Linezolid for drug-susceptible tuberculosis

We question why linezolid would be included in a regimen for drug-susceptible tuberculosis, as described by Jung-Kyu Lee and colleagues,[1] given its known toxicity profile. Regardless of the underlying premise, we have substantial concerns about the manner in which the data have been analysed and presented, and about the conclusions that have been drawn.

It is unclear why some patients were excluded from the modified intention to treat (mITT) analysis. For example, those who did not take adequate trial medication should have been included in the mITT population.

Although participants were enrolled on the basis of having a positive Xpert MTB/RIF assay, only 285 (74%) were subsequently culture positive at baseline. Therefore, the mITT population includes participants who were culture negative at enrolment and consequently could not contribute to the primary outcome of culture conversion. Therefore, the numbers at risk presented in figure 2 of the Article[1] are clearly incorrect.

Too much weight is given in the paper to the per-protocol analysis—a biased assessment not appropriate in a trial with a superiority hypothesis. This overemphasis has influenced the authors' conclusions that linezolid has a potential role in treating drug-susceptible tuberculosis because they have focused on an analysis that does not properly reflect the treatment effect of the regimen.

Selecting regimens to take forward into treatment-shortening trials is a complex decision. For the reasons we outline above, we do not think the authors' conclusions are supported by the data. Phase 3 trials are costly and time consuming, and it is essential that early phase studies are appropriately designed, analysed, and reported to ensure the best candidates are taken into phase 3.

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1 Lee JK, Lee JY, Kim DK, et al. Substitution of ethambutol with linezolid during the intensive phase of treatment of pulmonary tuberculosis: a prospective, multicentre, randomised, open-label, phase 2 trial. *Lancet Infect Dis* 2019; **19:** 46–55.

We would like to thank Jung-Kyu Lee and colleagues[1] for the impressive work they have executed. This prospective, multicentre, randomised trial reports the short-term treatment outcomes of linezolid compared with standard treatment in drug-susceptible tuberculosis. However, we would like to point out several important aspects regarding the time to culture conversion and culture conversion rates after 8 weeks of treatment in patients with cavitary and non-cavitary tuberculosis.

Lee and colleagues randomly assigned 428 patients and detected cavitary lesions in 159 (40%) patients. It is regrettable that the authors did not analyse patients with cavitary lesions for the primary outcome. Treatment of cavitary tuberculosis is troublesome since the starting bacilli burden is high and the time to culture conversion is longer than with non-cavitary tuberculosis.[2–4] In one study,[5] the presence of cavitary lesions was an independent risk factor for the prolonged time to culture conversion. Su and colleagues[6] showed the association of directly observed therapy and non-cavitary disease with sputum culture conversion rates in multivariate analysis.

We would like to encourage a subgroup analysis of the patients with cavitary lesions to find out whether the time to culture negativity and the proportion of patients with sputum culture conversion differs between the study groups. We believe this issue is of importance regarding infection prevention and control measures in the hospital and the community. Higher and faster culture conversion rates would affect the duration of patient isolation and would affect patient-to-patient and patient-to-health-care worker transmission of tuberculosis.

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