Model-informed precision dosing of protein kinase inhibitors: benefits and limits. The example of imatinib.

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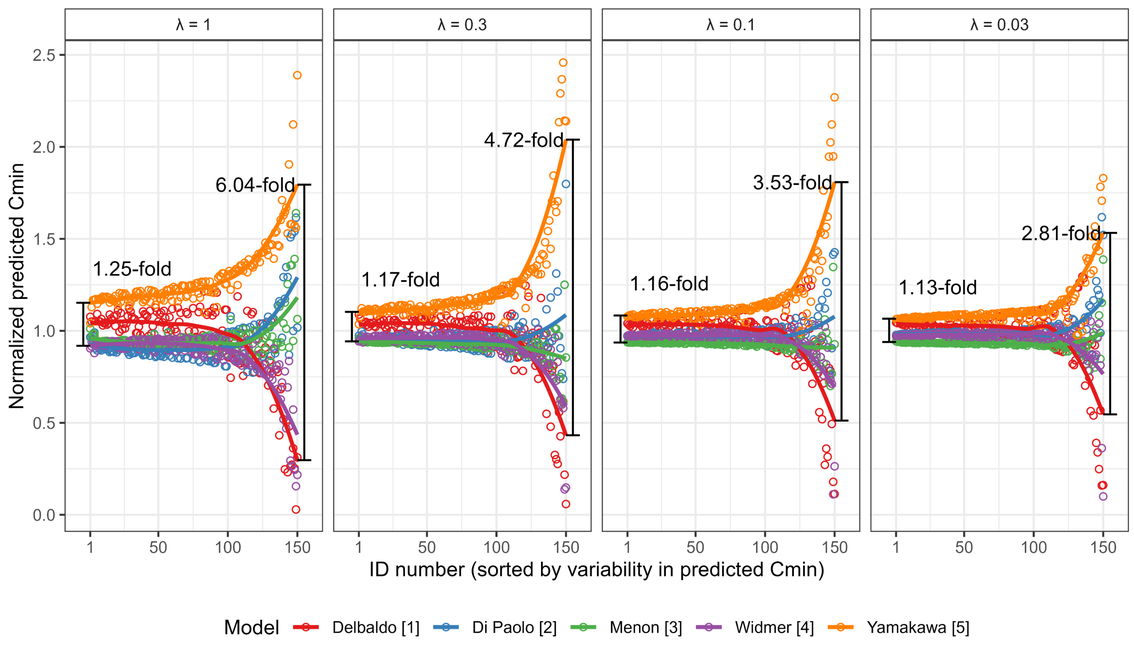
CONTEXT

- Imatinib : anti BCR-ABL protein kinase inhibitor, given orally 400 mg qd
- Therapeutic drug monitoring: measure of a trough concentration (Cmin)
- Efficacy if Cmin > 1.0 µg/mL in chronic myeloid leukemia
- Possibility of MIPD based on MAP-Bayesian estimation from 1 concentration:
  - Prediction of Cmin at the current occasion if inadequate sampling time
  - Simulation of *a posteriori* dosing to inform exposure at next occasion
- Objective: impact of the PK model? of model-averaging? of flattened *priors*?
  - on the predicted Cmin at the current occasion?
  - on the predicted concentration at the next occasion?

