

Linezolid for patients with multidrug-resistant tuberculosis/ extensively drug-resistant tuberculosis in China

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SUMMARY Linezolid has been one of the key anti-tuberculosis agents for the treatment of multidrug-resistant tuberculosis (MDR-TB)/extensively drug-resistant tuberculosis (XDR-TB). It used to be very expensive and was not covered by social insurance from local governments. Nevertheless, a growing number of patients in China received linezolid in their anti- MDR/XDR TB regimens over the past decade. Many scholars in China have reported their experience using linezolid to treat patients with MDR/XDR-TB. In view of this, existing evidence of the efficacy and safety of linezolid and problems faced by Chinese patients with MDR/XDR-TB are summarized here.

Keywords Linezolid, MDR/XDR-TB, China, drug resistance

1. Introduction

Linezolid has been endorsed by the WHO as one of the Group A anti-tuberculosis agents for the treatment of multidrug-resistant tuberculosis (MDR-TB)/extensively drug-resistant tuberculosis (XDR-TB) since 2018 (1). China is one of the world's countries with the highest TB burden (2). Concerns have led to an emphasis on the care and control of MDR-TB and XDR-TB in China (3). Over the past decade, a growing number of patients in China received linezolid in their anti-MDR/XDR TB regimens. Many scholars in China have reported their experience using linezolid to treat patients with MDR/XDR-TB (4-7). In view of this, existing evidence of the efficacy and safety of linezolid and problems faced by patients with MDR/XDR-TB in China have been summarized here.

2. Use of linezolid to treat Chinese patients with MDR/XDR TB

Linezolid is an artificial synthetic oxazolidinone antibiotic. It binds to the 50S subunit of the ribosome and prevents protein synthesis. Linezolid has proven to be a potent anti-tuberculosis drug both *in vitro* and *in vivo* (8,9). Before 2021, the cost of the drug rendered it unaffordable for typical patients with MDR/XDR-TB in China except for those participating in clinical trials, and this even included patients covered by government-subsidized medical insurance (10). Uneven

economic development may have also contributed to the underutilization of linezolid in China since MDR/XDR-TB is markedly more prevalent in low-income groups. Moreover, MDR/XDR TB is extremely costly and can significantly burden individuals and the healthcare system. The exact proportion of patients receiving an anti-TB regimen that includes linezolid is unknown. As such, linezolid was presumably only included in the treatment regimen received by a small number of patients with MDR/XDR-TB in China over the past decade. In recent years, the drug has become more accessible cost-wise as the central government has revised the subsidy for medical insurance and more local pharmaceutical manufacturers have started production. Linezolid will presumably be given to more patients to treat MDR/XDR-TB in China in the coming days.

3. The efficacy and safety of linezolid in MDR/XDR-TB

The current authors searched for use of linezolid to treat MDR/XDR-TB in articles and reports by Chinese authors published in CNKI, PubMed, Embase, and the Cochrane Central Library from the start of the given database until December 31, 2021. There is growing evidence of the efficacy of linezolid against MDR-TB, from studies of varying scales carried out across different cities in China. From the earliest study of 8 patients with XDR-TB in Shanghai in 2009 to an RCT initiated by Tang *et al.* in 2015 in Beijing, these sources have all found linezolid

to be efficacious against MDR/XDR-TB (4,11). A recent multi-center study on administration of bedaquiline in a regimen to treat MDR/XDR-TB in China found that more than 90% of patients administered linezolid in that regimen were also administered bedaquiline (12). The high rate of culture conversion further demonstrated the efficacy of linezolid combined with bedaquiline. The potential efficacy of linezolid against MDR/XDR-TB was evident even in a small group of pediatric patients (7). A prospective non-randomized controlled single center trial conducted by the current authors' team found no difference in treatment outcomes between patients with MDR/XDR-TB receiving or not receiving bedaquiline in a regimen that included linezolid (6). The most commonly used dose of linezolid in these regimens was 600 mg/d, though this was sometimes reduced to 300 mg/d due to linezolid-related toxicity (6,12). All of these studies noted an average two- to three-month sputum culture conversion rate of more than 80% within six months from the initiation of treatment (6,12,13). Patients receiving linezolid were more likely to have favorable treatment outcomes compared to those not receiving linezolid (13).

Adverse events are believed to be associated with the dose and duration of treatment, which are consistent with the international literature (14-16). Frequently reported adverse reactions to long-term use of linezolid are peripheral neuropathy, anemia, and thrombocytopenia, which are the main risk factors for reduced patient compliance and discontinuation of treatment. Optimizing both the dose and duration of treatment to improve the antibiotic's tolerability profile is a major focus for larger scale studies in the future. At present, the prospective efficacy of linezolid in China is supported mainly by small-scale studies. Randomized controlled studies on a massive scale need to be conducted to accumulate more evidence. Numerous clinical studies in China are recruiting patients with MDR/XDR-TB to receive a treatment regimen including linezolid (NCT: ChiCTR:2000032298, ChiCTR:2100042287, and ChiCTR:210004593) (17). These studies are expected to yield more definitive clinical findings.

4. Resistance to linezolid

Findings from *in vitro* testing and molecular testing have indicated that only a small percentage (4.5-5.6%) of patients with MDR/XDR-TB in China exhibited linezolid resistance; this resistance was mainly caused by alterations to the specific linezolid binding site (18,19). A study of 399 isolates from southwest China revealed that 4 were linezolid-resistant and 2 carried mutations in the *rplC* gene (19). Another study of 93 isolates reported that 5 were linezolid-resistant; only 2 (40.0%) were found to contain the Cys154Arg allele in the *rplC* gene (18). In a multi-center study involving the use of bedaquiline and linezolid in 277 patients,

115 patients with prior linezolid exposure yielded 19 isolates (6.9%) exhibiting linezolid resistance. Genetic mutations were observed in 10 (52.6%, 10/19) linezolid-resistant isolates, the most prevalent of which was a Cys154Arg (36.8%, 7/19) substitution within ribosomal protein L3 (20). A subsequent study of nationwide drug resistance surveillance in China revealed linezolid resistance in 15 (3.8%) of 391 culture-positive specimens (21). Notwithstanding the low resistance rate, induced linezolid resistance caused by intermittent administration as a result of drug cost and adverse reactions remains a major concern in China in the coming future.

5. Conclusion

In the face of the limited number of new drugs to treat MDR/XDR-TB, a regimen that includes linezolid will remain an important weapon to treat MDR/XDR-TB in China over the next few decades. Considering the importance of linezolid, precision dosage and close monitoring of treatment are vital to achieving optimal drug efficacy and balancing its tolerability profile. These efforts will benefit more patients with drug-resistant TB and reduce community transmission.

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