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Therapeutic drug monitoring: how to improve drug dosage and patient safety in tuberculosis treatment

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SUMMARY

In this article we describe the key role of tuberculosis (TB) treatment, the challenges (mainly the emergence of drug resistance), and the opportunities represented by the correct approach to drug dosage, based on the existing control and elimination strategies. In this context, the role and contribution of therapeutic drug monitoring (TDM) is discussed in detail. Treatment success in multidrug-resistant (MDR) TB cases is low (62%, with 7% failing or relapsing and 9% dying) and in extensively drug-resistant (XDR) TB cases is even lower (40%, with 22% failing or relapsing and 15% dying). The treatment of drug-resistant TB is also more expensive (exceeding €50 000 for MDR-TB and €160 000 for XDR-TB) and more toxic if compared to that prescribed for drug-susceptible TB. Appropriate dosing of first- and second-line anti-TB drugs can improve the patient's prognosis and lower treatment costs. TDM is based on the measurement of drug concentrations in blood samples collected at appropriate times and subsequent dose adjustment according to the target concentration. The 'dried blood spot' technique offers additional advantages, providing the rationale for discussions regarding a possible future network of selected, quality-controlled reference laboratories for the processing of dried blood spots of difficult-to-treat patients from reference TB clinics around the world.

1. Introduction

In this article we describe the key role of tuberculosis (TB) treatment, the challenges (mainly the emergence of drug resistance), and the opportunities represented by the correct approach to drug dosage based on the existing strategies of the World Health Organization (WHO). In this context, the role and contribution of therapeutic drug monitoring (TDM) is discussed in detail.

The European Respiratory Society (ERS) and the WHO developed the Framework for Tuberculosis Elimination in Low-incidence Countries[1] in Rome, Italy in July 2014; this is focused on the concept of pre-elimination (defined as <10 TB cases per million population) and TB elimination (defined as <1 TB case per million population).[2–5] The vision of a TB-free world (zero death, disease, and suffering due to TB) is consistent with the new post-2015 WHO global TB strategy, which has been named the 'End TB Strategy'.[6] The overall goal of the strategy is to end the global TB epidemic, with corresponding 2035 targets of a 95% reduction in TB deaths and a 90% reduction in TB incidence (both compared with 2015). The strategy also includes a target of zero catastrophic costs for TB-affected families by 2020.

To reach this goal, a set of coherent additional actions needs to be implemented in order to improve access to high-quality TB services (prevention, diagnostic, and treatment), especially for vulnerable groups. Also, efforts should be made to address the underlying determinants that put people at risk of TB.

A recent ERS/WHO survey demonstrated that several actions or 'areas' relevant to TB elimination, particularly in the clinical field, are not fully covered in Europe;[5] thus, any information that sheds light on the best clinical and public health practices contributing to improved clinical management will favour TB elimination.

TDM is a tool that may be of help in optimizing TB treatment and is thereby likely to support TB elimination strategies. The aim

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of this study was to pinpoint the role of TDM for the most urgent cases and to present a TDM strategy that could be implemented in a programmatic setting with the scope of controlling and eliminating TB.

2. Methods

By exploring the recent literature we sought to detect TB subpopulations with the highest burden of disease or consuming the greatest health care budget. We subsequently evaluated whether TDM could be of help to solve the problems in this TB population and how it could be implemented in a programmatic treatment setting.

3. Results

A challenge to the attainment of TB elimination is represented by multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. In 2013, the WHO estimated that there were 9 million TB incident cases globally, equivalent to 126 cases per 100 000 population; out of these, an estimated 480 000 cases were affected by MDR *Mycobacterium tuberculosis* strains.[6] Among newly diagnosed patients, approximately 3.5% were infected with MDR-TB strains. Of particular worry, however, is that the prevalence of MDR-TB among new cases in some of the Former Soviet Union countries exceeds 30%.[6–9] XDR-TB has been identified in 100 countries, and the average proportion of MDR-TB cases with an XDR-TB pattern is 9.0%.[6] Furthermore, an additional problem is the emergence and spread of mycobacterial strains with 'total drug resistance',[10–12] a term currently not recognized by the WHO and replaced with 'drug resistance beyond XDR'.[13]

