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Bezlotoxumab: Assessing its current role in *C. difficile* management

Introduction

Clostridium difficile infection (CDI) is estimated to cause over 220,000 cases and 12,800 deaths annually in the United States.[1] Around 25-35% of patients are expected to experience recurrent CDI despite therapy, and a second CDI recurrence is estimated to occur among 40% of those who have had one recurrence.[2-4] Between these high recurrence rates and the substantial associated morbidity and mortality per infection, much study has been devoted to evaluation of effective CDI therapies and prevention of CDI relapse.

In 2021, the IDSA and SHEA provided a focused update to their CDI management guidelines that recommended use of oral fidaxomicin over oral vancomycin or metronidazole for initial and recurrent non-fulminant CDI.[5] This recommendation was based on pooled results from four studies that showed fidaxomicin was associated with sustained relapse-free response at 4 weeks. However, this response was not observed at 90-day follow-up, and notably cost and availability of fidaxomicin are substantial barriers to its use for many patients and hospital systems (see Shoff, et al 2022[6] for an in-depth review of the ethical considerations of the IDSA guideline update).

In addition, this guideline update recommended the use of bezlotoxumab (Zinplava) as a co-intervention to standard-of-care antibiotics for patients with a CDI recurrence within the previous 6 months and, "where logistics are not an issue," among patients with primary CDI and ≥1 risk factor for recurrence.[5]

In this newsletter, we would like to review bezlotoxumab and our current understanding of its role in CDI management.

Overview of Bezlotoxumab

Because the virulence of *C. difficile* is largely driven through its production of toxins A and B, anti-toxin therapies for CDI like bezlotoxumab have been of interest for several years. Multiple animal studies have demonstrated reduced mortality due to CDI with active and passive administration of anti-toxin antibodies.[7] Furthermore, an oral *C. difficile* toxin-binding drug known as tolevamer was found to have much lower rates of recurrent CDI compared to oral vancomycin or metronidazole (<5% compared to >20%) among patients in which it was effective.[8] Unfortunately, it was found to be inferior to oral vancomycin and oral metronidazole as a stand-alone treatment for CDI.

Given the potential of anti-toxin therapy to reduce CDI recurrence, bezlotoxumab and a related antibody known as actoxumab were developed. Bezlotoxumab is a fully human monoclonal antibody that targets two separate sites of toxin B and prevents its interaction with host cells. It is thought that disruption of the colonic mucosa by CDI allows bezlotoxumab to translocate into the lumen and more effectively neutralize toxins.[7]

Bezlotoxumab is administered as a single intra-venous infusion at 10mg/kg over 60 minutes.[9] It has a half-life of approximately 19 days, and no renal or hepatic dose adjustments are recommended based on clinical data (as expected, given it is primarily eliminated through protein catabolism).[10] Heart failure exacerbations were noted as a potential adverse event in clinical trials, primarily among those with pre-existing congestive heart failure. Infusion-related reactions within 24 hours of administration were noted in 10% of patients, which included symptoms such as nausea, fever, fatigue, headache, and hypertension; these resolved within 24 hours of onset. Otherwise, side effects within 4 weeks of infusion included nausea, fever, and headache but still occurred in <10% of trial participants.[9] Most hospitals and health systems are going to position this drug as an

outpatient infusion given the cost estimates for a single-dose of bezlotoxumab range from $3500-$4500.

Available Evidence of Clinical Efficacy

Clinical efficacy of bezlotoxumab as an adjunctive CDI therapy to standard-of-care (SOC) has been assessed with two multicenter randomized control trials as well as a few retrospective studies.[11-15]

Randomized Control Trials: MODIFY I and II

MODIFY I and II are the primary studies upon which the 2021 update to the IDSA/SHEA CDI update is largely based.[11-12] In MODIFY I and II, over 2600 adults with CDI were randomized to receive SOC plus either bezlotoxumab, actoxumab plus bezlotoxumab, or placebo on day 1 of enrollment.[11] Due to lack of efficacy on interim analysis, actoxumab alone plus SOC was not evaluated in MODIFY II. SOC antibiotics were either oral metronidazole, vancomycin, or fidaxomicin as chosen by the treating physician. It should be noted that most patients either received metronidazole (47%) or vancomycin (48%), therefore the recurrence benefit of the combination of bezlotoxumab with fidaxomcin is yet to be determined. Furthermore, the majority of participants (73%) had primary CDI episodes rather than recurrences.

