Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis

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Published in:
Journal of Antimicrobial Chemotherapy

DOI:
10.1093/jac/dks154

Publication date:
2012

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother 2012; **67**: 2055–2057
doi:10.1093/jac/dks154
Advance Access publication 27 April 2012

Comment on: Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients

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Keywords: TB, efficacy, tolerability, adverse events, therapeutic drug monitoring

Sir,

We read with great interest the article 'Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients' by Koh *et al.*,[1] in which they describe retrospectively examined records of one of the largest case series of patients treated with linezolid for multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDR-TB). They describe the long-term outcomes of 51 patients, whereas the previous study only described the short-term outcomes of 17 patients.[2] Their objective was to evaluate the efficacy, tolerability and adverse events of a 300 mg daily dose of linezolid in the treatment of MDR/XDR-TB. Based on a favourable treatment outcome of 78%, compared with 60%–100% in the literature albeit in smaller case series, they suggest that linezolid is effective against intractable MDR/XDR-TB at a daily dose of 300 mg. In our opinion it is difficult to draw this conclusion from the presented data. The lack of a control group makes it impossible to attribute a favourable outcome in patients to a single drug such as linezolid as it is only a part of an expanded treatment regimen. Favourable treatment outcomes could very well be caused by other drugs of the expanded regimen the patients received.

To implicate the efficacy of their linezolid-containing regimen, Koh *et al.*[1] make assumptions on the MIC of linezolid for their population and the linearity of linezolid pharmacokinetics. They assume their patients are infected with *Mycobacterium tuberculosis* with an MIC of linezolid of 0.25 mg/L. Koh *et al.*[1] base this on a recent study that described wild-type MIC distributions of linezolid and six other second-line drugs for 78 consecutive susceptible clinical isolates.[3] Although most isolates had an MIC of linezolid of 0.25 mg/L, the wild-type MIC distribution ranged from 0.125 to 0.5 mg/L and an epidemiological cut-off (ECOFF) value of 0.5 mg/L was suggested.[3] The fact that we found the MIC to be 0.5 mg/L in eight isolates, 1 mg/L in eight isolates and even >1 mg/L in one isolate in a previous study of 23 isolates,[4] may raise some doubt about the assumption that all clinical isolates have an MIC value of 0.25 mg/L.

Koh *et al.*[1] assume the pharmacokinetics of linezolid to be linear. Unfortunately, the pharmacokinetics of linezolid are not linear in TB patients, as we demonstrated in a previous study.[5] Besides, substantial intra- and interpatient variability of linezolid in TB patients can be observed. We found the AUC_{0-12} of 300 mg twice daily to be 56 mg·h/L, but with an IQR of 38.5–64.2 mg·h/L.

We agree with Koh *et al.*[1] that for linezolid the $fAUC_{0-24}$/MIC ratio is often used as a predictive model for efficacy.[5] Koh *et al.*[1] refer to data of Schon *et al.*[3] suggesting that a daily dose of 600 mg linezolid would lead to an *f*AUC of 56 mg·h/L, resulting in an *f*AUC/MIC ratio of ∼100 for a wild-type MIC_{ECOFF} of 0.5 mg/L and of ∼200 for the more common MIC of 0.25 mg/L. In both cases, the pharmacodynamic target of *f*AUC/MIC >100 is met. However, during the study period, drug susceptibility testing (DST) as well as plasma concentration monitoring [therapeutic drug monitoring (TDM)] were not performed for linezolid. This is very unfortunate, since linezolid is the drug of interest in their study. As a consequence, it is unknown if the pharmacokinetic/pharmacodynamic target of $fAUC_{0-24}$/MIC >100 is met. Therefore, in our opinion, it is not correct to assume linezolid to be effective without DST and TDM for linezolid or without a control group.

Finally, we also do not support the conclusion that Koh *et al.*[1] draw from the presented data that a daily dose of 300 mg of linezolid may be associated with fewer neuropathic side effects than a daily dose of 600 or 1200 mg. It was necessary to cease linezolid therapy in 14 patients (27%) due to neurotoxicity, which is within the range of the highly variable incidence of neurotoxicity of 4%–89% at daily doses of 600 or 1200 mg as presented by Koh *et al.*[1] in an overview of the literature. Despite the daily dose of linezolid being low, the duration of administration of linezolid is long, with a median of 278 days. This concurs with the current notion that the risk of adverse events of linezolid increases time-dependently.[6]

Transparency declarations

None to declare.

