Physiology-based PK (PBPK) models for drug-drug interaction (DDI) trials and trials waiver

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Aim at the presentation

• Background: why is PBPK modeling used for DDI risk assessment?
  – Supported by regulatory agencies
  – Scientific justification

• Guidance on the reporting PBPK modeling and simulations by EMA and FDA

• Case examples: support clinical trials and/or trials waiver
  – Perpetrator DDI via CYP enzymes
  – Victim DDI via CYP enzymes
  – Oral absorption DDI

• Potential further applications of PBPK modeling to other DDI areas

• Summary
Applications of PBPK modeling to clinical research

*Model building → PK(PD) predictions in untested case scenarios*

*In vitro*
(physicochemical, binding, enzyme, transporter parameters, etc.)

*Animal and human PK(PD)* (incl. e.g. human single and multiple ascending doses, food effect, drug-drug interaction (DDI) and mass balance)

Note: PBPK modeling supports anticipated human dose projection before Ph1

Establishment of PBPK models in HVs and/or patients

**Application**

**Feedback**

**Predictions of PK(PD) and DDI profiles in untested case scenarios: among different populations and at different doses**
- DDI (oral absorption / elimination)
- Organ impairment (hepatic / renal)
- Pediatrics
PBPK modeling: an established approach to impact on regulatory decisions

PBPK modeling is most frequently applied for DDI evaluation

Submissions of procedures including PBPK models to EMA (2004-2015)
Luzon et al., 2017

PBPK modeling and areas of intended applications in IND/NDA reviewed by FDA (2008-2017, n=254)
Grimstein et al., 2019

PBPK application in NDA reviewed by PMDA (2014-2016, n=17)
Sato et al., 2017
Why is PBPK modeling frequently used for DDI risk assessment?

- Regulatory DDI guidance documents by FDA (2017) and EMA (2012)
  - (A) DDI risk assessment: static calculation (tier 1) → PBPK modeling (tier 2)
  - (B) A PBPK model-based framework
- (C) DDI potential evaluation methods have been well-established with mechanistic understanding the drug disposition and interaction properties (small molecules) - *Fit with the concept of PBPK modeling*

\[\text{Drug A provided complete inhibition of CYP3A4 by co-medications, an AUC increase could be 2.7-fold } (=100/(100-63))\]
Regulatory perspectives

**PBPK evaluation and reporting for DDI assessment**

- **Ultimate goal**: waiving of clinical DDI trials by performing PBPK modeling
  - DDI prediction performance of an established model is to be reasonably verified
  - Otherwise, patients would not get the benefit from a newly approved drug in case of use of co-medications

- **High regulatory impact analyses** *(EMA, 2019)*
  - Use of PBPK model in place of clinical data
  - Victim DDI in a pharmacogenetic subpopulation
  - Complex DDIs where *e.g.* the combined effect of two inhibitors
  - ....

- **Qualification of PBPK platform for the intended purpose**

- **Verification of models of compounds and interacting drugs**
  - *In vitro/pre-clinical data, clinical DDI and mass balance*
  - Drug disposition diagram
  - Model building workflow
  - Identifiability of input parameters with uncertainties
Question 1/2
What can the following cases be predicted with PBPK modeling?

a) Projection of anticipated human doses before Ph1

b) Exposure change of the compound when a concomitant drug is administered

c) Plasma concentration profiles in clinically untested case scenarios

d) All above
Case example (1/7): reduction of clinical studies

Panobinostat: reversible and time-dependent inhibitor on CYP3A4

- PBPK modeling: a predicted AUC ratio of midazolam = 1.04
  - Static ‘Net Effect Model’: the predicted AUC ratio of midazolam = 1.95 (i.e. >1.25)
- No DDI trials

Impact on product label

...Weak TDI in vitro, low dose/exposure, Monday/Wednesday/Friday dosing...
(Einolf et al., 2017)

CYP3A Substrates: Simulations using PBPK models predict that an exposure increase of less than 10% for the sensitive CYP3A substrate midazolam is likely following coadministration with panobinostat. The clinical implications of this finding are not known.
Case example (2/7): in place of clinical data