Overall, rates of CDI recurrence within the 12-week follow-up period were significantly lower in the bezlotoxumab group as compared to the placebo group (16-17% versus 26-28% recurrence rate). This effect was noted across groups at high risk of CDI recurrence, which included those with age ≥ 65, history of CDI in past 6 months, immunocompromised state, severe CDI at presentation, or *C. difficile* ribotype 027. As a secondary end-point, no difference was found in initial clinical cure rates across any of the studied groups.[11]

A post hoc analysis of MODIFY I and II found bezlotoxumab did not reduce rates of recurrence among patients with primary CDI and no risk factors for recurrence.[12] However, it was effective in reduction of CDI recurrence among patients primary CDI with factor for recurrence and, most notably, among those with ≥1 CDI episode in the prior 6 months.[5, 12]

Retrospective Studies

Two recent retrospective multicenter "real-world" studies found similar outcomes with bezlotoxumab, but they also offer data to help determine who might benefit most from this adjunctive therapy.

Johnson TM, et al. compared outcomes between 106 patients who received bezlotoxumab + SOC versus SOC alone (53 patients per group).[14] In the adjusted analysis using inverse probability-of-treatment weighting, the bezlotoxumab group had lower odds of 90-day recurrence (32% absolute risk reduction) and all-cause hospital readmission. Bezlotoxumab had the strongest effect on reducing CDI recurrence among those with 1-2 risk factors for recurrence (compared to ≥3) and those with <2 prior episodes of recurrence (compared to ≥2 episodes). These findings suggest bezlotoxumab may offer more benefit early in the course of recurrences, and perhaps, in the sweet spot of those with 1-2 risk factors for recurrence. Bezlotoxumab was administered at a median of 19 days (IQR, 12-35 days) after SOC was initiated. Notably, among the few recurrences that occurred in the bezlotoxumab group, all were receiving SOC at the time of administration. While more study is needed, this suggests that rushing to administer bezlotoxumab for inpatients may not be the best approach (unless their stay lasts well beyond SOC treatment duration).

One caveat needs to be highlighted from this retrospective study. Fidaxomicin was used more in the bezlotoxumab cohort (32% vs 9%, P=.004) which can certainly affect the unadjusted comparison.

A second study by Hengel RL, et al. evaluated 200 patients who all received bezlotoxumab and SOC.[15] They also described higher risk of recurrence among patients who had ≥2 CDI recurrences pre-bezlotoxumab compared to those with primary infection or 1 recurrence (HR 2.77; 95% CI, 1.14-6.76; P=.026).[15] They found no difference in recurrence based on initial treatment (vancomycin, 13.7%, vancomycin tapered, 18.3%, and fidaxomicin, 15.2%) when administered bezlotoxumab.

Discussion

These findings guide the IDSA Focused Update recommendation for bezlotoxumab use along with SOC among those with a CDI episode in the prior 6 months and, "where logistics are not an issue", among those with primary CDI and risk factors for recurrence.[5]

We highlight the following additional considerations:

- Benefit for bezlotoxumab appears most notable among those with primary infection or 1 recurrence, with smaller benefits noted among those with ≥2 recurrences.
- Patients with 1-2 risk factors for CDI recurrence seem to receive the most benefit from bezlotoxumab administration, as compared to those with primary disease without additional risk factors or those with ≥3 risk factors for CDI recurrence.
- Administration of bezlotoxumab after initiation of SOC (i.e. likely in the outpatient setting for most patients) appears to be reasonable and perhaps associated with better outcomes based on retrospective data.
- Despite promising results from retrospective studies, further study is needed to understand bezlotoxumab's effect in CDI recurrence reduction among those who are prescribed fidaxomicin.
    - Fidaxomicin was not commonly administered in the MODIFY trials.
    - Furthermore, fidaxomicin itself is thought to be protective against 30-day CDI recurrence as compared to vancomycin or metronidazole, which may theoretically reduce the observed benefit of bezlotoxumab.

All-in-all, bezlotoxumab offers a novel mechanism of action in the therapy of CDI. Further study is needed to evaluate its role in the context of use with fidaxomicin, but studies have demonstrated its effectiveness as an adjunct to standard-of-care in CDI management to prevent recurrence, particularly among those with multiple prior episodes of CDI.

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