Therapeutic drug management: is it the future of multidrug-resistant tuberculosis treatment?

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TDM can be helpful for multidrug-resistant tuberculosis therapeutic decisions. DBS can bypass logistical issues http://ow.ly/otsFp

Multidrug- and extensively drug-resistant (M/XDR) tuberculosis (TB) are emerging public health concerns [1, 2]. In 2011, the World Health Organization (WHO) estimated 12 million prevalent cases of TB globally, which is equivalent to 170 cases per 100 000 population, out of these an estimated 630 000 cases were affected by MDR *Mycobacterium tuberculosis* strains [3]. Among the newly diagnosed patients ~3.7% were infected by MDR-TB strains, but the worrisome fact is that the prevalence of MDR-TB among new cases in some Former Soviet Union countries exceeds 30% [4, 5], XDR-TB has been identified in 84 countries and the average proportion of MDR-TB cases with an XDR-TB pattern is 9.0% [3]. Further adding to the problem are the reports of ''totally drug resistant'' TB [6, 7], a term currently not recognised by WHO [8, 9].

Treatment of drug resistant TB is more expensive and more toxic if compared with that prescribed for drug-susceptible TB, and currently takes up to 2 years of therapy [10]. The cost per patient to treat MDR-TB cases is incredibly high [11, 12] and, in spite of international public health efforts, the treatment outcome is not very promising [13–15]. DIEL *et al.* [16] showed that direct treatment-related costs of MDR-TB patients can amount to €52 259 in Germany (table 1).

In the largest MDR-TB cohort analysed to date [13] the proportion of cases treated successfully was 62%, with 7% failing or relapsing, 9% dying and 17% defaulting; in the XDR-TB subgroup 40% achieved treatment success, 22% failed treatment or relapsed, whereas 15% died and 16% defaulted [14, 15].

In this issue of the *European Respiratory Journal* (*ERJ*) a Dutch group from Groningen [17] reported on the results of a prospective pharmacokinetic (PK) study aimed at quantifying the effect of clarithromycin on the exposure to linezolid. In simple terms they observed that clarithromycin, which has some activity against TB bacilli and is well tolerated, increases linezolid exposure (*i.e.* increases the blood levels of linezolid, which is a very expensive and toxic drug). The authors decided to quantify this phenomenon administering a fix dose of linezolid (300 mg twice a day) plus a variable one of clarithromycin (250–500 mg once a day). Using validated PK methods they demonstrated that linezolid exposure significantly increased after the co-administration of 500 mg clarithromycin by a median (interquartile range) of 44% (23–102%), when

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TABLE 1 Direct costs of multidrug-resistant tuberculosis (MDR-TB) therapy in a European low-income country

Patient classification	Cost €[#]	Notes
Primary out-patient MDR-TB patient	36 543.22	
In-patient MDR-TB patient	24 986.89	~70% of the patients are admitted to the hospital
Post-hospital out-patient MDR-TB patient	27 271.95	
In- and out-patient MDR-TB patient	52 258.84	

[#]: data refer to adult cases only. Data from [16].

compared with baseline conditions, whereas 250 mg clarithromycin had no statistically significant effect. Co-administration was well tolerated by most patients; no patients experienced severe adverse events.

The clinical implications of these findings are as follows: 1) clarithromycin might be used as a booster for linezolid, exactly as low-dose ritonavir is used to increase protease inhibitor exposure in combined antiretroviral therapy; and 2) the relatively cheap clarithromycin could reduce the prescribed dose of the expensive linezolid while the same exposure is maintained (and the same toxicity is expected), making more economic resources available to treat other (more) MDR-TB cases.

Also in this edition of the *ERJ*, a letter by the same Dutch group provides an example of the clinical applications of therapeutic drug monitoring (TDM) [18]. The study provides, for the first time, evidence of anti-TB drugs' penetration into a human tissue (a TB-destroyed lung in this case) in parallel to their blood concentration. The case described in their article is complicated and is of a young Somalian female where the *M. tuberculosis* strain is resistant to all first-line drugs as well as a WHO group V one (prothionamide).