References

1 Koh WJ, Kang YR, Jeon K *et al*. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; **67**: 1503–7.

2 Koh WJ, Kwon OJ, Gwak H *et al*. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. *J Antimicrob Chemother* 2009; **64**: 388–91.

3 Schon T, Juréen P, Chryssanthou E *et al*. Wild-type distributions of seven oral second-line drugs against *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2011; **15**: 502–9.

4 Alffenaar JWC, Laan T van der, Simons S *et al*. Susceptibility of clinical *Mycobacterium tuberculosis* isolates to a potentially less toxic derivative of linezolid, PNU-100480. *Antimicrob Agents Chemother* 2011; **55**: 1287–9.

5 Alffenaar JWC, Altena R van, Harmelink IM *et al*. Comparison of the pharmacokinetics of two dosage regimens of linezolid in multidrug-resistant and extensively drug-resistant tuberculosis patients. *Clin Pharmacokinet* 2010; **49**: 559–65.

6 Migliori GB, Eker B, Richardson MD *et al*. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; **34**: 387–93.

J Antimicrob Chemother 2012
doi:10.1093/jac/dks211
Advance Access publication 30 May 2012

Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients—authors' response

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Keywords: MDR, XDR, TB, oxazolidinones

Sir,

We would like to thank Bolhuis *et al*.[1] for their recent comments regarding our paper.[2] The treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) presents a major challenge. As noted by Bolhuis *et al*.,[1] the lack of a control group in our study was a major limitation; however, we must point out that our patients had 'intractable' MDR/XDR-TB. Of the 51 patients examined in our study, 51% had XDR-TB, and the rate of resistance to ofloxacin was 98%.[2] Aggressive management using linezolid resulted in a favourable outcome for more than 75% of patients who had been unsuccessfully treated with second-line anti-TB drugs for a median of 40 months.[2] These figures are comparable to those reported by other studies that show that linezolid (600–1200 mg/day) is effective for the treatment of MDR/XDR-TB.[3,4] As linezolid was used as part of a multidrug regimen that included higher generation fluoroquinolones, the favourable treatment outcomes may not be attributable to linezolid alone. However, in our opinion, it is unethical to perform a comparative trial (patients treated with or without linezolid) in patients with intractable MDR/XDR-TB because, in such patients, current treatments including linezolid may be the last chance of being cured. Instead, we believe that a clinical trial comparing the efficacy and tolerability of different doses of linezolid should be performed. At present, a clinical trial comparing 600 mg/day and 300 mg/day linezolid for the treatment of XDR-TB is under way in Korea (ClinicalTrials.gov number NCT00727844).[5–7]

The absence of drug susceptibility results and pharmacokinetic data for linezolid was another major limitation in our study. However, irrespective of this, the major finding in our paper was that a substantial portion of intractable MDR/XDR-TB patients successfully completed treatment. Our previous paper showed that the mean serum C_{min} of linezolid (300 mg/day) was 2.1 ± 1.3 mg/L (range 0.4–4.5 mg/L), the mean serum C_{max} was 11.6 ± 4.4 mg/L (range 1.5–15.9 mg/L) and the MIC_{99} for *Mycobacterium tuberculosis* was 0.25 mg/L for 30% of the isolates and 0.5 mg/L for 70%.[8] Therefore, we were unable to draw any final conclusions from our study regarding the drug susceptibility and pharmacokinetic parameters of linezolid.[2]

Our data could not support a definitive conclusion that a 300 mg daily dose of linezolid would reduce the incidence of neuropathy. Previous studies from Korea had reported that neuropathy developed in 50%–80% of patients treated with 600 mg/day linezolid.[9,10] Therefore, to achieve a balance between potential efficacy and drug toxicity, we used 300 mg/day linezolid in this study.

Transparency declarations

None to declare.

References

1 Bolhuis MS, van Altena R, Alffenaar JW. Comment on: Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; **67**: 2055–7.

2 Koh WJ, Kang YR, Jeon K *et al*. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. *J Antimicrob Chemother* 2012; **67**: 1503–7.

3 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012; **16**: 447–54.

4 Sotgiu G, Centis R, D'Ambrosio L *et al*. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; doi:10.1183/09031936.00022912.