Editorial

Ridinilazole—a novel antibiotic for treatment of Clostridium difficile infection

Niels Steinebrunner, Wolfgang Stremmel, Karl H. Weiss

Department of Gastroenterology and Hepatology, University Hospital Heidelberg, Heidelberg, Germany

Correspondence to: Prof. Karl Heinz Weiss, MD. Department of Gastroenterology and Hepatology, University Hospital Heidelberg, Heidelberg 69120, Germany. Email: karl-heinz.weiss@med.uni-heidelberg.de.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Ming Zhong (Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Comment on: Vickers RJ, Tillotson GS, Nathan R, *et al*. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Lancet Infect Dis 2017;17:735-44.

Submitted Dec 04, 2017. Accepted for publication Dec 18, 2017.
doi: 10.21037/jtd.2017.12.117
View this article at: http://dx.doi.org/10.21037/jtd.2017.12.117

Clostridium difficile (*C. difficile*) infection has become a major health problem worldwide and is considered to be one of the most common hospital-acquired (nosocomial) infections with increasing incidence and severity (1). In Germany, the number of *C. difficile* infections (CDI) increased from 7 to 39 reported cases per 100,000 hospitalized patients between 2000 and 2004, with yet another doubling of numbers between 2004 and 2006 (2). The recent rise has been associated with the spread of hyper-virulent strains of the bacteria such as the NAP1/ribotype 027 strain (3). The disease is primarily associated with prior broad-spectrum antibiotic therapy causing a disruption of the normal gut microbiota; leading to an overgrowth of *C. difficile* bacteria (4). Therefore, prudent use of antibiotics by antibiotic stewardship is central in preventing CDI. *C. difficile* is a Gram-positive, spore-forming, non-invasive bacterium, which is usually transmitted via the faecal-oral route. The spectrum of clinical manifestations of CDIs ranges from asymptomatic colonization of the gut to more severe disease manifestations by toxigenic strains. The release of the toxins A (enterotoxin) and B (cytotoxin) results in a disruption of the colonic mucosal interface; with symptoms ranging from mild secretory diarrhoea to the full clinical presentation of pseudomembranous colitis with typical endoscopic findings. In severe cases, the progression of the disease can lead to complications such as toxic megacolon, perforation of the gut and potentially fatal sepsis (5). As a key clinical issue, CDIs are associated with high rates of recurrence, affecting up to one-third of patients, after completing initial therapy. Risk factors for recurrence of CDI include gastric acid suppression by proton pump inhibitor therapy, gastrointestinal tract surgery, underlying immunosuppression (malignancy, cirrhosis, chemotherapy, immunosuppressive therapy), as well as older age (>65 years) of affected patients (6-11). Recurrent infections are associated with an increased risk of further episodes of infection, which become more difficult to treat. Subsequent repeated hospitalisations and antibiotic therapies inevitably lead to a higher financial burden on the healthcare system (12,13).

Treatment options are limited to three antibiotics, these being metronidazole, vancomycin and fidaxomicin. Metronidazole and vancomycin, the standard options of treatment for decades, are associated with disruption of the gut microbiota that might trigger recurrence of disease (14). Fidaxomicin has a narrower spectrum of activity, with lower rates of disease recurrence (15). However, its wider application has been hindered by financial considerations (9). Although fidaxomicin lowers the rates of recurrence and subsequently the costs of treating relapses, its regular use would increase total costs of treatment over time (16). Additional therapeutic approaches for the prevention of CDI relapses have been evaluated, including the adjunct use of probiotics and transplantation of faecal microbiota. However, so far, there are limited data to recommend the use of probiotics routinely (17). Faecal microbiota transplantation has been shown to reduce the rate of recurrence of CDIs, especially in patients

who had multiple relapses. However, further work is needed to address remaining issues such as the route of administration (duodenal, colonic, packaged in capsules for oral application) and how to determine eligibility for treatment (18,19). Additional investigations evaluate the oral administration of non-toxigenic *C. difficile* strains to compete with toxigenic strains (20).

Other approaches include the development of vaccines or antibodies. The administration of the fully human monoclonal antibody bezlotoxumab against *C. difficile* toxin B, in addition to antibiotic therapy, has been shown to decrease recurrence rates of CDI substantially (21). It is noteworthy that the use of vaccines and antibodies for treatment does not contribute to an increased risk of antibiotic resistance. However, resistance of *C. difficile* to the available antibiotics has been reported rarely in the literature, despite their widespread use (22).

Ridinilazole is a novel, narrow-spectrum antibiotic, which has been developed for the treatment of CDI (23). An earlier study has shown that this drug causes minimal disruption of the normal gut microbiota (24). Vickers and colleagues report the results of a phase 2 study of ridinilazole, in which the safety and efficacy of the new drug was compared to vancomycin in patients with CDI (25). Accordingly, 100 patients were randomly assigned to receive a ten-day course of either ridinilazole (200 mg orally twice daily) or vancomycin (125 mg four times daily). Patients in the ridinilazole group also received two doses of placebo daily in order to maintain the same dosing schedule. Patients recruited to the study were confirmed to have CDI by detection of toxin in the stool. Sixty-nine patients (36 treated with ridinilazole and 33 treated with vancomycin) were included in the primary analysis of efficacy. The clinical response rates were defined as a composite endpoint of cure at the end of treatment and no recurrence for 30 days after treatment. Ridinilazole was shown to be significantly more effective than vancomycin regarding the endpoint of sustained clinical responses (66.7% for ridinilazole *vs.* 42.4% for vancomycin). The cure rate for ridinilazole also met the pre-specified endpoint of non-inferiority at the end of treatment compared with vancomycin (77.8% for ridinilazole *vs.* 68.7% for vancomycin). Recurrent infections were seen in 14.3% of patients treated with ridinilazole and in 34.8% of patients treated with vancomycin. The rates of adverse events were similar in both treatment groups. Adverse events were reported in 82% (41 of 50) of patients receiving ridinilazole, compared with 80% (40 of 50) of patients receiving vancomycin. No adverse events that required treatment to be discontinued were seen in the ridinilazole group. However, safety assessments are limited because of the relatively small number of patients. Further limitations of the trial included over-representation of younger patients recruited to the study. Additionally, only 14% of patients in the ridinilazole group and 18% in the vancomycin group had severe disease and few of the participants in the trial had a history of previous episodes of CDI (10% in the ridinilazole group and 8% in the vancomycin group). Also, it remains unclear, why only 64% (21/33) of the sites in this multicentre study recruited patients to the trial. Furthermore, future studies designed to compare the clinical response rates of ridinilazole with those of fidaxomicin, might yield additional insights.

