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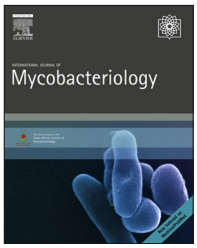

Individualized treatment of multidrug-resistant tuberculosis using therapeutic drug monitoring

Mathieu S. Bolhuis [a,*], *Onno W. Akkerman* [b], *Marieke G.G. Sturkenboom* [a], *Wiel C.M. de Lange* [b], *Tjip S. van der Werf* [b,c], *Jan-Willem C. Alffenaar* [a]

[a] *University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands*

[b] *University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands*

[c] *University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands*

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ABSTRACT

Objective/Background: Globally, approximately 50% of patients with multidrug-resistant tuberculosis (MDR-TB) experience treatment failure. MDR-TB treatment is hindered by adverse events, toxicity of the second-line anti-TB drugs, logistics and costs, especially in low-income countries, and problems with medication adherence. Pharmacokinetic variability is also attributed as one of the reasons contributing to treatment failure. In our reference Tuberculosis Center Beatrixoord (University Medical Center Groningen, Groningen, The Netherlands), we strive to individualize treatment of all MDR-TB patients based on drug-susceptibility testing using minimal inhibitory concentrations and pharmacokinetic parameters. The aim of this work is to give an overview of our efforts to individualize treatment of MDR-TB patients and to provide insights into practical tools that might be implemented in other clinical settings worldwide.

Methods: We critically looked at clinical practice guidelines implemented in our center to give an overview of practically applied tools to individualize treatment of MDR-TB patients. Furthermore, we selected studies carried out in our clinic on treatment individualization of MDR-TB patients and combined their results with recent studies in this area to suggest practical tools for implementation in other clinical settings.

Results: We regularly perform therapeutic drug monitoring (TDM) of several second-line anti-TB drugs, such as amikacin, kanamycin, linezolid, and moxifloxacin. New analyses of Group D and experimental drugs, such as co-trimoxazole (sulfamethoxazole/trimetho prim), bedaquiline, delamanid, and clarithromycin, have been or are being developed. By implementing TDM methods, variability in pharmacokinetics is often detected and treatment is adjusted, possibly preventing toxicity in patients with very high drug exposure or treatment failure, or resistance in patients with very low drug exposure. Over the past 10 years in the Netherlands, 86% of 104 patients had a successful outcome using a median of six active drugs. Many studies were performed using dried blood spot (DBS) analysis of second-line TB drugs. These studies may be used to implement TDM worldwide, even in low-income countries. Furthermore, several studies are performed to determine limited

* Corresponding author at: University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, PO Box 30.001, 9700 RB Groningen, The Netherlands.
E-mail address: m.s.bolhuis@umcg.nl (M.S. Bolhuis).

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sampling strategies (LSSs). By limiting the number samples required for adequate sampling, TDM will become easier to implement. Other examples of LSSs included development of oral fluid sampling methods or development of semiquantitative thin-layer chromatography methods.

Conclusion: TDM is highly valuable to individualize and optimize treatment of complex MDR-TB patients. TDM is routinely applied in Tuberculosis Center Beatrixoord, and high success rates for treatment of MDR-TB patients have been achieved. DBS and LSS make implementation of TDM feasible, even in low- and middle-income countries.

Conflicts of interest

Dr. Bolhuis and Dr. Alffenaar have received grants and personal fees outside the submitted work.