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Linezolid in multidrug-resistant tuberculosis

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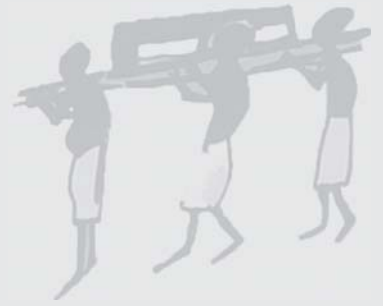
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Chapter 5B

Linezolid: safety and efficacy monitoring

M.S. Bolhuis, A.D. Pranger, and J.W.C. Alffenaar

We read with interest the article “Linezolid, an effective and cheap drug in MDR-TB treatment failure patients in India” by Singla *et al.* (1), which described the treatment outcome of 29 (pre-)extensively drug-resistant (XDR) tuberculosis (TB) patients from Delhi, India. All patients received linezolid as part of their anti-TB regimen. The high percentage favorable treatment outcome in the study led Singla *et al.* (1) to conclude that “linezolid could have played a key role”. However, in our opinion, conclusions on the role of a single agent, such as linezolid, are difficult to draw from a series of cases without controls, in which every patient received linezolid in addition to an injectable and a fluoroquinolone. Indeed, the important role of later-generation fluoroquinolones is addressed, but neither drug susceptibility testing (DST) nor drug concentration monitoring for linezolid, is performed. Therefore linezolid treatment itself could even be sub-therapeutic (2).

Singla *et al.* (1) conclude that “an aggressive, comprehensive management program using linezolid along with other drugs can favorably treat significant number of patients”. Although we concur with this statement, a closer look at the management program applied in this study suggests that the program might not be too aggressive or comprehensive. For instance, no Directly Observed Therapy (DOT) is applied, nor did the patients receive nutritional or good psychosocial support. Compliance was only assessed indirectly by checking empty blisters. Since non-compliance could lead to treatment failure and increase of resistance against the few drugs that are still effective in (pre-)XDR-TB treatment, we would strongly advise to abandon DOT only in exceptional cases where compliance is highly probable (3). Therapeutic drug monitoring (TDM) can be recommended to ensure adequate drug exposure during treatment. In rural areas dried blood spot analysis may enable TDM by offering an affordable tool for drug concentration measurement in a centralized laboratory using stable easy-to-obtain samples (4).

The very low incidence of major adverse events (AEs) of 10.3% as reported by Singla *et al.* (1) is in contrast with findings in literature where 41.2% of 85 MDR/XDR-TB patients treated with linezolid experienced major AEs (5). The authors provided no explanation for low AE incidence found in their study. Perhaps the fact that temporary discontinuation of linezolid is scored as a minor adverse event along with the absence of DOT resulted into a lower score of AEs in the study of Singla *et al.* Unfortunately, the authors provided no information on the manufacturer of the linezolid. Only the low cost of linezolid of less than \$1 per tablet is mentioned, compared to approximately \$80 per tablet in The Netherlands. It is well established that counterfeit drugs pose a great threat and counterfeit drugs sometimes contain little to none of the claimed drug (6). Although there is no evidence that the

administered drugs in this study are counterfeit, it can also not be excluded based on the information as provided by Singla *et al.* (1). This, combined with the absence of DOT and TDM, could very well be a reason for the low incidence of major adverse events as observed in the study by Singla *et al.* (1).

In our opinion, only a randomized controlled trial of linezolid vs. placebo as add on to an adequate background regimen using DST and TDM will provide comprehensive results on efficacy and safety of linezolid as potential drug for (pre-)XDR-TB treatment regimen.

Statement of interest: none.

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