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Early View

Research letter

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Therapeutic drug monitoring practice in patients with active tuberculosis; assessment of opportunities

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Recently updated World Health Organization (WHO) and American Thoracic Society (ATS) guidelines include recommendations for therapeutic drug monitoring (TDM) during treatment for *Mycobacterium tuberculosis* (TB) in patients at risk of altered drug exposure or poor prognosis (1, 2). Sub-optimal drug exposure may be associated with acquired resistance and poor treatment outcomes (3) whereas supra-therapeutic concentrations may lead to toxicity. TDM is indicated in patients at risk of altered pharmacokinetics (e.g. HIV, diabetes mellitus, gastrointestinal abnormalities, drug-drug interactions, renal impairment) and/or worsened treatment prognosis (inadequate treatment response despite adherence or on second line drugs, especially for fluoroquinolones, linezolid and aminoglycosides) (1, 2, 4). Despite such importance, implementation of TDM is low, and guidelines do not provide specific pharmacokinetic/pharmacodynamic (PK/PD) target ranges, mainly due to the lack of available high-quality prospective studies validating these markers (5). In light of current gaps in the evidence and rationale for future TDM studies, our study aimed to evaluate how patients could potentially benefit from TDM based on the updated guidelines (1, 2).

A retrospective study was conducted in patients who met the inclusion criteria of being > 18 years old and started TB treatment between January 2018 and June 2019 at Parramatta Chest Clinic, Western Sydney Local Health District (WSLHD), Australia. The study was approved by the WSLHD Human Research Ethics Committee. Medical records were evaluated for the indications for TDM. We compared patients with *vs* without TDM indications, including time to smear/culture conversion, treatment duration and adverse effects (AE) and hepatotoxicity [the highest value during treatment expressed as a fold-change from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP)]. Parametric or non-parametric statistical tests for comparing independent groups were performed using IBM SPSS® software with significance set at $p<0.05$.

In total, 160 patients were included for analysis after excluding 8 patients who were aged ≤ 18 years, and 14 patients who were transferred to another setting within 1 month of treatment initiation. Of the included patients, 56/160 patients had indications for TDM including potential drug-drug interactions (23/56, 41%), second line drug use (18/56, 32%), diabetes mellitus (16/56, 29%), renal impairment

(eGFR<60ml/min/1.73m^2) including dialysis (13/56, 23%), severe gastrointestinal abnormalities (7/56, 13%), poor treatment response despite drug adherence and a susceptible TB strain (5/56, 9%), and positive HIV status (1/56, 2%).

Details of patient characteristics, treatment, TDM and outcomes are summarized in Table 1. Demographics were comparable between patients with and without TDM indications, except that patients with TDM indications were older (Table 1). In both groups, most patients were newly diagnosed with drug-susceptible pulmonary TB. Seven patients had multidrug-resistant TB and were treated with second line drugs including moxifloxacin, linezolid, bedaquiline, clofazimine and amikacin.

Clinical uptake of TDM was low, with only 4/56 patients receiving TDM when it was indicated. Only one patient received routine TDM for linezolid and amikacin. All other patients who received TDM during treatment had drug concentration measured only once or twice, and mostly without dose adjustments due to incorrect sampling times, change of drug or a lack of follow-up.

Derangements in LFTs were significantly greater for AST and ALT in patients where TDM was indicated compared with non-TDM indicated patients (Table 1). Increase in ALP was also statistically significant but was not considered clinically significant (1.5 *vs* 1.1 fold).

The overall incidence of AE was high, and more frequently reported in patients where TDM was indicated compared to those without (68% *vs* 51%; p=0.040), as well as a greater incidence of Grade 3 (severe) AE (18% *vs* 4% of total ADR, respectively). These patients required treatment interruptions/drug re-challenges, and even hospital admissions. Common AEs were rash/itch (43%) and nausea/vomiting (32%), as well as abdominal pain (9%), joint/muscle pain (5%), hyperuricaemia (5%), headache (3%), fatigue (2%) and other reactions (5%).

Treatment duration was longer in patients where TDM was indicated [8.2 (6.2-9.7) *vs* 7.2 (6.1-9.0) months; p=0.044] after excluding drug-resistant TB patients.

Although data on sputum smear and culture conversion were available in only 44 patients, as induced sputum was not part of standard of care, we observed a trend of a longer time to smear and culture conversion in patients where TDM was indicated [smear conversion: 23.0 *vs* 47.5 days; culture conversion: 46.9 *vs* 66.6 days]. Future prospective TDM studies in high TB burden-settings, including induced sputum collection to assess microbiological response, could provide more conclusive evidence on the benefit of TDM.

Increases in LFTs up to > 10-fold was observed in patients where TDM was indicated. Current guidelines indicate treatment interruption when ALT or AST > 3 times upper limit of normal (ULN) with symptoms or > 5 times ULN without symptoms (1, 2). TDM could potentially allow for a more proactive approach to prevent this drug exposure-related toxicity rather than a reactive management of transaminitis. For example, a previous study reported an association between isoniazid $AUC_{0\text{-}24}$ and Grade 1 ALT elevation (> ULN of 51 U/L) and greater probability of hepatotoxicity (0.82 *vs* 0.12) in patients with isoniazid $AUC_{0\text{-}24} \geq 55.0$ *vs* <55.0 mg·h/L (6).