In summary, due to the still limited effectiveness of available therapies for CDI, and despite considerable advances in the field, further development of innovative treatment options is needed. The promising results of this phase 2 study of the new drug ridinilazole definitely warrant further clinical assessment in patients with CDI.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Rupnik M, Wilcox MH, Gerding DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. Nat Rev Microbiol 2009;7:526-36.
2. Vonberg RP, Schwab F, Gastmeier P. Clostridium difficile in discharged inpatients, Germany. Emerg Infect Dis 2007;13:179-80.
3. He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare-associated Clostridium difficile. Nat Genet 2013;45:109-13.
4. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. N Engl J Med 2015;372:825-34.
5. Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. N Engl J Med 2008;359:1932-40.
6. Steinebrunner N, Sandig C, Sommerer C, et al. Reduced residual gene expression of nuclear factor of activated T cells-regulated genes correlates with the risk of

cytomegalovirus infection after liver transplantation. Transpl Infect Dis 2014;16:379-86.
7. Steinebrunner N, Sandig C, Sommerer C, et al. Pharmacodynamic monitoring of nuclear factor of activated T cell-regulated gene expression in liver allograft recipients on immunosuppressive therapy with calcineurin inhibitors in the course of time and correlation with acute rejection episodes--a prospective study. Ann Transplant 2014;19:32-40.
8. Steinebrunner N, Sandig C, Zimmermann S, et al. Salmonella enterica serovar Minnesota urosepsis in a patient with Crohn's disease in the absence of recent or current gastrointestinal symptoms. J Med Microbiol 2013;62:1360-2.
9. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2013;108:478-98; quiz 99.
10. Abou Chakra CN, Pepin J, Sirard S, et al. Risk factors for recurrence, complications and mortality in Clostridium difficile infection: a systematic review. PLoS One 2014;9:e98400.
11. Aseeri M, Schroeder T, Kramer J, et al. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients. Am J Gastroenterol 2008;103:2308-13.
12. Cornely OA, Miller MA, Louie TJ, et al. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clin Infect Dis 2012;55 Suppl 2:S154-61.
13. Marsh JW, Arora R, Schlackman JL, et al. Association of relapse of Clostridium difficile disease with BI/NAP1/027. J Clin Microbiol 2012;50:4078-82.
14. Rea MC, Dobson A, O'Sullivan O, et al. Effect of broad- and narrow-spectrum antimicrobials on Clostridium difficile and microbial diversity in a model of the distal colon. Proc Natl Acad Sci U S A 2011;108 Suppl 1:4639-44.
15. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012;12:281-9.
16. Bartsch SM, Curry SR, Harrison LH, et al. The potential economic value of screening hospital admissions for Clostridium difficile. Eur J Clin Microbiol Infect Dis 2012;31:3163-71.
17. Gao XW, Mubasher M, Fang CY, et al. Dose-response efficacy of a proprietary probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R for antibiotic-associated diarrhea and Clostridium difficile-associated diarrhea prophylaxis in adult patients. Am J Gastroenterol 2010;105:1636-41.
18. Youngster I, Russell GH, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. JAMA 2014;312:1772-8.
19. Kociolek LK, Gerding DN. Breakthroughs in the treatment and prevention of Clostridium difficile infection. Nat Rev Gastroenterol Hepatol 2016;13:150-60.
20. Martin J, Wilcox M. New and emerging therapies for Clostridium difficile infection. Curr Opin Infect Dis 2016;29:546-54.
21. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. N Engl J Med 2017;376:305-17.
22. Tenover FC, Tickler IA, Persing DH. Antimicrobial-resistant strains of Clostridium difficile from North America. Antimicrob Agents Chemother 2012;56:2929-32.
23. Bassères E, Endres BT, Khaleduzzaman M, et al. Impact on toxin production and cell morphology in Clostridium difficile by ridinilazole (SMT19969), a novel treatment for C. difficile infection. J Antimicrob Chemother 2016;71:1245-51.
24. Vickers R, Robinson N, Best E, et al. A randomised phase 1 study to investigate safety, pharmacokinetics and impact on gut microbiota following single and multiple oral doses in healthy male subjects of SMT19969, a novel agent for Clostridium difficile infections. BMC Infect Dis 2015;15:91.
25. Vickers RJ, Tillotson GS, Nathan R, et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Lancet Infect Dis 2017;17:735-44.

Cite this article as: Steinebrunner N, Stremmel W, Weiss KH. Ridinilazole—a novel antibiotic for treatment of Clostridium difficile infection. J Thorac Dis 2018;10(1):118-120. doi: 10.21037/jtd.2017.12.117

