.

[g]Expanded ICC definition; no diarrhea during 2 consecutive days (regardless of the duration of antibacterial drug treatment for CDI and the timing of resolution of the initial episode).