Is there still room for therapeutic drug monitoring of linezolid in patients with tuberculosis?

To the Editor:

Bolhuis *et al.* [1] recently reported the results of a retrospective study aimed at investigating linezolid safety and tolerability in relation to linezolid exposure in 58 patients with multidrug-resistant tuberculosis. As one of the main findings, they observed no significant differences in linezolid area under the curve from 0 to 24 h (AUC_{0-24}) or linezolid trough concentrations between patients experiencing or not experiencing drug-related adverse events. These findings apparently argue against a potential role of therapeutic drug monitoring (TDM) as a feasible tool to optimise linezolid dosing in the day-by-day management of patients with tuberculosis.

The conclusion of Bolhuis *et al.* [1] is at variance with evidence from studies dealing with the role of TDM in patients given linezolid for the treatment of Gram-positive infections. Indeed, a first experience of TDM of linezolid was published by Matsumoto *et al.* [2] in 2010, showing that patients developing thrombocytopenia had significantly higher linezolid trough concentrations compared with those who did not develop haematological complications. A statistically significant negative correlation was also documented between linezolid clearance and creatinine clearance. Taken together, these findings allowed the authors to conclude that renal dysfunction may induce an accumulation of linezolid in patients treated with the conventional 600 mg twice-daily dose eventually exacerbating the development of linezolid-related haematological toxicity. These results were confirmed by findings from Pea *et al.* [3], who identified a linezolid trough concentration of 6.5 $mg \cdot L^{-1}$ and AUC_{0-24} of 280 $mg \cdot h \cdot L^{-1}$ as a cut-off associated with a 50% probability of experiencing thrombocytopenia. Interestingly, the authors also reported that episodes of thrombocytopenia appeared in 51.4% *versus* 0% of cases in the linezolid *versus* linezolid plus rifampicin group, respectively; this has been attributed to the previously reported inductive effect of rifampicin on linezolid transport across the body compartments, mediated by the permeability glycoprotein. It is worthy of mention that in 33% of patients who were experiencing thrombocytopenia, TDM-guided linezolid dose reductions allowed recovery from toxicity to continuation of therapy with a good clinical outcome. In a prospective, observational study, we [4] and others [5–7] established that patients who developed linezolid-related haematological toxicity had drug trough concentrations exceeding 7–8 $mg \cdot L^{-1}$. These studies also documented that patients who subsequently developed thrombocytopenia already had high linezolid trough levels at the first TDM assessment, performed during the first week of therapy. The opposite findings on the role of TDM of linezolid between tuberculosis and Gram-positive infected patients is intriguing; additional information would be important to address this issue and understand whether the two therapeutic settings are different or whether the difference is only apparent and can be reconciled.

The main limitation of the study by Bolhuis *et al.* [1] is represented, in our opinion, by the lack of inclusion in the statistical analyses of factors known to interfere with linezolid exposure, such as patients' age, body weight, renal function and/or comedications. Indeed, consistent evidence is now available showing that patients with renal dysfunction, who are elderly and/or weigh less, are more likely to accumulate linezolid [2, 4–9]. Similarly, the presence of concomitant medications, such as rifampicin, proton pump inhibitors, phenobarbital and amiodarone, may impact diversely on linezolid disposition [10]. Studies aimed at assessing the potential associations between linezolid concentrations and clinical outcome not taking into account these factors may reach misleading conclusions.

In addition, the authors do not provide clear-cut information on how data from TDM of linezolid were used in their clinical practice. As a matter of fact, table 1 clearly indicates that patients were treated with different linezolid doses. Accordingly, it cannot be excluded that if linezolid dose was reduced according to TDM results, this may translate into lower linezolid concentrations and a lesser risk of developing drug-related complications, introducing a "dilution" bias in the results.

The third issue of the study by Bolhuis *et al.* [1] that was, in our opinion, unaddressed relates to the episodes of thrombocytopenia. Indeed, whereas all the previous studies dealt with this most frequent adverse event [2–7], no information on the potential association (or lack thereof) between thrombocytopenia and linezolid pharmacokinetics were provided in the present investigation.

The above mentioned limitations do not allow us to reach a definitive conclusion on the role of TDM of linezolid in patients with drug-resistant tuberculosis. The need to reduce the doses of linezolid to be administered long term in patients with tuberculosis to limit the development of drug-related adverse events, and the risk that subtherapeutic exposure (as in the case of concomitant rifampicin administration) may limit the efficacy of linezolid-based antituberculous treatment, call for feasible tools to monitor the adequacy of drug exposure in clinical practice. We believe that, presently, TDM still represents the best available option to address these issues.

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A study of linezolid TDM in tuberculosis is at odds with studies in Gram-positive bacterial infections http://ow.ly/WXKQY

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Received: Nov 16 2015 | Accepted after revision: Dec 11 2015

Conflict of interest: None declared.

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Eur Respir J 2016; 47: 1287–1288 | DOI: 10.1183/13993003.01913-2015 | Copyright ©ERS 2016

From the authors:

We read with great interest the comments from D. Cattaneo and co-workers on our article describing a retrospective study in multidrug-resistant tuberculosis (MDR-TB) patients receiving linezolid tailored to the individual patient using therapeutic drug monitoring as part of their regular treatment [1]. Cattaneo and co-workers correctly summarise that one of our findings was that we did not observe any significant differences between exposure to linezolid and adverse events. Indeed, this observation may be surprising with a toxic drug like linezolid, but it is not a reason to rule out therapeutic drug monitoring as a tool for optimising the treatment regimens of TB patients. The explanation for this lies in the design of our study, the characteristics of the patient population, and the specific dosing regimen used for MDR-TB patients.

First, we would like to reiterate that we performed our study in a retrospective cohort of MDR-TB patients. We included 58 patients that received linezolid and that had therapeutic drug monitoring data available, but included no controls. Patients received individualised treatment regimens, based on drug susceptibility data. Therapeutic drug monitoring was performed and linezolid dosages were subsequently