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Linezolid: safety and efficacy monitoring

To the Editors:

We read with interest the recent *European Respiratory Journal* article 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 of favourable treatment outcomes 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 antimycobacterial agent and a fluoroquinolone. Indeed, the important role of later-generation fluoroquinolones is addressed, but neither drug sensitivity testing (DST) nor drug concentration monitoring for linezolid was performed. Therefore, linezolid treatment itself could even be subtherapeutic [2].

SINGLA *et al.* [1] conclude that “an aggressive, comprehensive management programme using linezolid along with other drugs can favourably treat significant number of patients”. Although we concur with this statement, a closer look at the management programme applied in this study suggests that the programme might not be too aggressive or comprehensive. For instance, no directly observed therapy (DOT) was applied, nor did the patients receive nutritional or good psychosocial support. Compliance was only assessed indirectly by checking empty blister packs. Since noncompliance 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 centralised laboratory using stable, easy-to-obtain samples [4].

The very low incidence of major adverse events (AEs) of 10.3% reported by SINGLA *et al.* [1] is in contrast with findings in literature, where 41.2% of 85 multidrug-resistant/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 was scored as a minor adverse event, along with the

absence of DOT, resulted in a lower score of AEs in the study by SINGLA *et al.* [1]. Unfortunately, the authors provided no information on the manufacturer of the linezolid. Only the low cost of linezolid of less than US\$1 per tablet is mentioned, compared with approximately US\$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 were counterfeit, it also cannot be excluded based on the information 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 AEs as observed in the study by SINGLA *et al.* [1].

In our opinion, only a randomised controlled trial of linezolid *versus* a placebo, in addition 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.

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From the authors:

We read with interest the comments by M.S. Bolhuis and co-workers on our article discussing the role of linezolid in treating multidrug-resistant (MDR) tuberculosis (TB) failures in India [1]. First, we would like to underline that our study was carried out in field conditions in a country with a high burden of MDR-TB cases and limited resources. We thank M.S. Bolhuis and co-workers for the opportunity to discuss the different perspectives of the Indian setting and those of a high-level tertiary hospital in a high-income country (India has one of the best existing TB control programmes).

M.S. Bolhuis and co-workers correctly conclude that only a randomised trial comparing linezolid *versus* a placebo, in addition to an adequate background regimen using drug susceptibility testing (DST) and therapeutic drug monitoring (TDM), would provide comprehensive results on efficacy and safety of linezolid. However, we have three main comments.

First of all, although the best way to provide high-quality data on the possible efficacy of a drug (or a combination of drugs) in TB treatment is to perform a randomised clinical trial (RCT), this is particularly complicated to organise in the treatment of patients affected by MDR-TB, and is even more complicated if they have previously been exposed to second-line anti-TB drugs (SLDs).

In fact, to date, no RCT has been developed showing the possible efficacy of any of the drugs presently used in the treatment of the MDR-TB patients [2], including fluoroquinolones and injectable antimycobacterial agents (which are presently recommended by the World Health Organization) [3].

Among the key difficulties to mention are the ethical issues related to randomisation of MDR-TB patients receiving SLDs when only a few drugs are still effective (*e.g.* in extensively drug-resistant TB cases and those failures who had been previously exposed to several cycles of treatment with different drugs) and the difficulty in attributing a specific outcome to a specific drug composing the prescribed cocktail merit a special discussion [2, 3].

Secondly, DST for linezolid has not been standardised and is difficult to perform both in low- and high-income countries, so that its clinical reliability is still largely unknown. There is still much debate over whether *in vitro* results can be extrapolated to a clinical response [4].

Thirdly, although important, performing linezolid TDM systematically in all patients receiving the drug is unrealistic in India,

although it is recommendable in high-level reference centres located in high-income countries [5].

Based on the comments above, we reinforce the reason why we used the word “could”: “Linezolid could have played a key role” [1]. We cannot be totally sure that we are correct in attributing the encouraging outcome of our patients to linezolid only.

Although we agree on the importance of implementing directly observed therapy, this was not unfortunately possible for all cases treated in our setting. An argument indirectly demonstrating that the patients belonging to our cohort received the drugs is that treatment outcomes were satisfactory. This is why we still believe that the low proportion of adverse events is not a consequence of poor compliance.

We have a last comment on price and quality of drugs. It is well known that the price of drugs is largely influenced by the market location and by many other factors, so that a lower cost in India is not necessarily associated with lower quality. Indian manufacturers producing the drug we used in our study are subject to quality controls according to the national legislation in force, including the approval of the Drug Controller General of India before marketing. Also, as discussed above, the positive outcome achieved indirectly demonstrates the drug was active.

In conclusion, although our study [1] is affected by several limitations, it represents a useful contribution to support those clinicians who are dealing with difficult-to-treat MDR-TB patients daily, those desperately needing linezolid as a third or fourth active drug, and those designing an effective regimen. We agree that more evidence on linezolid efficacy, safety and tolerability is necessary: any well-designed study shedding light on the topic will be most welcome.

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