Title:

Re: Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China

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To the editor: Heterogeneity amongst cohorts of patients treated for drug-resistant tuberculosis (DR-TB) make assessing the efficacy of new drugs and regimens unreliable without randomisation (1). We warmly welcome the randomised controlled trial (RCT) "Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China" presented by Tang et al. (2). Linezolid is now included on the WHO list of essential medicines (3) and falling prices will improve access. That Tang et al. report a 35.3% absolute reduction in the risk of a poor outcome by adding linezolid to an optimised background regimen argues in favour of wider use. Linezolid remains a WHO 'Group 5' drug, classifying it as an 'anti-TB drug with limited data on efficacy and/or long term safety in the treatment of DR-TB'(4). The limited data on the efficacy of drugs in this class has recently been reviewed (5). These WHO classifications will shortly be reviewed and the exciting results from this study have the potential to alter guidance regarding the treatment of extensively drug-resistant tuberculosis (XDR-TB). We note the proposal to re-classify linezolid into Group 3 in an editorial in the October edition of the ERJ (6). It is with this in mind that we seek some clarifications.

The journal rightly requires that reports of randomised controlled trials conform to the CONSORT guidelines (7). We were therefore concerned to note that limited details were presented regarding the randomisation process and steps taken to ensure adequate allocation concealment. Details on the target sample-size calculation were also absent. The authors do not state whether the trial was registered in a clinical trial registry as per journal guidelines.

A recent systematic review and meta-analysis by Zhang et al (8) highlighted Linezolid's significant side-effect profile. The data presented by Tang and colleagues on rates of nausea and on the timing of myelosuppression and neuropathy will be of great interest to clinicians and patients. The manuscript states: 'Most adverse events resolved after reducing the dosage of linezolid or temporarily discontinuing linezolid, and only two patients were permanently discontinued from using the drug because of severe anaemia.' Details of symptom severity and the number of patients left with cytopaenias or significant residual neuropathy would be hugely valuable.

Figure 2 suggests that around a quarter of patients in the control group achieved sputum culture-conversion in the first three months of the study, despite all having been sputum smear-positive for the preceding twelve months. This suggests that new agents other than linezolid were introduced in both arms at enrolment. It would be helpful to know whether other drugs that patients had not used

previously were started when the patients were enrolled in the trial. In particular, many patients were reported to have been treated with clofazimine, an agent shown by the authors to be useful in the treatment of MDR-TB (9). It would also be relevant to know whether the background regimen was determined prior to randomisation; and whether there was any imbalance in newly-introduced drugs between the trial arms, both at enrolment and subsequently.

Finally, early relapse following treatment is common (10). Data on relapse-free survival from the other completed randomised controlled trial involving linezolid has been valuable in understanding the role of this drug(11). Relapse-free survival is a more robust end-point and follow up for at least one year should be routine in randomised evaluations of TB treatment regimens. We hope this will be considered in future trial designs.

If the authors could provide these additional details, it would greatly inform our understanding of the efficacy and place of linezolid in XDR regimens. This information would also be valuable to those who will shortly be drafting new international recommendations for DR-TB as well as to clinicians and programs providing XDR-TB care. We congratulate the authors on an important study and look forward to their response.

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