Commentary

DOI: 10.5582/ddt.2022.01025

Prospects of contezolid (MRX-I) against multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis

Min Yang[§], Senlin Zhan[§], Liang Fu, Yuxiang Wang, Peize Zhang[*], Guofang Deng[*]

Department of Pulmonary Medicine and Tuberculosis, The Third People's Hospital of Shenzhen, China.

SUMMARY Tuberculosis has become a great global public health threat. Compared with drug-susceptible tuberculosis (TB), the treatment regimens for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) involve more severe adverse events and poorer treatment outcomes. Linezolid (LZD) is the first oxazolidinones used for TB. Thanks to its potent activity against *Mycobacterium tuberculosis*, LZD has become one of the key agents in the regimens against MDR/XDR-TB. However, this drug may cause intolerability and other adverse events. Contezolid, another novel oxazolidinone, can also inhibit *M. tuberculosis*, still with fewer adverse effects compared with LZD. This paper is to prospect the potentials of contezolid in the treatment of MDR/XDR-TB, with focus on its efficacy and possible adverse effects.

Keywords *Mycobacterium tuberculosis*, contezolid, MDR-TB, XDR-TB

1. Introduction

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*. A total of about 2 billion people are infected with *M. tuberculosis* worldwide, and 5-10% of them will develop TB disease during their lifetime (*1*). Tuberculosis has become a great global public health threat. Compared with drug-susceptible TB, the treatment regimens for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) involve a longer course of treatment, heavier economic burden, and higher drug toxicity, as well as more severe adverse events and poorer treatment outcomes (*1*). Therefore, new and fast-acting anti-mycobacterial drugs with better efficacy to cure MDR/XDR-TB are in urgent demand. Oxazolidinones have been found potential inhibition against MDR Gram-positive bacteria and *Mycobacterium tuberculosis*, among which linezolid (LZD) is the first used for TB. Thanks to its potent activity against *M. tuberculosis*, LZD has become one of the key agents in the regimens against MDR/XDR-TB (*2*). However, this drug may cause intolerability and other adverse events, such as peripheral and optic neuropathy as well as myelosuppression. Contezolid, another novel oxazolidinone is preliminarily developed for Gram-positive infections. Some studies have shown that contezolid can also inhibit *M. tuberculosis* (*3*), still with fewer adverse effects compared with LZD (*4*). This paper is to prospect the potentials of contezolid in the treatment of MDR/XDR-TB, with focus on its efficacy and possible adverse effects.

2. The disadvantage of LZD for MDR/XDR-TB

Oxazolidinones are a series of antibiotics against MDR Gram-positive bacteria, including vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* (MRSA) (*5*). The mechanics of action is to bind the 50S ribosomal subunit of archaea and bacteria, inhibiting the biosynthesis of their proteins, but without influence on human cytoplasmic ribosomes (*6*). Their promising activity against MDR-TB was also found soon after their discovery. LZD, the first oxazolidinone used for TB, is now one of the key drugs in both longer and shorter MDR/XDR-TB regimens. However, myelosuppression greatly limits the use of LZD. Potential irreversible optic neuropathy and peripheral neuropathy are also the major adverse effects of LZD (*7*). These neurotoxic adverse effects are due to the inhibition of MAOs, a family of enzymes that are essential for the metabolic inactivation of the neurotransmitters, such as serotonin, dopamine, and epinephrine. To avoid such adverse effects and improve tolerability and safety, the development of better drugs is imperative.