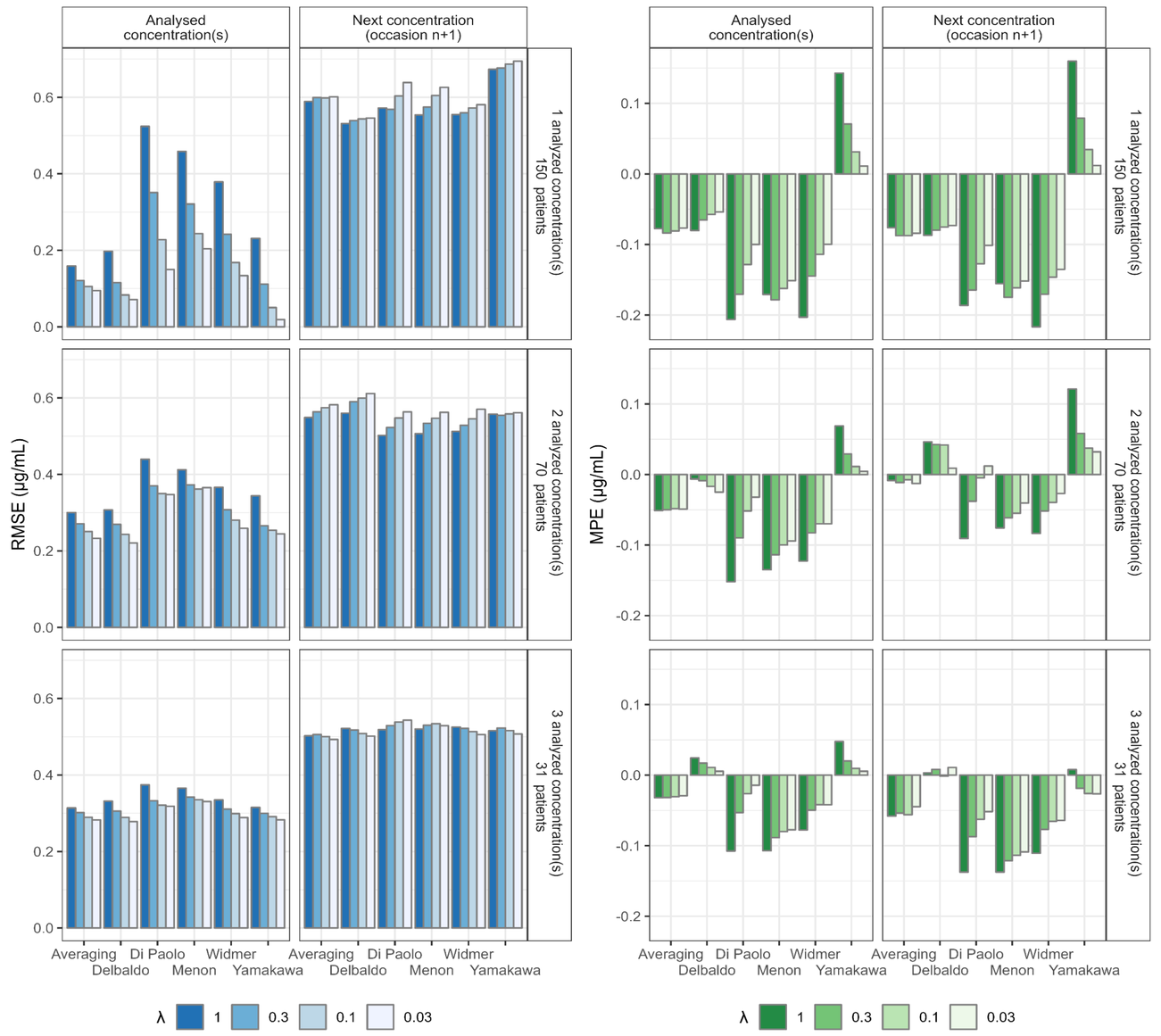
METHODS

- Retrospective analysis of 401 imatinib conc obtained during TDM (150 patients):
  - Median dose was 400 qd (ranging from 100 to 800 mg qd)
  - Median concentration was 1.01 µg/mL (ranging from 0.1 to 10 µg/mL)
  - Median sampling time after last intake was 23.4h (ranging from 0.13 to 147 h)
- Five different population PK models [1-5] coded in mrgsolve/mapbayr [6]
- A model-Averaging procedure (based on the likelihood) [7]
- Four levels of inter-individual variability (prior) flattening [8] :
  from λ = 1 (reference) to λ = 0.03 (33-fold IIV increase)
- MAP-Bayesian estimation of parameters and quantification of :
  1. the variability of predicted Cmin across models and patients at the current occasion
  2. the performance to predict the concentration at next occasion, whether 1, 2 or 3 previous concentrations had been used for parameter estimation.
- Performance metric: imprecision (root mean square error), bias (mean prediction error)

