

Clostridium difficile infection: Antibodies *versus* antibiotics

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Abstract

Recently, the dramatic changes in the epidemiology of Clostridium difficile infection (CDI) as well as increases in both incidence and severity of disease in many countries have made it a global public health problem. This increasing severity and incidence could be partially because of frequent antibiotic use and the emergence of a hypervirulent strain of Clostridium difficile. Antibiotics such as metronidazole and vancomycin could be considered as frontline treatment for CDI. But recurrent CDI occurs in ~ 25 percent of cases and causes morbidity, mortality and healthcare costs. Due to antibiotic treatment failure in this population, novel treatment options are required. Recently, anti-toxin antibodies are developed as new therapeutic approach to the treatment of CDI. Bezlotoxumab, the first therapeutic monoclonal antibody, which is approved for the prevention of CDI recurrence. The aim of this manuscript is to provide the latest information about CDI treatment, with a particular focus on antibiotics and therapeutic antibodies that are utilized in CDI treatment.

Introduction

Clostridium difficile-associated disease (CDAD) which is caused by an anaerobic toxigenic bacterium could lead to significant morbidity and mortality worldwide [1,2]. Furthermore, it can cause a significant problem for solid organ transplant (SOT) recipients too [3]. Primary prevention of Clostridium difficile infection is considered as patients, without diarrhea symptoms, who receive antibiotics and are given the intervention within 2 months of treatment and do not develop diarrhea. Secondary prevention of CDI in cases who have recovered from at least one prior episode of CDI, without diarrhea at the time of the intervention and would not develop a recurrence of CDI within one or two months of follow-up [4]. Identification of both C. difficile toxin A (TcdA, enterotoxin) and toxin B (TcdB, cytotoxin) in diarrheal stool is required since these toxins are essential for C. difficile to induce both diarrhea and gut pathological changes [5,6]. It has been proved that tolevamer was inferior to antibiotic therapy for C. difficile infection (CDI) as well as metronidazole was inferior to vancomycin [7]. Both metronidazole and oral vancomycin have been clinically used for treatment of Clostridium difficile infection. However, clinical failure and concern about promotion of resistance motivated the search for new non-antibiotic treatments [8]. Furthermore, combination therapy (metronidazole and vancomycin) is not superior to monotherapy since it seems to be associated with an increase in the rate of adverse events [9]. In cases subgroups with C. difficile infection at increased recurrence risk, fidaxomicin, as first-line therapy, was cost-effective versus vancomycin. Moreover, it was less costly and more effective in cases with cancer [10]. Reduction in C. difficile environmental contamination by hospitalized cases that are treated with fidaxomicin was achieved [11]. In animal studies, the pooled relative risk of eight potential experiments indicated that the antibody therapy can reduce the risk of C. difficile infection [12]. Although preclinical studies confirmed the efficacy of actoxumab, bezlotoxumab alone was proved to be effective in clinical trials [13]. The antitoxin antibodies, actoxumab and bezlotoxumab, could bind to and neutralize TcdA and TcdB, respectively. Moreover, bezlotoxumab was approved by the U.S. Food and Drug Administration in 2016 to reduce the recurrence of CDI in cases above 18 years of age who receives antibiotics for C.

difficile infection and can be at a higher risk of recurrence [13,14]. Though only bezlotoxumab is shown to reduce recurrence of Clostridium difficile infection, studies using a combination of human monoclonal antibodies, actoxumab and bezlotoxumab, have indicated that bolstering the host immune response against both the C. difficile toxins might be effective in prevention of both primary and secondary C. difficile infection. But, since actoxumab development was halted, passive immunotherapy with both actoxumab and bezlotoxumab can be actually impracticable [15]. The superior effect of bezlotoxumab (10 mg/kg) in the prevention of recurrent CDI shows that the agent could be effective in Japanese patients [16]. Antibiotic therapy is augmented by using humanized monoclonal antibodies, actoxumab and bezlotoxumab, for the prevention of exotoxins A and B, respectively [14]. Bezlotoxumab, with a safety profile similar to that of placebo, had been associated with a substantially lower rate of recurrent infection than placebo (among cases who are receiving antibiotic treatment for primary / recurrent CDI). Furthermore, the addition of actoxumab could not improve efficacy [17]. It has been demonstrated that these monoclonal antibodies can be protective against CDI in hamsters [18] and piglets [19]. Moreover, they have shown promising results against recurrent CDI in humans [20, 21]. It has been demonstrated that actoxumab-bezlotoxumab treatment can facilitate normalization of the gut microbiota in C. difficile infection mice [22]. A combination of these antibodies (referred to herein) is now in phase III clinical trials for the prevention of recurrent CDI. It has been shown that herein caused a 73 percent decrease in recurrence rates in phase II clinical trials When it was administered concurrently with the standard of care antibiotics such as vancomycin and metronidazole [20]. In another study, the use of chimeric fusion proteins is considered as an attractive approach to

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produce multivalent antitoxin vaccines as well as therapeutic polyclonal antibodies for both prevention and treatment of CDI [23].

Conclusion

C. difficile infections are considered as a leading cause of antibiotic-associated diarrhea in both hospital and care facility cases. Antibiotics are known to target the infecting bacteria but not the exotoxins. Therefore, administering neutralizing antibodies against both TcdA and TcdB to cases who are receiving antibiotic therapy may modulate the effects of the exotoxins directly. Due to the limited number of drugs that have proven to be effective, treatment of CDI can be challenging followed by concerns about antibiotic resistance and recurring disease. More recent studies have provided additional insights into the potential value of utilizing monoclonal antibodies for treatment of CDI. Antibodies for the treatment of CDI have been confirmed to be effective in clinical practice and research. Monoclonal antibodies against *C. difficile* toxins may protect against symptomatic CDI and subsequent CDI recurrences. A new approach for the prevention of recurrent CDI can be the use of therapeutic antibodies, as an adjunct to antibiotic therapy, directed against the toxins that are responsible for *C. difficile* infection. Bezlotoxumab is the first therapeutic monoclonal antibody for secondary prevention of recurrence of CDI. Though only bezlotoxumab is shown to reduce recurrence of CDI, previous data using a combination of actoxumab–bezlotoxumab have demonstrated that bolstering the host immune response against the *C. difficile* toxins could be effective in CDI prevention. Moreover, combination of two monoclonal antibodies might offer an advantage for a yet to emerge *C. difficile* strain, which can be a steady threat for cases at high risk of CDI. Furthermore, it has been shown that a combination therapy could facilitate normalization of the gut microbiota in CDI mice. Future studies will be required to assess human monoclonal antibodies combination as a therapeutic approach in both clinical and microbiological cure of Clostridium difficile infection.

Conflicts of interest

The author declared no conflicts of interest.

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