3. The superiority of contezolid

Contezolid, a new member of oxazolidinone antibiotics,

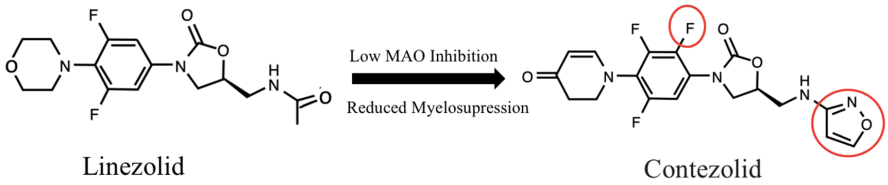

Figure 1. The superiority of contezolid.

can inhibit the formation of a functional 70S initiation complex that is necessary for bacterial reproduction (*4*). It is rationally designed to address the myelosuppression and MAO inhibition associated with linezolid. Serotonergic profiles for contezolid *in vitro* and in rodents have been reported. Compared with LZD, contezolid exhibits a reduction in reversible inhibition of MAO-A and MAO-B isoforms by 2-and 148-fold respectively (Figure 1) (*8*). The safety and tolerability studies of contezolid show that it was well tolerated and safe in healthy Chinese subjects (*9-11*). Even at doses up to 800 and 1,200 mg every 12 hours for 28 days, no severe adverse events were observed, and nobody discontinued the drug due to any adverse events. Compared with LZD, contezolid is associated with a lower incidence of myelosuppression. Noteworthily, in the high dose contezolid group, approximately half of the subjects had merely slight ALT elevations; however, with most of them < 2 ULN, and none of them persistent (*10*). Contezolid may prolong the QT interval slightly at a supratherapeutic dose (1,600 mg/d) but does not influence the QT interval at a therapeutic dose (800 mg/d) (*12,13*).

4. The anti-tuberculosis activity of contezolid

Only a few studies have been published on contezolid for its effect on tuberculosis. One study (*3*) tested the oxazolidinones (including contezolid and LZD) against both susceptible and MDR/XDR *M. tuberculosis* isolates *in vitro*. The MIC_{50} and MIC_{90} for LZD and contezolid were 1 mg/mL and 0.5 mg/mL, *vs*. 0.5 mg/mL and 0.125 mg/mL, respectively. Contezolid showed a same activity as LZD against all *M. tuberculosis* isolates. Because of the promising results *in vitro*, the evaluation of the drugs' efficacy was then performed *in vivo*. LZD and contezolid were studied in *M. tuberculosis*-infected mice further. The mice were randomly assigned into 6 groups as follows: untreated early control (EC) group for the *M. tuberculosis* baseline, late control (LC) group to determine the bacterial load at the end of therapy, one LZD group (100 mg/kg once daily), three contezolid groups (100 mg/kg once daily, 50 mg/kg twice daily, and 25 mg/kg twice daily). Treatment was started one week after infection, with administrations for 5 days per week for 4 weeks. Then the bacterial load in mouse lungs was determined, showing the bacteria in the LZD group and the contezolid 100 mg/kg group significantly reduced compared with the EC and LC groups ($p < 0.05$). The efficacy in the LZD group was equivalent to the contezolid 100 mg/kg group ($p < 0.05$). The contezolid 100 mg/kg once daily group showed significant better efficacy than the contezolid 50 mg/kg and 25 mg/kg twice daily groups ($p < 0.05$). The efficacy in the contezolid 50 mg/kg group was equivalent to the contezolid 25 mg/kg group ($p < 0.05$). The contezolid 50 mg/kg and 25 mg/kg groups showed significant favorable result than the LC group ($p < 0.05$). However, currently no clinic study on contezolid against *M. tuberculosis* is reported. Meanwhile, contezolid is active against *M. abscessus in vitro* too, with compatibility to those antibiotics most frequently used to treat such infections. It inhibits intracellular replication of *M. abscessus*, exhibiting equivalent activity in culture compared with linezolid. Therefore, contezolid is also a potential candidate to be included in novel therapeutic anti-*M. abscessus* regimens (*14*).

5. Conclusion

In summary, compared to LZD, contezolid has a similar activity against both drug-resistant and drug-susceptible *M. tuberculosis in vitro* and *in vivo*, but with fewer side effects, especially neuropathy and myelosuppression. The inclusion of contezolid possibly makes MDR-TB/XDR-TB therapy regimens more efficacious and less toxic than LZD. However, further clinical studies are required to confirm it.

