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Low minimal inhibitory concentrations of linezolid against multidrug-resistant tuberculosis strains

To the Editor:

We are following the debate about the administration and the preferred dosage of linezolid in the treatment of multidrug-resistant (MDR) tuberculosis (TB) and extensively drug-resistant (XDR) TB with great interest. Linezolid is a high potent drug against *M. tuberculosis*, but its widespread use is limited due to severe side-effects in long-term treatment, which often occurs after the usage of 600 mg twice a day in bacterial disease for >28 days and mainly includes severe haematotoxic effects (*i.e.* myelosuppression, anaemia, thrombocytopaenia) or polyneuropathy [1]. However, the current standards in MDR- and XDR-TB require several months of treatment. In addition, the administration of 1200 mg linezolid per day leads to high treatment costs, which limits the usage, especially in low-income countries [1, 2]. Lowering the dosage of linezolid could, therefore, be an effective step towards reducing costs and severe side-effects.

In a letter from Sotgiu *et al.* [3], published in the *European Respiratory Journal*, the authors analysed a subgroup of patients enrolled in their previous meta-analysis about the safety, efficacy and tolerability of linezolid in the treatment of MDR-TB [1]. They found, in a crude statistical comparison of their results to the findings by Lee *et al.* [4] who had provided prospective experimental data for the safety of linezolid in the treatment of XDR-TB, that the best risk-benefit profile was a daily dose of ⩽600 mg [3]. This suggestion was supported by three other studies, which showed some evidence that lower, but yet effective, dosage of linezolid may reduce both toxicity and cost [2, 5, 6]. In this context, drug susceptibility testing is necessary to determine efficacy of linezolid against a wide range of *M. tuberculosis* strains and could provide a further rationale for the application of a lower dosage.

For this purpose we retrospectively evaluated the *in vitro* susceptibility test results of linezolid from clinical routine assessment via minimal inhibitory concentrations (MICs) against 148 *M. tuberculosis* strains including 18 MDR-TB strains isolated from patients treated in our centre from 2002 to 2012. Testing for MIC was performed on solid Middlebrook-7H10 agar plates as described elsewhere [7]. MICs were defined

TABLE 1 Minimal inhibitory concentrations (MIC) for the multidrug-resistant (MDR) tuberculosis (TB) and non-MDR-TB strains found in the study

Bacterial strain	Patients	MIC $\mu g \cdot L^{-1}$			
		0.125	0.25	0.5	1.0
MDR-TB	18	0	10	8	0
Non-MDR-TB	130	4	121	5	0

Data are presented as n.

as the lowest drug concentration, after a two-fold serially diluted concentration of linezolid, that inhibited the growth of >99% of a bacterial proportion of the tested *M. tuberculosis* strain on solid Middlebrook-7H10 agar plates within 14–21 days of incubation at 37°C [7]. We found the MICs for 18 MDR-TB-strains in the range of 0.125–0.5 $\mu g \cdot mL^{-1}$ and 130 non-MDR-TB strains between 0.125–0.5 $\mu g \cdot mL^{-1}$ (n=4 with MIC=0.125 $\mu g \cdot mL^{-1}$, n=121 with MIC=0.25 $\mu g \cdot mL^{-1}$ and n=5 with MIC=0.5 $\mu g \cdot mL^{-1}$) (table 1). These results show a similar MIC distribution (0.125–0.5 $\mu g \cdot mL^{-1}$) compared to the study by SCHÖN *et al.* [8] but in a higher number of tested *M. tuberculosis* strains.

In long-term treatment the use of linezolid is limited by severe neurotoxic and haematopoetic side-effects, but it seems that their occurrence and severity is dose dependent [1, 2, 3]. KOH *et al.* [6] investigated the administration of 300 mg linezolid once daily in 24 patients with MDR-TB or XDR-TB and found a reduction in the occurrence of severe side-effects as compared to patients treated with 600 mg or 1200 mg once daily. Furthermore, in a prospective study of linezolid in patients with XDR-TB LEE *et al.* [4] showed a reduction of adverse events in the group, which received a daily dose of 300 mg compared to the group that was administered 600 mg once daily (69% *versus* 82%, respectively). Recently two meta-analyses studies suggested that there was no significant difference in the treatment success comparing a daily linezolid doses of ⩽600 mg *versus* >600 mg [1, 2].

