Comments on TDM of additional medicines

Albert Figueras, FICF, Barcelona – February 2019.

This short document reviews the evidences about recommendations of TDM for medicines not included in Lee Schroeder’s article, which is analyzed in the report: “Review of the evidence to include TDM in the Essential in vitro Diagnostics List and prioritization of medicines to be monitored”.

Feedback from Experts after an accurate review of the report asked for the inclusion of additional medicines to the recommendations. The comments and suggestions are:

“The drugs included are appropriate, whereas the list needs to be updated according to the progress of TDM. For Example: isoniazid for tuberculosis treatment; tacrolimus for person after solid organ transplant. Some more publications need to be reviewed, e.g.


TDM in the treatment of TB

The Global incidence and impact of TB is well-known, and the growing reports of multidrug-resistant (MDR)-TB and extensively drug resistant (XTR)-TB is one of the most worrying problems associated with this infectious disease. Many studies and reviews on the potential usefulness of TDM have been published, together with new results from techniques which try to improve the traditional TDM techniques with other approaches.

Alsultan and Peloquin [1] published a review article in 2014. The authors analyzed advantages of TDM to ‘Otherwise healthy patients with TB’ and ‘More complicated patients with TB’; the paper also reviews TDM for individual drugs, including isoniazid. Among the conclusions, these authors wrote: ‘Plasma concentrations cannot explain all the variability in patient responses to TB treatment and cannot guarantee patient outcomes’, and remember that ‘TDM is never a substitute for sound clinical judgement, nor is it a substitute for DOT’, although they recognise TDM as a useful tool, especially in complicated clinical situations with multiple concomitant treatments and among patients at high risk of treatment failure.

Also in 2014, Reynolds and Heysell [2] conclude their review suggesting that ‘incorporating TDM with the MIC from an individual patient’s M. tuberculosis isolate may be particularly
beneficial for second-line drugs used in the treatment of drug-resistant TB’. In this review, it is acknowledged that if validation studies continue to show that PK variability contributes as significantly to TB outcome as has been found in different studies, organizations and guiding bodies will be compelled to adopt a degree of individualized management by using applied pharmacokinetics, and recommend additional research to demonstrate the good results of novel techniques such as dried blood spots analyses.

More recently, Zuur et al [3] have published a comprehensive review of the current status and new opportunities regarding TDM in patients with TB. Different points are raised by these authors:

- The use of TDM is not yet standard in the treatment of TB, neither is the way it is performed.
- The PK/PD index and the relationship with treatment outcome is difficult to study in ‘real-life’. Regarding toxicity, there is still research needed to determine reference values for toxic concentrations of most anti-TB drugs for adequate implementation of TDM.
- Dried blood spots (DBS) analysis seems promising, however further research should be performed. For example, validated DBS methods have been only provided for a few TB drugs (rifampicin, moxifloxacin, clarithromycin or rifapentin).

Up to now, it seems that there are not enough evidences or validated methods to justify the recommendation for the general use of TDM in patients with TB, even in selected patients. Notwithstanding this, due to the incidence of resistant TB and the prevalence of the disease, the topic should be revised in future reports.

Meanwhile, efforts should be made to improve the use of TB medicines and to avoid intermittent treatments due to non-clinical factors in order to reduce the appearance of multiresistant TB.

**β-lactam antibiotics**

The alarming increase of antimicrobial resistances worldwide has prompted campaigns to improve their use and is also raising doubts on the classical ‘one-dose-fits-all’ approaches. Within this scenario, different authors propose TDM of β-lactam antibiotics in specific clinical situations (e.g., critically-ill, elderly or obese patients and chronic treatments).

Huttner et al [4] reviewed this topic and concluded that ‘ideally, isolated pathogens should undergo MIC testing along with TDM on a regular basis, allowing clinicians to address the triad of bug, drug and patient (“mug”) in equal measure’. But these authors also stated that ‘clinical experience with β-lactam TDM remains relative scarce’, and estimate that when the paper was published (2015), approximately 30 hospitals worldwide were performing β-lactam TDM on a routine basis, the majority for critically ill patients, and attributed this situation to:
the absence of prospective controlled trials demonstrating either a clinical or an
economic benefit of TDM, and

the requirement for a chromatography-based method for analysing β-lactam
concentrations, which has a cost and requires time.

Osthoff et al [5] published a review on the prolonged administration of these antibiotics in
intensive care units. The authors are for a personalised approach to truly optimise treatment
with β-lactam antibiotics in critically-ill patients, ideally based on TDM, although they
recognize that this question ‘is not ready for “prime time” as evidence for its clinical benefit is
modest’, and put on the table the need for prospective randomised clinical trials to assess
patient-centred outcomes.

Veiga and Paiva [6] have recently published a comprehensive bibliographic review about
relevant questions on the clinical use of β-lactam antibiotics also in critically-ill patients. Their
recommendation is ‘to use higher than standard dosing, preferably with continuous or
prolonged infusions, especially when treating less susceptible bacterial strains, as the
pharmacodynamics profile may improve with no apparent increase in toxicity’. Despite this,
published evidences reported ‘high PK variability of β-lactams in sepsis/septic shock, both in
different patients and in the same patient over time’. But, once again, although ‘case reports
have shown that TDM improved clinical outcome, the clinical efficacy of using drug levels to
achieve adequate concentrations had never been properly evaluated and there are reports
concerning cost-effectiveness’.

At present, there are no published evidences showing the clinical efficacy of using TDM for β-
lactam antibiotics in critically-ill patients or those who need chronic treatments. Additionally,
TDM considerably increases the cost healthcare in these patients.

The topic should be followed-up in future reviews.

Meanwhile, as it happen with the remaining antimicrobials, efforts should be placed to avoid
its irrational use, non-adherence to clinical recommendations and dispensing without
prescription.
References