Acknowledgements

The authors wish to thank Dr. Guofeng Zhu for his valuable advice on this work.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Global Tuberculosis Report 2021. *https://www.who.int/publications/i/item/9789240037021* (accessed March 17, 2022).
2. Mirzayev F, Viney K, Linh NN, Gonzalez-Angulo L, Gegia M, Jaramillo E, Zignol M, Kasaeva T. World Health

Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. Eur Respir J. 2021; 57:2003300.
3. Shoen C, DeStefano M, Hafkin B, Cynamon M. *In vitro* and *in vivo* activities of contezolid (MRX-I) against *Mycobacterium tuberculosis*. Antimicrob Agents Chemother. 2018; 62:e00493-18.
4. Hoy SM. Contezolid: First approval. Drugs. 2021; 81:1587-1591.
5. Foti C, Piperno A, Scala A, Giuffrè O. Oxazolidinone asntibiotics: Chemical, biological and analytical aspects. Molecules. 2021; 26:4280.
6. Yamada M, Yasuhara H. Clinical pharmacology of MAO inhibitors: Safety and future. Neurotoxicology. 2004; 25:215-221.
7. Vinh DC, Rubinstein E. Linezolid: a review of safety and tolerability. J Infect. 2009; 59:S59-74.
8. Wang W, Voss KM, Liu J, Gordeev M. Nonclinical evaluation of antibacterial oxazolidinones contezolid and contezolid acefosamil with low serotonergic neurotoxicity. Chem Res Toxicol. 2021; 34:1348-1354.
9. Wu X, Li Y, Zhang J, *et al*. Short-term safety, tolerability, and pharmacokinetics of MRX-I, an oxazolidinone antibacterial agent, in healthy Chinese subjects. Clin Ther. 2018; 40:322-332.e5.
10. Eckburg PB, Ge Y, Hafkin B. Single- and multiple-dose study to determine the safety, tolerability, pharmacokinetics, and food effect of oral MRX-I versus linezolid in healthy adult subjects. Antimicrob Agents Chemother. 2017; 61:e02181-16.
11. Wu J, Wu H, Wang Y, Chen Y, Guo B, Cao G, Wu X, Yu J, Wu J, Zhu D, Guo Y, Yuan H, Hu F, Zhang J. Tolerability and pharmacokinetics of contezolid at therapeutic and supratherapeutic doses in healthy Chinese subjects, and assessment of contezolid dosing regimens based on pharmacokinetic/pharmacodynamic analysis. Clin Ther. 2019; 41:1164-1174.e4.
12. Wu J, Cao G, Wu H, Chen Y, Guo B, Wu X, Yu J, Ni K, Qian J, Wang L, Wu J, Wang Y, Yuan H, Zhang J, Xi Y. Evaluation of the effect of contezolid (MRX-I) on the corrected QT interval in a randomized, double-blind, placebo- and positive-controlled crossover study in healthy Chinese volunteers. Antimicrob Agents Chemother. 2020; 64:e02158-19.
13. Wu J, Wang K, Chen Y, Yuan H, Li L, Zhang J. Concentration-response modeling of ECG data from early-phase clinical studies to assess QT prolongation risk of contezolid (MRX-I), an oxazolidinone antibacterial agent. J Pharmacokinet Pharmacodyn. 2019; 46:531-541.
14. Guo Q, Xu L, Tan F, Zhang Y, Fan J, Wang X, Zhang Z, Li B, Chu H. A novel oxazolidinone, contezolid (MRX-I), expresses anti-mycobacterium abscessus activity *in vitro*. Antimicrob Agents Chemother. 2021; 65:e0088921.

Received March 18, 2022; Revised March 26, 2022; Accepted April 5, 2022

[§]These authors contributed equally to this work.

**Address correspondence to:*
Guofang Deng and Peize Zhang, Department of Pulmonary Medicine and Tuberculosis, The Third People's Hospital of Shenzhen, China; The National Clinical Research Center for Infectious Diseases. No.29 Bulan Road, Longgang District, Shenzhen, Guangdong, China.
E-mail: jxxk1035@yeah.net (Deng GF), 82880246@qq.com (Zhang PZ)

Released online in J-STAGE as advance publication April 12, 2022.