**Ribociclib: a substrate as well as weak time-dependent inhibitor for CYP3A4**

- PBPK modeling could show reduction of the number of DDI studies
- Extrapolation to the victim DDI potential prediction at steady-state (untested case scenario) for dose adjustment with concomitant use of CYP3A4 perpetrators (600 mg → 400 mg)

1) Ribociclib dose for simulations: 600 mg; otherwise 400 mg was used. *Kisqali® Clinical Pharmacology Review* (FDA, 109092Orig1s000)
Case example (3/7): model verification of interacting drugs

Ritonavir: a strong (time-dependent) CYP3A inhibitor

- Ribociclib: a fraction metabolized by CYP3A4 (fm,CYP3A4) could not be confirmed by the *in vitro* assay
  - The ribociclib – ritonavir DDI study was conducted
  - To recover the clinical findings, verification of a ritonavir PBPK model was additionally investigated

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**FIGURE 1** Plasma concentration profiles of ritonavir over time after multiple oral administration. Lines give the predicted PK profiles of ritonavir (thick solid: 20 mg; thin solid: 50 mg; broken: 100 mg; and dotted: 200 mg p.o., q.d., n = 10). Open circles and triangles show plasma concentrations as measured at day 11 over multiple oral administration of ritonavir at 20 mg and 200 mg, respectively (n = 10–11) (Mathias et al., 2009)
Case example (4/7): two-dimentional approach to estimate \( fm,CYP3A4 \)

**Alectinib: a CYP3A4 substrate in vitro**

- **Two-dimentional analysis**
  - \( F_g \) and \( fm,CYP3A4 \) of alectinib could be identified to recover the AUC and Cmax ratios observed in the posaconazole (400 mg b.i.d.) DDI study
  - Observed AUCR = 1.60 and Cmax R=1.25 at 40 mg alectinib

(Cleary and Gertz et al., 2017)
Case example (5/7): PK and victim DDI in a pharmacogenetic subpopulation

Siponimod: a sensitive CYP2C9 substrate

- Prediction of the impact of CYP2C9 genotypes on the PK and DDI potential
  - PBPK modeling is a powerful tool to estimate the PK in CYP genotypes with significantly less frequencies (as 0.003 for CYP2C9*3*3) – highly likely being untested case scenario

(Jin et al., 2017)
Case example (6/7): complex DDIs

**Ruxolitinib: a dual substrate of CYP3A4 and CYP2C9**

(A) *In vitro* CYP phenotyping

- CYP3A4 (75.1%)
- CYP2C9 (18.5%)
- CYP2A6 (0.12%)
- CYP1A2 (4.2%)
- CYP2B6 (0.58%)
- CYP2D6 (0.06%)
- CYP2C19 (0.58%)
- CYP2C8 (1.44%)
- CYP2C19 (0.58%)
- CYP2D6 (0.06%)

(B) *In vivo* ketoconazole (200 mg b.i.d.) DDI study (observed AUCR = 1.91 at 10 mg ruxolitinib)

- CYP3A4 (53.6%)
- CYP2C9 (40.0%)
- Other CYPs (6.4%)

Untested case scenario: the dual inhibition effect of fluconazole on CYP3A4 and CYP2C9

**Fluconazole**: Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady state ruxolitinib AUC by approximately 100% to 300% following concomitant administration of 10 mg of Jakafi twice daily with 100 mg to 400 mg of fluconazole once daily, respectively [see Dosage and Administration (2.3) and Drug Interactions (7.1)].

