Translational Model-Informed Selection of Tuberculosis Drug Combination Regimens for Early Clinical Development

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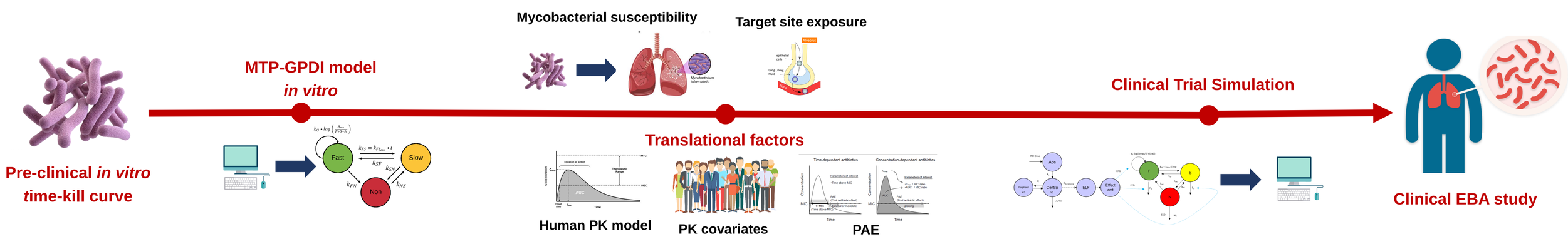

Fig. 1 The illustration of pre-clinical to clinical translation using MTP-GPDI model framework

Introduction

There is still a gap between pre-clinical and clinical phase in tuberculosis (TB) drug development. New innovative tools are needed to streamline TB drug development. Since TB treatment contains several drugs, pre-clinical information about pharmacodynamics (PD) interactions needs to be used more optimally when designing early drug development clinical trials i.e. the so-called Early Bactericidal Activity (EBA) studies.

Objective

In this work, we aim to develop a pre-clinical model-informed translational approach to guide dose selection of TB drug combinations in EBA trials using rifampicin (RIF) and isoniazid (INH) as an example.

Methods

Pre-clinical *in vitro* time-kill curves in *Mycobacterium tuberculosis* H37Rv strain of RIF and INH in monotherapy and in combination were used to estimate exposure-response relationships as well as PD interaction using Multistate Tuberculosis Pharmacometric (MTP) and General Pharmacodynamic Interaction (GPDI) model [1,2]. The clinical trial simulation of EBA prediction was performed by linking the *in vitro* models with following translational factors:

1) post-antibiotic effects (PAE) [3,4,5],
2) mycobacterial susceptibility (INH: [6], RIF: EUCAST),
3) Inoculum effect,
4) human pharmacokinetics (PK) model [7,8],
5) exposure in epithelial lining fluid (ELF) [9,10],

The modelling of *in vitro* data was performed in NONMEM 7.3. The EBA prediction was simulated in 'R' and compared to clinical EBA data.

