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Precision and personalized medicine and anti-TB treatment: Is TDM feasible for programmatic use?

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A R T I C L E   I N F O

A B S T R A C T

Therapeutic Drug Monitoring (TDM) is increasingly recommended to ensure the correct drug dose thereby minimizing adverse events and maximizing regimen efficacy. To facilitate implementation in TB programs, a framework for TDM is urgently needed. TDM is only useful for dose optimization if a patient is on an appropriate regimen guided by drug susceptibility testing. TDM using a targeted approach selecting patients with risk factors for suboptimal drug exposure (e.g. diabetes) or not responding to treatment for drugs with a clear concentration-response relationship may provide the best value for money. Semiquantitative point-of-care tests for detection of low or high drug concentration should be implemented at community level while quantitative assays can be performed at regional or central level. Expanding PK/PD research followed by clinical trials including both clinical outcome as well as cost-effectiveness will increase the level of evidence supporting TDM.

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Introduction

Traditionally, tuberculosis (TB) control programmes focus their resources on rapid diagnosis and effective treatment to ensure individual benefit to the patient and break the chain of transmission (if the patient is infectious) (Migliori et al. 2019; Nahid et al. 2019). In spite of a comprehensive effort of the international community, the treatment success rates of multi-drug-resistant (MDR)-TB are globally in the order of 55%, (lower on extensively drug-resistant (XDR)-TB cases) although recent evidence suggests that the use of new drugs (e.g. bedaquiline) (Borisov et al. 2017) can increase it to 80% and beyond even outside clinical trials (Ahmad et al. 2018). Recently, more attention has been paid to monitoring and management of adverse events, particularly with new and repurposed drugs (Akkerman et al. 2019; Borisov et al. 2019).

Recently the concept of 'precision medicine' (Alffenaar et al. 2019) has been a subject of discussion: more and more new guidelines (Nahid et al. 2017, 2019) are recommending individualised treatment based on drug-susceptibility testing (DST) results and DST ideally coupled with actionable knowledge of antibiotic pharmacokinetics (PK) and pharmacodynamics (PD). The Pharmacology Committee of the Global Tuberculosis Network (GTN) (Alffenaar et al. 2019) has worked intensively to promote Therapeutic Drug Monitoring (TDM), a technique which is rendering it increasingly easy to dose anti-TB drugs in the blood, to ensure the correct drug dose (not more, not less), minimizing adverse events and maximizing regimen efficacy.

The aim of the manuscript is to discuss the programmatic feasibility of TDM (Ghimire et al. 2016) taking into account the specific features and interplay of pathogen, patient and drug and drug assay characteristics used to perform TDM.

Pathogen (relationship between PK/PD and pathogen MIC)

DST is essential for ensuring that a patient is on an appropriate regimen and preventing drug resistance development. Phenotypic DST is however costly (requiring lab capacity), technically demanding (non-viable samples, contamination and interpretation can lead to delays) and time consuming (1–2 weeks or longer). In order to help guide physicians more rapidly, genotypic and whole genome sequencing methods are being employed and may be able to detect mutations where there is no correlation to MICs. The WHO endorses both phenotypic and genotypic DST (World Health Organization 2019), the GeneXpert Ultra is a rapid molecular test (result in under 80 min), to triage patients between RR-TB and DS-TB. A molecular line probe assay GenoType MTBDRsl V2 can detect resistance to first (isoniazid, rifampicin, ethambutol and pyrazinamide) and second line drugs (fluoroquinolones, ethionamide/prothionamide and aminoglycosides) in order to help triage patients onto the shorter WHO regimen, however changes in regimen (linezolid, bedaquiline and clofazimine replacing aminoglycosides and ethionamide) means that we will need newer tests that can triage MDR/XDR TB patients more effectively.

Phenotypic susceptibility allows for MIC determination, which can be combined with AUC TDM to determine the appropriate dose of an individual drug. Virtual MICs based on association of phenotypic susceptibility with single or multiple mutations is developing and it is possible to base treatment on the following genotypic DST results (Kambli et al. 2015b; Miotto et al. 2017); for rifampicin some mutations suggest that higher doses of rifampicin >20 mg/kg may be considered, moreover rifabutin may retain activity and rifampicin 35 mg/kg may be effective. Normal dose Isoniazid can be given in the presence of inhA mutations (at normal doses), requiring higher doses in the presence of katG), with both inhA and katG, isoniazid should not be used (Cambau et al. 2015; Rieder and Van Deun 2017). Fluoroquinolones also appear to have resistance mutations that may characterise low resistance MIC <1 and high resistance mutations (Kambli et al. 2015a; Chien et al. 2016). Moxifloxacin can therefore be expected to have activity at a higher dose of 800 mg a day in the presence of low-level resistance.

We have now identified several mutations correlated with resistance. We will continue to need the phenotypic MIC testing in certain cases when lacking molecular or sequencing results or when discrepancies or unknown mutations are encountered (Faksri et al. 2019). Furthermore the CRyPTIC consortium are using next generation sequencing to evaluate genetic resistance prediction by cataloguing resistant strains; this may lead to rapid universal drug susceptibility testing (DST).

