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Editorial

Linezolid for multidrug-resistant tuberculosis: How should we approach it?

Linezolid para la tuberculosis resistente a múltiples fármacos: ¿cómo debemos abordarlo?

Miguel Santin

Unit of Tuberculosis, Service of Infectious Diseases, Bellvitge University Hospital – IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least rifampicin and isoniazid, poses a major threat to public health and TB control worldwide. According to the World Health Organization (WHO), MDR-TB accounted for 480,000 new cases of TB in 2013, of which 9% were extensively drug-resistant TB (XDR-TB), defined as MDR-TB with resistance to a fluoroquinolone and at least one second-line injectable anti-TB agent.[1] In contrast to drug-sensitive disease, in which a 6 to 9-month first-line treatment achieves more than 95% efficacy, resistant TB requires a lengthy course of less effective, less tolerated and more expensive second-line anti-TB drugs. Treatment success rates are around 60%, 40% and below 20% for MDR-TB, XDR-TB, and beyond XDR-TB respectively.[2]

The Cape Town Declaration in February 2000 provided a roadmap for the development of new anti-TB drugs and set the scene for the launch of clinical trials to evaluate multiple-drug regimens. As a result, two new drugs, delamanid and bedaquiline recently gained approval from the European and US regulatory agencies, and the WHO issued guidelines for their rational use in the treatment of MDR-TB.[3] In addition, existing antibiotics with *in vitro* activity against *Mycobacterium tuberculosis* are now being tested for the treatment of MDR-TB. Among them, linezolid in combination with other second-line anti-TB drugs has been extensively evaluated in recent years. Linezolid belongs to the oxazolidinone antibiotic class, which blocks protein synthesis by binding to the 50S ribosomal subunit of the bacteria. It exhibits bacteriostatic activity against *M. tuberculosis*, including MDR and XDR strains, modest activity in *in vivo* models, and marginal early and extended bactericidal activity.[4] Though this performance did not look promising, the uncontrolled clinical evidence gathered so far has shown that linezolid improved the results of treatment for MDR-TB when added to a background of second-line drugs. In a small randomized clinical trial (RCT),[5] patients with XDR-TB were treated with linezolid started either immediately or after two months, together with the background regimen. By four months, 79% of the immediate start group had converted to negative sputum culture, compared with 35% in the delayed-start group. In a follow-up study a One year after the end of treatment, no relapses had been recorded and 71% of patients who completed the study were cured.[6] In another multicenter RCT, patients with XDR-TB assigned to receive linezolid in addition to the background regimen had significantly higher rates of sputum culture conversion (78.8%) and treatment success (69.7%) by month 24 than the control group, in which the respective figures were 37.6% and 34.4%.[7] A recent systematic review and meta-analysis of 15 studies, of 239 patients with MDR- and XDR-TB showed that 89% had culture conversion and 83% were cured or completed the treatment.[8]

Toxicity is the main limitation for the use of linezolid in prolonged anti-TB regimens. According to published data, between 40% and 90% of patients suffer adverse events, and between 6% and 68% discontinue linezolid, mainly due to neuropathy (including optic neuritis) and myelosuppression.[9] In this issue of *Enf Infecc Microbiol Clin*, Ramírez-Lapausa et al.[10] reported their experience in a retrospective study of 55 patients with MDR-TB, 21 of whom had linezolid included in their anti-TB regimen because of the lack of other likely active drugs to complete the treatment scheme. The culture conversion and cure rates are in line with previous studies. However, only four (19%) patients developed major toxicity attributed to linezolid, despite a median duration of treatment of 24 months. In two patients, the dose of linezolid had to be reduced to 600 *q.d.*; interestingly, no patients required permanent discontinuation of treatment. Similarly, in a study in India, linezolid had to be withdrawn in three of 29 patients because of serious adverse events. All three were receiving 600 mg *b.i.d.*[11] The low number of discontinuations observed in these two studies, albeit in a small number of patients, probably reflects the benefits of close monitoring of adverse events and expertise in the management of complex MDR-TB patients, as is the case of the Isolation Ward of the center where the present study was conducted.

The WHO guidelines on the programmatic management of MDR-TB issued in 2008 classified anti-TB drugs into five groups (1–5), starting with the safest and most effective (group 1). The WHO group 5 comprises drugs with limited data regarding their activity, efficacy and/or long-term safety in the treatment of drug-resistant TB. This group includes linezolid and, the new drugs

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E-mail address: msantin@bellvitgehospital.cat

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bedaquiline and delamanid among others. Despite the favorable experience with these drugs for treating MDR- and XDR-TB, the WHO reserves them for cases in which no adequate regimen can be designed with medications from groups 1 to 4. However, since drugs from group 5 are often needed to construct effective anti-TB regimens, linezolid is increasingly being used "off-label" in clinical practice in developed countries to treat patients with drug-resistant TB or drug intolerance. Coincidentally, some experts have already called for a change in the classification – including the upgrading of these three drugs, due to the evidence of their effectiveness and safety compared to the other drugs in the group and drugs in group 4 (oral bacteriostatic second-line drugs).[2] In fact, according to the results of a systematic review with a cohort analysis and meta-analysis including all the group 5 drugs except bedaquiline and delamanid, linezolid was the only one associated with a significant increase in the probability of a favorable outcome in MDR- and XDR-TB treated patients.[12]

In my view, sufficient evidence is now available to support the use of linezolid to treat MDR-TB. However, resistance, toxicity and cost are major concerns. The emergence of resistance in Lee's study in 11% of patients treated for six months or more should not be ignored.[5] While doses lower than 600 mg *q.d.* seem to reduce the incidence of adverse events and the need to discontinue the drug, they may increase the risk of acquired resistance. Therefore, until more data are available, doses below 600 mg *q.d.* should not be given, particularly during the intensive phase of treatment. Measurement of linezolid levels in blood may help to improve efficacy and tolerance, and may become standard practice in the near future.

The use of linezolid for the treatment of MDR-TB is likely to increase. However, the benefits of its use (and of other new anti-TB drugs) for treating MDR-TB will depend on the ability of clinicians to avoid the emergence of resistance. The most effective way of achieving this is to apply the highest possible standards when treating these patients and to ensure that they are attended at specialist TB units by clinicians with experience in the management of complex cases.

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