Importantly, the concept of a lower linezolid administration was supported by earlier pharmacokinetics/pharmacodynamics (PK/PD) studies, which indicated a sufficient tissue penetration occurred despite a reduced drug dose being administrated. The main PK/PD precondition for efficacy of an antibacterial drug is a high concentration in the tissue and a very low MIC. HONEYBOURNE *et al.* [9] measured the concentration of linezolid in bronchial mucosa, pulmonary macrophages, and epithelial lining fluid in 10 adult patients and compared them with simultaneous blood levels and found a mean concentration of 13.4 $mg \cdot L^{-1}$ in serum, 8.1 $mg \cdot L^{-1}$ in alveolar macrophages and 25.1 $mg \cdot L^{-1}$ in epithelial lining fluid, suggesting a good penetration of linezolid into the pulmonary tissues. Although this study administered a higher dose (600 mg twice a day), in another study a single daily administration of 375 mg linezolid led to a similar maximum concentrations (C_{max}) in serum (10.8 $mg \cdot L^{-1}$), which is exceeding the predicted MICs in our study twenty-fold [10]. KOH *et al.* [5] could even show that a mean C_{max} of 11.6 $mg \cdot L^{-1}$ (range 1.5–15 $mg \cdot L^{-1}$) could be achieved by a daily use of 300 mg [5].

In conclusion, our study found very low MICs in a wide range of *M. tuberculosis* strains. This adds to the evidence for lowering the daily dosage of linezolid in *M. tuberculosis* treatment, because it will probably not jeopardise the efficacy, but will, most likely, reduce the side-effects. Clinical efficacy and safety with daily doses of 300 mg should, therefore, be evaluated in prospective studies.

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Reducing linezolid dose in the treatment of MDR-/XDR-TB to a 300 mg OD could reduce severe side-effects and cost http://ow.ly/AtU7F

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From the authors:

We thank T. Weiss and colleagues who wrote an interesting correspondence citing our research letter published in a previous issue of the *European Respiratory Journal* [1]. We compared the findings of an individual data meta-analytic observational cohort of extensively drug-resistant (XDR) tuberculosis (TB) patients [2] with those of the first experimental study on linezolid in XDR-TB subjects [3]. The results of both studies on the safety of this anti-TB drug underlined the advantage of prescribing a daily dosage of linezolid at a concentration ⩽600 mg, when compared with a dosage >600 mg, once daily, in terms of a reduced proportion of adverse events [2, 3]. Interestingly, the positive tolerability response with ⩽600 mg once daily of linezolid identified in both XDR-TB cohorts, had previously been confirmed in the larger, observational cohort of patients with a TB disease caused by *Mycobacterium tuberculosis* strains that were at least resistant to both isoniazid and rifampicin (multidrug-resistant (MDR) TB) [2].

T. Weiss and his colleagues discussed the importance of a low linezolid dosage (*i.e.* ⩽600 mg once daily) in patients with MDR-TB, providing the most significant *in vitro* evidence of the above mentioned clinical, observational and experimental, data; in particular, they described the minimal inhibitory concentrations (MICs) of linezolid in a collection of MDR (n=18) and non-MDR (n=130) *M. tuberculosis* strains, evaluated retrospectively in a German reference centre. The MIC for the MDR group ranged from 0.12 $\mu g \cdot mL^{-1}$ to 0.5 $\mu g \cdot mL^{-1}$, similarly to previous findings published by Schön *et al.* [4]. The MIC pattern was almost equal to that obtained in the non-MDR group. On this basis, the authors suggested a reduction of the current recommended linezolid dosage to 300 mg once daily, to decrease the probability of occurrence of linezolid-related adverse events, as well as their severity.

The current clinical trials should carefully keep into account the safety and tolerability profile of the new anti-TB drugs or of the new anti-TB regimens, not only for ethical issues ("*Primum non nocere*" or "first, do no harm", as stated by the French clinician Auguste Francois Chomel [5]), but also for the strict association between the occurrence of adverse events (particularly the severe ones), and the low adherence to anti-TB medications [6]. Patients can interrupt their prescribed treatment with relevant clinical and public-health consequences: clinical conditions can worsen and contagiousness can persist with potential transmission of *M. tuberculosis* strains (new infections) within the community. Additionally, the partial or permanent discontinuation of an antibiotic can favour the emergence of further resistances to other anti-tuberculosis drugs (*i.e.* reduction of the combined antibiotic pressure, which favours the emergence of resistant sub-populations). Those issues are amplified in individuals infected by *M. tuberculosis* strains with complex resistance patterns (*i.e.* resistance to first-, second-, and third-line drugs). When the therapeutic options are scant, such as when XDR-TB is diagnosed, it is crucial not to "lose" any single drug that can allow for the design of an efficacious anti-TB regimen.

We looked for the available evidence on the subject, carrying out a non-systematic PubMed-based review of the most important manuscripts published in the time period from 2007 to 2014. The keywords selected were linezolid and MDR-TB, and the recruited manuscripts included a significant proportion of