(Umehara et al., 2019, in press)
Case example (7/7): absorption DDI modeling

Support for the Filing of Alectinib

Impact:
- Support for lack of interaction with gastric acid reducing co-medications – no need for further clinical studies
- Support for impact of time of dosing with a meal – no need for further clinical studies
- Delivered understanding of exposure vs dose relationship guided dose and dose regimen selection and supported market formulation selection

Highlights:
- Prediction of DDI with PPIs confirmed strengthening case for no interaction
- Convincing simulation of food effect to be used in label
- Predicted effect of SLS in formulation confirmed and verified model used to support selection of market formulation

Current status & Next steps:
- A convincing model integrating in vitro and clinical data has been constructed
- Documentation and model files were mentioned in FDA review of NDA filing
- Roche/Chugai paper AAPS Journal July 2016
- Model applied for further formulation development in collaboration with Chugai

(Parrott et al., 2016)
Question 2/2

Drug A is eliminated by hepatic CYP3A4. What is a «clinically untested case scenario» which can be predicted? The PBPK model of drug A is verified as a CYP3A4 substrate using PK data in healthy adults.

a) PK change at fed state
b) Inhibition effects of drug A on the PK of CYP2C9 substrates
c) Dose adjustment of drug A when a CYP3A4 inhibitor is co-administered
d) Dose adjustment of drug A in infants
e) PK differences in healthy volunteers and target disease populations
PBPK-DDI modeling: current achievements and expected applications

• Achievements
  – Waiving of unnecessary (untested) PK / DDI studies
    o Victim DDI via major CYP enzymes
    o Perpetrator DDI e.g. time-dependent inhibition (and induction)
    o Absorption DDI with acid-reducing agents
  – Dose adjustment with e.g. co-medications (incl. prediction of PK variability)
  – Support clinical DDI study designs

• Expected applications
  – Complex DDI of a drug showing time-dependent inhibition and induction on CYP enzymes
  – DDI via non-CYP enzymes (e.g. UGTs)
  – Transporter DDI
  – DDI among target patients/populations
Transporter DDI prediction

Partial verification of model performance for transporter DDI via OATP1B1 and OCT2/MATEs

Model limitations:

- **DDIs on statins**
  - Under-estimation of Cmax ratio by 2-fold to 3-fold due to lack of mechanistic Vh (mainly governing Vss) change by strong OATP1B1 inhibition (likely not the case of weak OATP1B1 inhibition)
  - Intestinal DDI via P-gp (atorvastatin) and BCRP (rosuvastatin): no verification due to lack of numbers of the reference clinical data

- **DDIs on metformin**
  - The current value OCT2 Ki (0.25 µM) of cimetidine, which is approximately 500-fold lower than the in vitro K<sub>i</sub> value in transfected HEK cells, reflects the inability of the current model to recover the indirect effect of MATE transporter inhibition of cimetidine on the activity of OCT2 (Burt et al., 2016).

Pitavastatin, atorvastatin, rosvastatin and metformin were orally administered at 4 mg (single dose), 40 mg (single dose), 5 mg (single dose) and 250 mg (once daily), respectively, after co-medication of rifampicin RIF (600 mg i.v. or p.o., single dose for statins) and cimetidine CMD (400 mg p.o., twice daily for metformin). Predicted AUC (inf or tau) and Cmax ratios of victim drugs were expressed as geometric mean with 90% confidence interval (n = 12 or 50).
Summary: take home messages

• An application of PBPK modeling for supporting the clinical DDI trials is most frequently considered among the areas of the intended use in submission dossiers reviewed by regulatory agencies
  – A concept of DDI risk assessment has been well-established
  – Strongly supported by regulatory DDI guidance documents (FDA, 2017; EMA, 2012)

• Conducting PBPK modeling for untested case scenarios potentially results in waiving of clinical DDI trials
  – Benefit-risk decisions should be made for patients to avoid unexpected adverse events by exposure increase / decrease of drugs by co-medications: categorization of high regulatory impact analyses (EMA, 2019)
  – Dose adjustment with e.g. co-medications (incl. prediction of PK variability)
  – Prerequisite: Qualification of the software and scientific verification of models of compounds and interacting drugs

• Case examples: CYP-based and oral absorption DDI
  – Note: population PK analyses will support PBPK model verification (e.g. CL among pharmacogenetic populations, absorption rate constant ka)

• Applications of PBPK modeling to other DDI areas (as via transporter) are highly expected while there are several scientific limitations for the moment
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Doing now what patients need next