1. Variability of predicted Cmin across models and patients



2. Performance to predict the current and the next concentrations



RESULTS

1 concentration, λ = 1

- Predicted Cmin differed of a 1.25 to 6-fold across models and patients
- Goodness of fit of the analyzed concentration differs between models
- Averaging is better than any other model
- Poor prediction of the next concentration whatever the model

1 concentration, λ = 0.03

- Predicted Cmin still differed of a 1.13 to 2.8-fold across models and patients
- Goodness of fit of the analyzed concentration improves…
- … but the prediction of the next concentration worsens.
- Averaging is not the best

2 or 3 concentrations

- Goodness of fit of the analyzed concentrations worsen
- Prediction of the next concentration slightly improves but is still poor.
- Models tend to perform identically, as well as Averaging
- The effect of flattening priors is less and less important.

DISCUSSION

Accuracy of the prediction of the Cmin at the current occasion:

- could not be evaluated here because only one concentration was available per occasion.
- is likely to differ across models given the range of predicted Cmin.
- Decreased variability in predicted Cmin when λ < 1

Prediction of a concentration at the next occasion:

- is poor (RMSE ≥ 0.5 µg/mL)
- even when the fit of analyzed ones is improved with λ < 1
- suggesting it is due to random inter-occasion variability
- Least biased: Delbaldo *et al* [1]

As compared to drugs for which MIPD was proved to be feasible, like vancomycin (cf. table beside), the implementation of MIPD for PKIs has strong limitations.

Characteristic	Vancomycin	Imatinib
Limited capacity of modelling to deal with an oral drug		
PK phenomena to be modeled	Distribution, Elimination	Absorption, Distribution, Elimination
Amount of data to discern these phenomena	Moderate (multiple samples)	Low (one sample)
Bioavailability	100%	Variable (low solubility, antacid food effects)
Accuracy of drug administration records	Good, known	Unknown, prone to non-adherence
Limited need of PK modelling to estimate exposure or clearance from TDM data		
Theoretical administration record	Variable (different rate of infusion, different inter-dose interval)	Simple (fixed repeated dose at steady-state)
Sampling design	Often several samples, often since the first administration	One sample, at steady-state
PK parameter inference without modeling	Complicated	Easier (simplification to a continuous infusion)
Correlation between Cmin and AUC	Low to moderate	Moderate to high (long half life and dose regimen)
Influence of distribution on measured concentrations	Yes	Probably limited (Css,average only depending on clearance)
Limited transposition of precise parameter estimates into a precise next dose calculation		
Reported inter-occasion PK variability	Limited	Substantial
Duration of TDM follow-up	hours/days	weeks/months
Predictability of intra-individual variability	Partially (renal elimination & GFR)	Poor (CYP3A4 metabolism)
Statistical identifiability of PK IOV	Theoretically possible	Non-identifiable (one sample per occasion)
Application of the dose recommendation	Based on medical decision	Based on medical decision & patient adherence
Scale of doses	Continuous	Discrete (e.g. 100mg, 200mg)

[1] Delbaldo et al, Clin Cancer Res, 2006. [2] Di Paolo et al, Pharmacogenomics J, 2014. [3] Menon-Anderson et al, Cancer Chemother Pharmacol, 2009. [4] Widmer et al, Br j Clin Pharmacol, 2006. [5] Yamakawa et al, Ther Drug Monit, 2011. [6] Le Louedec et al, CPT: Pharmacometrics Syst Pharmacol, 2021. [7] Hughes et al, CPT: Pharmacometrics Syst Pharmacol, 2021. [8] Uster et al, Clin Pharmacol Therap, 2021.

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