TDM was performed, as routinely undertaken in this clinic, for the core drugs prescribed including linezolid [19] and moxifloxacin. The study results show that penetration in the lung was excellent, based upon tissue homogenates, in both the more and less destroyed segments of the lung.

This study provides for the first time two important pieces of clinical evidence: 1) the feasibility of measuring in parallel, through TDM, blood and lung tissue concentrations of anti-TB drugs and 2) linezolid's and moxifloxacin's excellent penetration even in the destroyed lung tissue.

TDM, although not yet popular among TB specialists, is well known in clinical pharmacology [20–22]. It is based on the collection of blood samples and allows the *ex vivo* evaluation of blood-drug concentration, and, consequently, of its potential quantitative effect on the pharmacological target. Development of drug resistance in *M. tuberculosis* is attributed to inadequate treatment [23, 24], particularly inadequate dose or dosing frequency, non-adherence to the prescribed regimen, and PK variability [25, 26]. While new technologies/assays have been developed for the rapid detection of drug resistance [27] TDM has not been used to its full potential for the management of TB therapy [22], where a drug's low serum level is readily corrected with dose adjustment.

Table 2 summarises the PK parameters of the second-line anti-TB drugs. Such adjustments are important when treating patients who are slow to respond to treatment (*i.e.* malabsorption, inaccurate dosing, altered metabolism, drug–drug interactions [13, 21], or PK variability [25]), have drug-resistant TB, are at risk of drug–drug interactions, have adverse events or intolerance to a given drug when this drug is essential to ensure a positive outcome or have concurrent disease states that significantly complicate the pharmacological metabolism. Such patients may benefit from TDM precluding the development of further drug resistance because of mycobacterial exposure to sub-inhibitory drug concentrations. In the more complicated situation (*e.g.* XDR-TB strain) where only four to five effective drugs are available, TDM can even be life-saving if it detects and corrects malabsorption before further resistance is selected.

While TDM seems a promising approach, logistical and cost-related problems are still limiting its application to research-oriented institutions. An alternative cost-effective approach is "dried blood spot" (DBS) [29] (fig. 1), which makes TDM a much easier technique to perform, even in remote settings. DBS compared with conventional venous blood sampling, which requires hospitalisation, has the advantages of easier sampling, smaller blood volume usage, storage and transportation. DBS is in its infancy and requires additional considerations for development of drug analysis methods and their validation.

The cost of TDM varies from laboratory to laboratory and from country to country. In one study the cost has been calculated to be US$80 per individual drug [20], whereas others charge US$80 for a single test of a

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TABLE 2 Pharmacokinetic parameters of the second line anti-tuberculosis drugs [28]

Drug	Dose	C_{max} μg·mL^{-1}	Time to C_{max} h	$t_{1/2}$ h	AUC_{0-24} μg·h^{-1}·mL^{1}
Linezolid	600 mg	20.4	1.4	5.8	140.8
Clarithromycin	500 mg	1–1.5	2–4	3–7	
Para-aminosalicylic acid (granules)	4 g	51.3	5.2		368
Clofazimine	100 mg	05–2	2–7	10 days–2 weeks	1.5
Ofloxacin	800 mg	10.5	1	7	103
Levofloxacin	1 g	15.5	1	7.37	131
Moxifloxacin	400 mg	6.13	1	6.53	60
Amikacin	15 mg·kg^{-1} *i.v.*	46		2.5	
Kanamycin	15 mg·kg^{-1} *i.v.*	44		2.2	
Capreomycin	1 g *i.m.*	32			
Ethionamide	500 mg	1.35	2	1.63	2.8
Prothionamide	250 mg	2.5	3.4	3	11.3
Cycloserine	250 mg	8–9	2–3	25.1	

$t_{1/2}$: half-life; AUC: area under the curve from 0 to 24 h.

single drug, and US$70 per test if two or more time points are tested, per patient (personal communication; Charles A. Peloquin, College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA). In other words, the total cost to test four drugs at 2 and 6 h post observed oral doses will add to 8 × $70 or $560, and this does not include the cost of collecting, processing, and shipping the samples. Although this seems to add a significant financial burden, if one has to consider the total cost of MDR-TB treatment/patient (including the cost of adverse events' management, the cost of consequences of unsuccessful outcomes (*i.e.* failure/death/relapse) and drug-resistant *M. tuberculosis* transmission to close contacts), early intervention to adjust the dose and potentially shorten the duration of therapy, TDM will likely prove cost-effective given the very high overall cost to treat M/XDR-TB [11, 12, 16].