Results

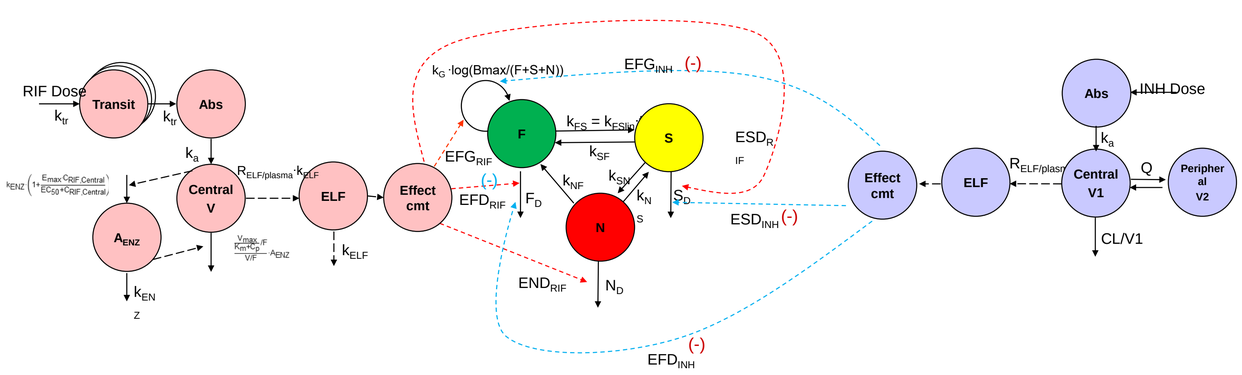

Fig. 2 Compartmental representation of RIF pharmacokinetic (left) and INH pharmacokinetics (right) liked to pharmacodynamic model (MTP-GPDI model, middle).

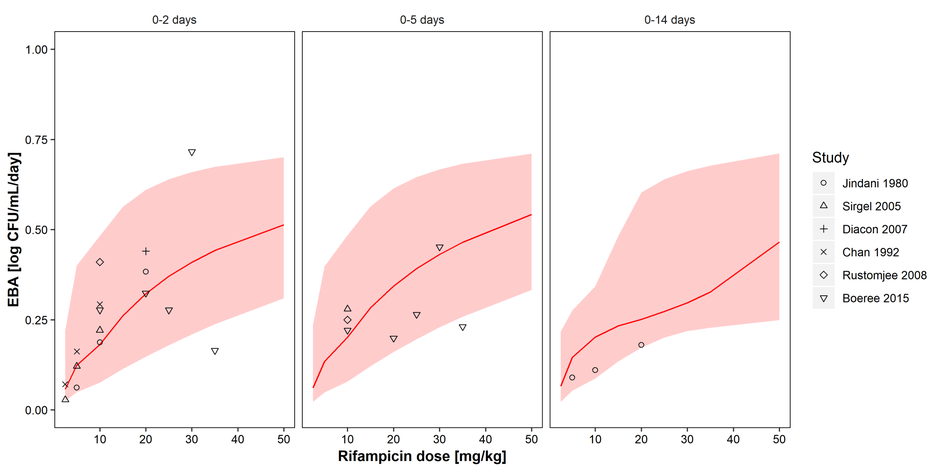

Fig. 3 Prediction of EBA 0-2 days (left), EBA 0-5 days (middle) and EBA 0-14 days (right) for RIF monotherapy. Median prediction (lines), 95% prediction interval (shaded area), and clinical data (points).

Translational model for RIF monotherapy was able to predict the clinical EBA data from different studies (Fig. 3). The prediction also indicated that increasing RIF dose can increase bactericidal activity.

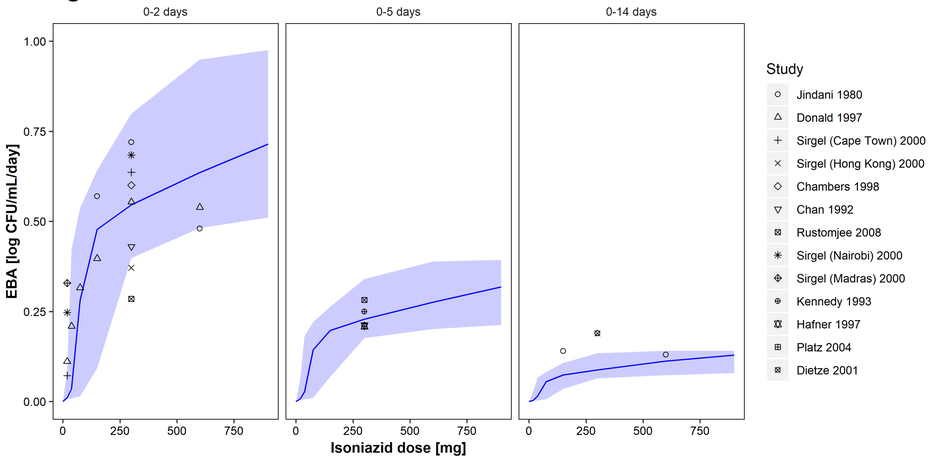

Fig. 4 Prediction of EBA 0-2 days (left), EBA 0-5 days (middle) and EBA 0-14 days (right) for INH monotherapy in mixed population (86.8% slow acetylator and 13.2% fast acetylators). Median prediction (lines), 95% prediction interval (shaded area), and clinical data (points).

