NEW DRUGS

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Bezlotoxumab

Approved indication: *Clostridium difficile*

Zinplava (Merck Sharp and Dohme)
vials containing 1000 mg/40 mL concentrate
Australian Medicines Handbook section 14

Infection with *Clostridium difficile* is a potential adverse effect of antibiotic therapy.[1] The *C. difficile* toxins cause diarrhoea and colitis and the infection can be fatal. Some patients develop recurrent infection. While antibiotics are used to treat recurrent *C. difficile* infections, bezlotoxumab may have a role in preventing recurrences.

Bezlotoxumab is a monoclonal antibody. It binds to the B toxin produced by *C. difficile*, thereby neutralising its pro-inflammatory effects. Bezlotoxumab has to be diluted then infused intravenously over an hour. The half-life of the drug is about 19 days, so only a single infusion is needed during a course of antibiotic treatment for *C. difficile*. As bezlotoxumab is an antibody, it is catabolised like other proteins. Renal and hepatic impairment have no effect on clearance and pharmacokinetic drug interactions are unlikely.

The two main placebo-controlled trials of bezlotoxumab involved 2655 adults with primary or recurrent infections with *C. difficile*. These patients were being treated with oral antibiotics and were randomised to continue this standard of care or to receive infusions of bezlotoxumab or actoxumab or both. Actoxumab is another monoclonal antibody (against *C. difficile* toxin A) but it was discontinued after an interim analysis suggested a lack of efficacy. The end point for the two trials was the proportion of patients who had a recurrence within 12 weeks of being cured by antibiotic therapy. However, a clinical cure (two consecutive days without diarrhoea) was not achieved by all the patients in the trials. In the first trial, 77% of the bezlotoxumab group and 83% of the placebo group had a clinical cure. The corresponding figures in the second trial were 83% and 78%.[2]

The rate of recurrent infection during the follow-up of both trials was 16.5% in the bezlotoxumab groups and 26.6% in the placebo groups (see Table). Ten patients need to be treated with bezlotoxumab to prevent one recurrent infection. The proportion of patients who had an initial clinical cure and then no recurrence was 64% with bezlotoxumab and 54% with placebo.

Approximately 10% of the patients had a reaction to the infusion of bezlotoxumab, compared with 7.6% of the placebo group. Symptoms include nausea, headache and fever. In the month following the study the frequency of adverse events was similar in both groups. Common complaints were abdominal pain, vomiting and diarrhoea.[2] Heart failure was more frequent in patients given bezlotoxumab, particularly when there was a history of congestive heart failure. In patients with such a history, 19.5% (23/118) of those given bezlotoxumab died compared with 12.5% (13/104) in the placebo group.

While the rate of recurrence of infection is 10% less in patients given bezlotoxumab, rather than placebo, there is some uncertainty about the efficacy of the drug. As the trials included patients whose initial infection had not been cured, it is not clear how bezlotoxumab prevents the recurrence of something that has not resolved. Bezlotoxumab is not indicated for the treatment of *C. difficile* infection and it only had a significant effect on sustained cure in one of the trials (see Table). The optimum timing of the infusion

Table **Efficacy of bezlotoxumab in preventing recurrent infection with *Clostridium difficile*** [2]

Trial	Number of patients	Recurrences	Sustained cure*	Recurrence rate in patients after initial clinical cure†
MODIFY I				
Bezlotoxumab	386	67 (17%)	232 (60%)	22% (67/299)
Placebo	395	109 (28%)	218 (55%)	33% (109/327)
MODIFY II				
Bezlotoxumab	395	62 (16%)	264 (67%)	19% (62/326)
Placebo	378	97 (26%)	197 (52%)	33% (97/294)

* Sustained cure was an initial clinical cure and no recurrent infection for 12 weeks.
† An initial clinical cure after antibiotic therapy was achieved by 80% of patients in the bezlotoxumab and placebo groups (pooled data).

and which patients are most likely to benefit will require further study. The drug is indicated for adults at 'high risk for recurrence' so its use will probably be limited to patients such as those over 65 years old, the immunocompromised and those with severe infections. However, bezlotoxumab has little effect on mortality. In the 12 weeks after the infusion 7.1% of the bezlotoxumab group and 7.6% of the placebo group died.[2] There will also be a need to compare bezlotoxumab to other management strategies, such as fidaxomicin, for preventing recurrences.

T manufacturer provided the product information

REFERENCES

1. McFarlane M, Hajkowicz K. Controlling *Clostridium difficile*. Aust Prescr 2013;36:121-4. https://doi.org/10.18773/austprescr.2013.046
2. Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, et al.; MODIFY I and MODIFY II Investigators. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. N Engl J Med 2017;376:305-17. https://doi.org/10.1056/NEJMoa1602615

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.