Unfortunately, there are not many established laboratories offering TDM and interpretation of the results. However, the scenario is changing, in the USA some laboratories are starting to do drug testing in-house, with one lab (University of Florida, Florida, FL, USA) offering both the assays and their individualised interpretation (personal communication; Charles A. Peloquin and [20]). Whereas in Europe the group of scientists in Nijmegen (the Netherlands) has begun to set up a proficiency testing programme (personal communication; Charles A. Peloquin). Thus the number of international laboratories offering TDM should grow in the near future.

In perspective, we can dream of a future quality assurance system designed in a similar way as that developed by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) for first-line anti-TB drugs drug-susceptibility testing (the scheme for second-line drugs being presently under development) [3, 30]. A few, quality-controlled, reference laboratories might receive DBS from reference MDR-TB clinics (fig. 1). Although, as of today, TDM is perceived as a technique applicable to high income

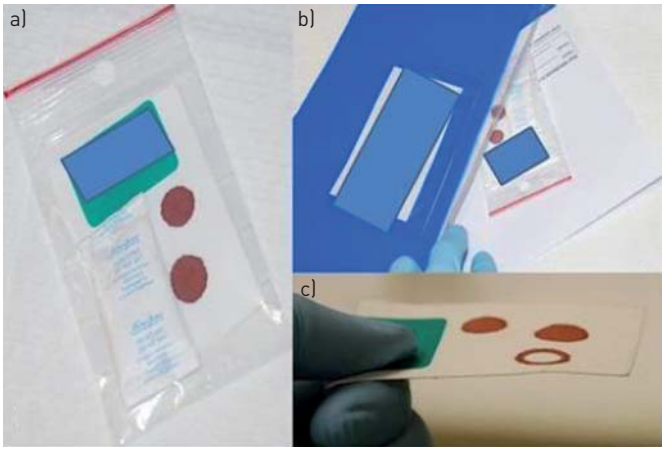

FIGURE 1 Dried blood spot (DBS) for therapeutic drug monitoring. Blood is collected on paper strips (a) and packed in a plastic bag with a desiccant to keep the strip dry. Samples can then be transported (b) via regular post or any other suitable means. The DBS is collected from the strip and the drug is extracted and concentrations subsequently measured using validated methods. Personal communication D.H. Vu (University of Groningen, Groningen, the Netherlands, and Hanoi University of Pharmacy, Hanoi, Vietnam).

countries only, a few arguments might open the way for future expansion in its use. 1) Although TDM, as discussed earlier, is a relatively expensive examination, the savings in the amount of anti-TB drugs prescribed and the (costs related to the) reduction of adverse events will be able to self-pay for it cost. 2) DBS is simple to collect, this operation can be done in any peripheral health clinic if needed. 3) DBS does not contain any infectious material and can be sent *via* normal mail, whereas shipment of *M. tuberculosis* strains should be done according to precise international regulations and is very expensive.

Last but not least, no existing guideline presently recommends the use of TDM in difficult-to-treat MDR-TB cases [10, 31, 32]. We hope that the evidence provided in these *ERJ* articles, together with the much needed evidence that will (hopefully) be available soon that will allow this technique to be included, sooner or later, among those ''officially'' endorsed to better manage the most severe M/XDR-TB cases.

While all of the suggestions discussed here are pharmacologically sound, and supported by anecdotal clinical data, it remains unlikely that definitive proof from prospective, randomised clinical trials will ever be forthcoming. Thus, as of today, it remains a clinical decision to perform TDM, very similar to the decision to order complete blood counts, computerised tomography scans, or magnetic resonance scans in TB patients. All of these tests, including TDM, are useful if they inform treatment decisions. With TDM, the decision is what dose and frequency to use for a given drug. When only four or five effective drugs are available to treat a complicated M/XDR-TB case, and losing a single drug might represent the patient's death sentence, any effort should be done to use these ''life-saving'' drugs in the best possible way.

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