In the largest MDR-TB cohort ever analyzed,[14] the proportion of cases treated successfully was 62%, with 7% failing or relapsing, 9% dying, and 17% defaulting. In the XDR-TB subgroup, treatment outcomes were even worse: 40% achieved treatment success and 22% failed treatment or relapsed, 15% died, and 16% defaulted.[15]

The treatment of drug-resistant TB is more expensive and more toxic compared to that prescribed for drug-susceptible TB, and currently takes up to 2 years of therapy.[16] The cost per patient to treat MDR-TB cases is incredibly high,[17,18] and in spite of international public health efforts, the treatment outcome is not very promising.[13–15] Diel et al. showed that direct treatment-related costs for MDR-TB patients can amount to €52 259 in Germany.[19] The same group demonstrated that the average cost to treat an XDR-TB case in Europe largely exceeds €160 000.

One of the most important causes of the emergence of drug resistance is the pharmacokinetic variability of anti-TB drugs resulting in the exposure of *M. tuberculosis* strains to subtherapeutic drug concentrations.[20,21] This also applies for patients on treatment for MDR-TB. A recent study showed that patients without baseline resistance acquired fluoroquinolone resistance and second-line injectable drug resistance, with 8.9% acquiring extensively drug-resistant TB.[22] Appropriate dosing of the few and less effective antibacterial options remaining could dramatically influence the prognosis. TDM is based on the measurement of drug concentrations in blood samples collected at appropriate times and subsequent dose adjustment according to the target concentration.[23–25] Based on pharmacokinetic and pharmacodynamic principles it can indirectly assess the effect of the drugs on the bacterial target.[26] Details of the pharmacokinetic and pharmacodynamic targets for second-line drugs have been published elsewhere.[27]

In addition to the pharmacokinetic variability of the anti-TB drugs, an inadequate dose or dosing frequency and non-adherence to the prescribed regimen are also deemed to be responsible for the development of drug-resistant TB.[28–30] Although the recent introduction of new diagnostics has allowed the rapid detection of drug resistance,[31] TDM has not been implemented properly for the management of TB therapy,[32] thereby providing opportunities to adjust the dosing in the case of a low serum concentration.[32–34]

Furthermore, TDM can indirectly change the prognosis when less than five effective drugs are available. It can help prevent the development of further resistance as a result of low serum exposure; moreover, the detection of high blood levels can allow adjustment of the dosage and thus reduce the occurrence of adverse events that could decrease patient adherence.

Additional information on the implementation of TDM is reported in Table 1.

Conventional TDM is characterized by the determination of drug concentrations in plasma or serum. Many assays describing the optimal analytical procedure can be found in the current literature. However, an assay enabling the measurement of multiple drugs in a single sample is preferrable.[35] Nevertheless, many laboratories have single drug assays that require a trained

Table 1
Implementation of TDM (therapeutic drug monitoring)

	Procedure	Comments
Analytical procedure	Assay that combines first-line or second-line drugs in a single run	Combination assays reduce the sample volume required TDM saves costs
	Select local or referral laboratory to analyze patient samples	Selection of a certified laboratory is necessary to assure accurate analytical TDM results
	In the case of DBS, verify appropriate blood collection protocol and materials to be used with the laboratory	Deviations produce erratic results
Case selection	Priority to: • Patients failing to convert within 2 months of standardized treatment • Patients showing adverse drug reactions • Patients with multiple risk factors for low drug exposure at diagnosis: HIV-positive, diabetes type 2, gastrointestinal tract problems, severely ill patients	A targeted approach reduces the number of patients for whom TDM has to be performed
Sample collection	Venipuncture used to collect plasma; finger prick used to collect DBS	DBS may be preferred in the outpatient setting or in the case where samples are sent to a referral laboratory to save transportation costs
	Time points should be properly selected to enable accurate optimization of the dose	Optimized sampling may be preferred over 'trough and peak'
Dose adjustment	Dose adjustment should be based on both drug exposure and the MIC of the *Mycobacterium tuberculosis* strain in order to attain the optimal PK/PD target	This strategy avoids unnecessary dose adjustment in patients with low drug exposure and a very susceptible *M. tuberculosis* strain
	Perform follow-up at 1–2 weeks after dose adjustment to ensure that the target drug concentrations are reached	Not every dose increase results in increased drug exposure; switch route of administration of the drug to IV when available

TDM, therapeutic drug monitoring; DBS, dried blood spot; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; IV, intravenous.