Host (host characteristics affecting pharmacokinetics)

TDM is recommended for patients with severe gastrointestinal abnormalities, diabetes mellitus (DM), HIV, renal impairment or on dialysis and patients with inadequate treatment response (Nahid et al. 2017, 2019). DM often causes gastroparesis, which may result in malabsorption or delayed absorption. Although impact of DM on drug exposure has been a subject of debate, two recent studies showed reduced exposure to first line drugs and moxifloxacin in patients with TB and DM (Dekkers et al. 2019; Mtabho et al. 2019). This reduced exposure was due to increased drug clearance and partly due to malabsorption.

A recently published systematic review of the effect of HIV infection on PK in TB patients showed no consistent results (Daskapan et al. 2019). For rifampicin most studies showed low total exposure in all TB patients, unrelated to HIV infection. Several studies showed significant lower AUC values for RIF in HIV infected TB patients. However one study also showed a significant higher AUC in HIV positive TB patients compared to HIV negative TB patients. For isoniazid none of the studies showed significant differences in AUC between HIV positive and HIV negative TB patients. For pyrazinamide some studies showed significantly lower AUC in HIV positive TB patients, while other studies showed no difference.

Other possible indications to perform TDM are patients who are malnourished or who are pregnant. Malnutrition due to TB itself leads to a decreased fat-free mass and is often related to malabsorption as well. The first might lead to a change in volume of distribution and the latter might cause low exposure. Studies on this topic are still lacking (Ter Beek et al. 2019). Pregnancy leads to an increased volume of body fluid, which causes an increase of the volume of distribution of drugs and that can lead to a decreased peak drug concentration. Furthermore pregnancy may enhance the elimination of drugs (Van Kampenhout et al. 2017).

Drug

Dose-exposure-response relationships of TB drugs are affected by mycobacterial and host-related variability. These include lineage-specific factors, growth phase, phenotypic and genetic susceptibility, location and extent of TB, cavity formation, host immune function, renal and hepatic function (Alffenaar et al. 2019).

American Thoracic Society (ATS) guidelines recommend TDM in case of treatment with second-line drugs, specifically for linezolid and cycloserine/terizidone (in renal impairment) (Nahid et al. 2019). Updated WHO guidelines also support TDM for second line drugs including linezolid, fluoroquinolones and injectables (i.e. aminoglycosides) (World Health Organization 2019).

Toxicity due to drugs such as ethambutol (ocular toxicity), isoniazid (peripheral neuropathy), pyrazinamide (hepatotoxicity), linezolid (haematological toxicity and peripheral neuropathy) and fluoroquinolone (QT prolongation) are drug concentration-dependent. ATS guidelines explicitly state avoiding cycloserine concentrations >35 mg/L to prevent CNS toxicity (Nahid et al. 2019).

Sub-optimal drug exposure can lead to acquired resistance, delayed culture conversion or relapse (Pasipanodya et al. 2013). Efficacy is often correlated with drug exposure, specifically with pharmacodynamically linked markers such as AUC_{0-24}/MIC (most commonly), $Cmax/MIC$ or T/MIC (Alffenaar et al. 2019). Such PK/PD targets are largely derived from the Hollow Fiber System Model of TB and Monte Carlo simulations. Optimal efficacy of linezolid appears to be driven by AUC_{0-24}/MIC >100 (Bolhuis et al. 2018). AUC_{0-24}/MIC ratio is also the best predictor of efficacy for fluoroquinolones (Van den Elsen et al. 2018; van den Elsen et al. 2019).

Limited sampling strategies have become available for a number of TB drugs such as isoniazid, rifampicin, pyrazinamide, ethambutol, linezolid, moxifloxacin and levofloxacin, and will allow accurate estimation of total drug exposures with a limited number of samples (Kamp et al. 2017; Van den Elsen et al. 2018; van den Elsen et al. 2019). For example, moxifloxacin AUC could be accurately estimated with 2 samples, i.e. a trough sample combined with a sample at 4 or 6 h after drug intake (van den Elsen et al. 2019).

Assay

TDM requires an analytical method suitable for fast and accurate quantification of anti-TB drug concentrations. Traditionally high-performance liquid chromatography (HPLC) with UV detection has been used to quantify drug concentrations. The extensive sample preparation, long run times in combination with cold chain shipments to central laboratories have been a major hurdle for broad scale implementation of TDM. The introduction of

highly sensitive liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) enabled detection of drugs in very small samples (<50 μL) and allowed the development of assays suitable for measurement of drug concentrations in dried blood spots (Vu et al. 2011; Veringa et al. 2016). Dried blood spots samples show an increased stability compared to plasma or serum and could therefore be shipped at room temperature and even by mail. Due to high purchase costs and need for skilled technicians, such methods can only be operated at a central level. The lack of awareness in the community in combination with long turnaround time hindered broad scale implementation (Alffenaar et al. 2019). Therefore, there is an urgent need for a semi-quantitative test to support physicians to make informed decisions on drug dosing (Alffenaar et al. 2019). Such a test should be able to distinguish between low,

normal and high drug exposure. Other matrixes than blood (serum/plasma) like saliva or urine could be used as they can be easily collected (non-invasive) and reflect the drug concentration in the body. Simple UV spectrophotometers could be employed to measure drug concentrations in these matrixes. The advantage of such easy to operate equipment is low purchase costs, allowing use in the community.