Translational model for INH monotherapy was able to predict the clinical EBA data from different studies (Fig. 4). The prediction also indicated that INH has strong bactericidal activity in EBA 0-2 days. However, increasing INH dose will not increase the EBA after 14 days in both fast and slow acetylator.

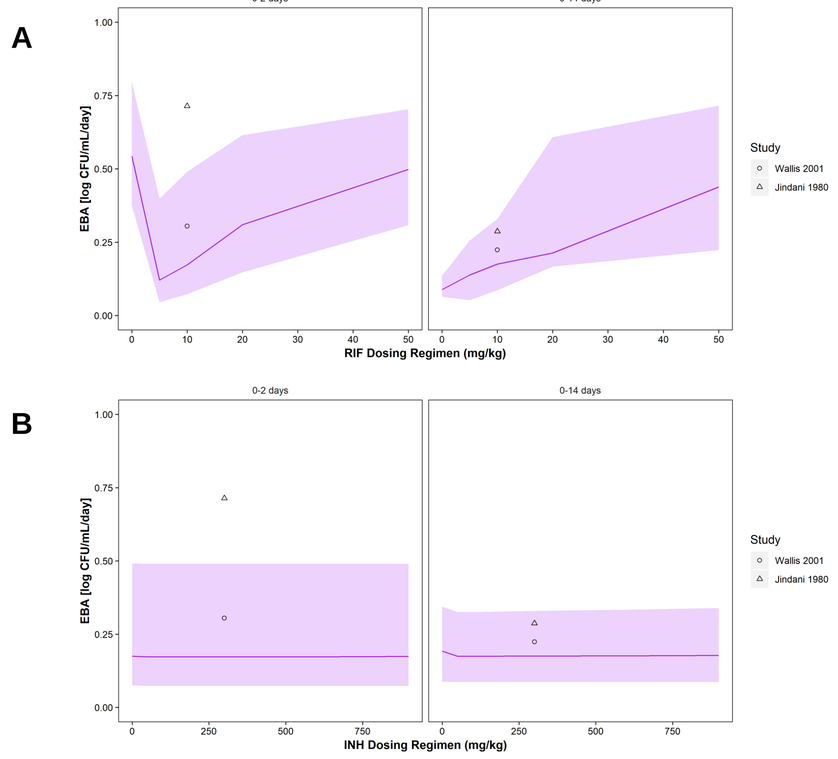

Fig. 5 Translational prediction of EBA 0-2 days and EBA 0-14 days for INH-RIF combination in mixed population (86.8% slow acetylator and 13.2% fast acetylators) : A) INH dose 300 mg/day and RIF dose 0-50 mg/kg/day), B) INH dose 0-900 mg and RIF dose 10 mg/kg/day). Median prediction (lines), 95% prediction interval (shaded area), and clinical data (points).

Translational model for INH-RIF combination was able to predict the clinical EBA data from different studies (Fig. 5A and B). RIF showed strong antagonism toward INH based on MTP-GPDI model we have developed from *in vitro* data (Fig. 2).
Based on the prediction of INH-RIF combination, increasing the RIF dose will potentially improve the EBA (Fig. 5A). In contrast, increasing INH dose will not give significant improvement for the EBA in both fast and slow acetylator (Fig. 5B).

Conclusion

Our translational framework based on preclinical *in vitro* study could be used for predicting EBA of TB drug combination in Phase 2A trial.

References

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