Furthermore, more (severe) AEs have been reported in diabetic patients treated with TB drugs (7), which adds to the complexity of existing comorbidity relationship between diabetes mellitus and TB, as well as being a potential contributor to AEs in our TDM-indicated patients.

Understanding the effect of these contributors as well as dose, on variability in drug exposure could yield a meaningful explanation of the observed outcomes in our study, especially as dose, which was comparable between the two groups, is a poor predictor of drug exposure (8). Identification of drug-specific PK/PD threshold values (e.g. $AUC_{0\text{-}24}$/MIC) together with WHO-recommended active pharmacovigilance (9) would be steps for the proactive prevention and increased detection or monitoring for AEs. Evaluation of TDM should not be restricted to older anti-TB drugs as recent evaluation of a large cohort receiving a bedaquiline-based treatment for drug resistant TB showed that 125/413 patients had at least one risk factor associated with suboptimal drug exposure (10).

Our study sheds light on the general lack of TDM uptake. Although we noticed more hepatotoxicity and AE incidence as well as prolonged treatment duration in patients with indications for TDM, this

does not automatically mean that TDM would have improved treatment outcome in these patients. For example, increased hepatoxicity is associated with age (1). Our findings clearly underpin the need for randomised controlled trials in TDM to increase the level of evidence for clinically actionable PK/PD thresholds, clinical benefit and cost-effectiveness of TDM in TB treatment, as well as to better inform the incremental gain for programmatic TDM implementation in both well-resourced and low-resourced settings (11-13). Following this, more specific guidelines on TDM including PK/PD markers and target ranges, availability of less invasive or less expensive point-of-care tests such as urine, saliva, and dried blood spot analysis (5, 14), as well as Bayesian dose optimisation (15) will increase the feasibility of TDM implementation and its widespread scale-up in various treatment settings (11, 12).

Table 1. Summary of patient characteristics, treatment and outcomes in patients with *vs* without TDM indications.

	Patients **without** TDM indications (n=104)	Patients **with** TDM indications (n=56)	p
Patient characteristics			
Age (years)	33 (26-43)	45 (33-63)	**0.001**[a]
Male	49 (47%)	24 (43%)	0.727[b]
Female	55 (53%)	32 (57%)	
Weight (kg)	58 (50-69)	61 (51-72)	0.387[a]
Region of birth			0.622[a]
Asia	87 (84%)	50 (90%)	
Africa	8 (7%)	3 (5%)	
Other	9 (9%)	3 (5%)	
Immigrant			1.000[c]
Yes	100 (96%)	54 (96%)	
No	4 (4%)	2 (4%)	
Site of TB			0.295[b]
Pulmonary TB	55 (53%)	24 (43%)	
Extra-pulmonary TB	37 (36%)	21 (38%)	
Both	12 (11%)	11 (19%)	
Type of TB			1.000[c]
New	97 (93%)	52 (93%)	
Relapsed	7 (7%)	4 (7%)	
Drug Susceptibility			0.197[c]
Drug-susceptible TB (DS-TB)	76 (92%)	40 (85%)	
Drug-resistant TB	7 (8%)	7 (15%)	
Unknown	21	9	
Comorbidities for TB			-
HIV	0	1 (2%)	

Diabetes Mellitus	0	16 (29%)	
Current smoker	4 (4%)	7 (13%)	
Alcohol/substance abuse	2 (2%)	1 (2%)	
Treatment regimen for DS-TB			-
Isoniazid (mg/day)	300mg	300mg	
Rifampicin	600mg	600mg	
Ethambutol	900 (800-1000mg)	900 (800-1200mg)	
Pyrazinamide	1500 (1500-1750mg)	1500 (1500-2000mg)	
TDM performed			-
≤ 2 events on			
HREZ	2	2	
Linezolid		1	
> 2 events on			
Linezolid/amikacin		1	
Treatment outcomes			
Hepatotoxicity (fold-change)			
AST	2.2 (1.1-2.6)	4.6 (1.5-6.8)	**0.013**[a]
ALT	2.5 (1.1-4.2)	4.9 (1.8-6.9)	**0.021**[a]
ALP	1.1 (1.0-1.3)	1.5 (1.0-1.7)	**0.048**[a]
AE	53/104 (51%)	38/56 (68%)	**0.040**[b]
Grade 3 (severe)	2	7	
Grade 2 (moderate)	15	16	
Grade 1 (mild)	36	15	
Treatment duration (months)	7.2 (6.1-9.0)	8.2 (6.2-9.7)	**0.044**[a]
Sputum culture/smear	(n=26)	(n=18)	
Time to smear conversion (days)	23.0 (16.5-30)	47.5 (18.75-111)	0.083[d]
Time to culture conversion (days)	46.9 (27-61)	66.6 (43-102)	0.072[a]

Data expressed as number (%) or median (IQR). ALT, AST and ALP values represent fold-change from baseline. p-value <0.05 in bold. a. Independent t-test. b. Chi-Square test. c. Fisher's Exact test. d. Mann-Whitney U test. HREZ: isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z); HIV: human

immunodeficiency virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; AE: adverse effect.

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