Programmatic treatment — TDM

A targeted approach to implement TDM in a programmatic setting is likely more effective and affordable than TDM for every patient. A targeted approach relies on selection of patients that may benefit from TDM. Host, pathogen and drug related factors can

Table 1
Therapeutic drug monitoring in a programmatic setting.

	Patients with risk factors	Patients with low or high exposure	Patients lacking treatment response	High TB burden		Low TB burden	
Screening first line drugs	x			Community level		Community level	
Screening second line drugs	x						Regional level
TDM for key first line drugs		x	x		Regional level		
TDM for key second line drugs		x	x	Regional level			Central level
TDM Other drugs			x		Central level	Central level	

X indicated the most suitable assay for each clinical situation. The grey shaded areas indicate the location (e.g. community, regional or central) where the assay should be made available for optimal use. TDM = therapeutic drug monitoring.

be used in developing a decision tree for TDM (Nahid et al. 2017; Alffenaar et al. 2019). Host factors associated with low drug exposure, less susceptible pathogens, and drugs with a high variability in drug exposure should be included to decide on the use of TDM. Based on frequency of use, level of expertise and facilities required to operate an assay and costs, we propose 3 levels of TDM (Ghimire et al. 2016; Alffenaar et al. 2019).

1) Community level; easy to access screening UV assays (saliva/urine) for key first (INH, RIF, PZA) and second line drugs (FQ, LZD) to determine low, normal and high drug exposure.
2) Regional level; quantitative assays, either HPLC-UV or entry level LCMSMS for key first and second line drugs should be available to perform individualized dosing in those patients with known low drug exposure and patients with high drug exposure in combination with signs of adverse effects.
3) Central level; quantitative assays using advanced LCMSMS can be used for measuring drug concentration in dried samples (blood, saliva) shipped by mail from the community.

With the 3 levels of TDM we recommend to make use of the available expertise. Results obtained from screening assays in the community should be easily translated in uniform clinical decisions, while results from quantitative assays at the regional level should be accompanied by individualized dose recommendations. Screening assays could be of value as well for patients on preventative treatment as it can help to detect malabsorption in patients with, e.g., Crohn's disease or to help assess adherence. For very difficult to treat cases requiring TDM for less frequently assayed drugs it could be recommended that these cases will be discussed in a national Consilium with appropriate expertise. At the central level, quality assurance for TDM at the programmatic level should also be accommodated, including proficiency testing programs and training of staff. A centralized model (Degeling et al. 2020) for TDM, with a reference center with adequate expertise, will likely be better equipped (e.g. funding) for implementation of innovative techniques in TDM (Table 1).

Knowledge gaps — what to do next

Adequate drug selection and precision dosing can be considered the best practice to increase response to therapy, reduce risk of acquired drug resistance and prevent adverse drug reactions. To support precision dosing for all TB drugs in vitro PK/PD studies using a hollow fiber system model of tuberculosis have to be performed and subsequent results have to be validated in clinical trials for those drugs where evidence is lacking. The next step is to perform a randomized controlled trial to compare TDM with standard of care to show the benefits of precision dosing. Although a double-blind design may not be feasible due to technical complexity appropriate control mechanisms can be included in the trial design to minimize bias and confounding factors. Patients for whom TDM is already being recommended in current guidelines (Nahid et al. 2019; World Health Organization 2019) should be prioritized. The primary end-point of a TDM trial should not focus on a single clinical end-point such as prevention of acquired resistance but on the cost-effectiveness of the optimized clinical management of TB patients. If costs related to the clinical management of TB can be reduced, a programmatic implementation is likely to be more feasible. To facilitate broad scale programmatic implementation, robust and affordable point-of-care tests have to be developed. Once evidence and tests are available, guidance documents (including information on evidence, cost-effectiveness, technical aspects of TDM) on local implementation should be issued like in the past for new tests or

drugs. Effectiveness of the use of TDM should subsequently be evaluated in a real-life setting.

Conclusion

Considerable progress has been in precision medicine for TB through drug selection based on molecular diagnostic tests and drug exposure evaluation in patients at risk for low or high drug exposure. Expanding in vitro PK/PD research followed by clinical trials will complete the evidence supporting TDM. Development of point-of-care tests and TDM in a multistep approach will provide the framework for testing cost-effectiveness of programmatic TDM. Following favourable trial results, guidance on programmatic implementation should be issued.

Declarations of interest

None.

Ethics

No ethical clearance was required for this study

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