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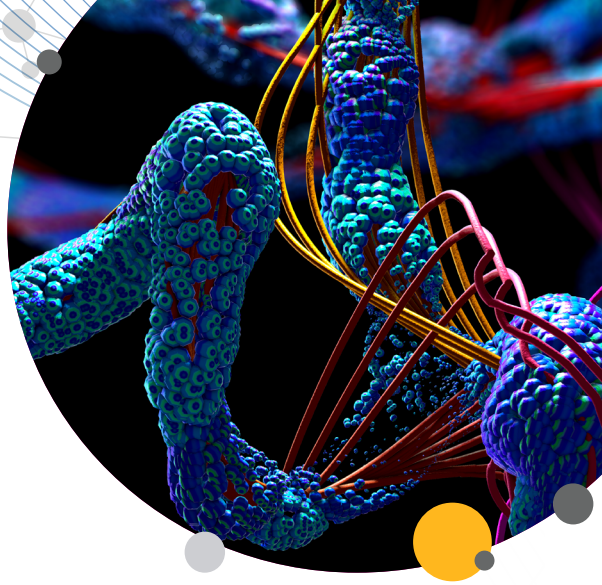
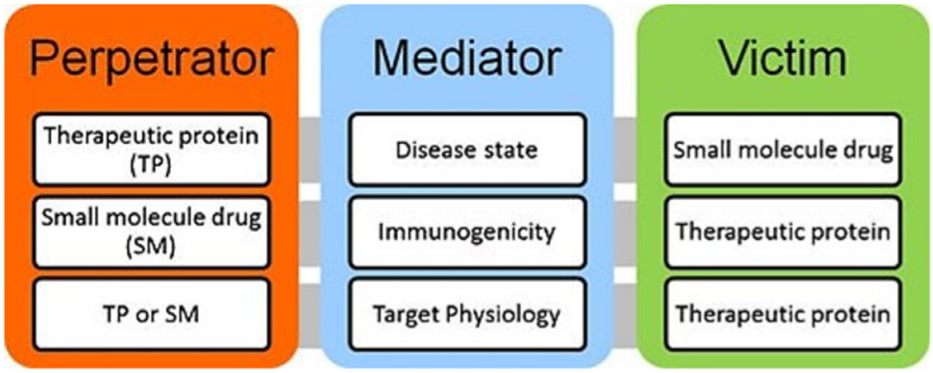


Drug interactions with therapeutic proteins, regulatory expectations and modeling and simulation approaches

By Eva Gil Berglund, Felix Stader, Khaled Benkali, and Krithika Shetty

Drug-drug interactions (DDIs) are a frequent cause of drug-related adverse effects and can pose a significant risk to patient safety. While the best practices for DDI assessment of small molecule drugs are well established, the regulatory view of therapeutic protein DDI risk assessment has been evolving over recent years. Development programs for TP (therapeutic protein) drug programs need to design the DDI part of the Clinical Pharmacology package on a case-by-case, risk-based manner as factors like disease state and target biology are often key mediators in TP DDIs (Figure 1). While the DDI portion of the clinical pharmacology package for TPs may be leaner than that for small molecules, some clinical studies may be needed, and it is important to address DDIs for these non-small molecule drugs. Modeling-informed drug development (modeling and simulation) uses biostatistical models to inform decision making regarding the risk of DDIs.

Figure 1: Disease state and target biology are often key mediators of TP DDIs

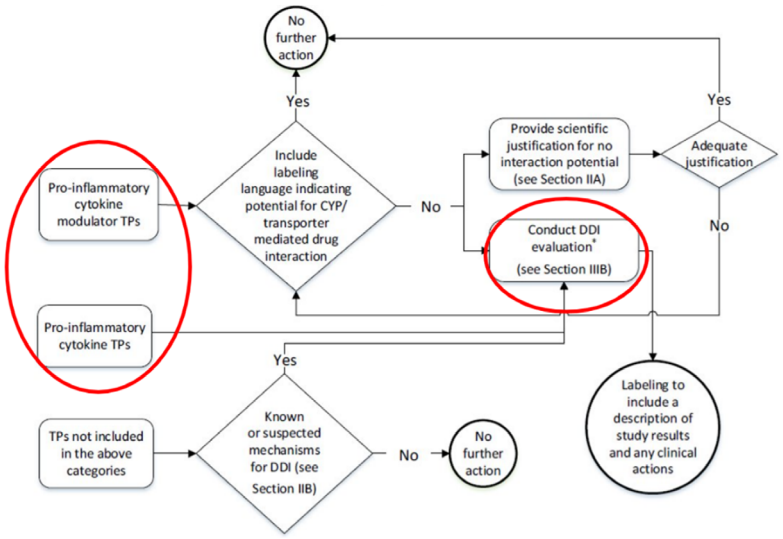


Kenny et al, The AAPS Journal, Vol. 15, No. 4, October 2013

The FDA (Food and Drug Administration) provides substantial advice for therapeutic proteins in their draft DDI guidance for therapeutic proteins. Some high-level advice is provided in the 2007 EU Therapeutic proteins guideline. China's NMPA (National Medical Products Administration) provides recommendations regarding DDI for therapeutic proteins in two recent published guidances: "Technical guideline for drug interaction studies (draft)" (2021) and " Technical guideline for clinical pharmacokinetic studies of therapeutic proteins" (2021), respectively. These guidances are consistent with the FDA guidance. Globally, regulators including EMA (European Medicines Agency), PMDA (Pharmaceuticals and Medical Devices Agency), NMPA, MHRA (Medicines and Healthcare products Regulatory Agency) and TGA (Therapeutic Goods Administration) have been aware about the interaction risk for decades, keeping updated with science and data submitted in applications. Thus, global expectations are similar. The ICH (International Conference on Harmonization) M12 draft DDI guideline also supplies some general recommendations on this topic.

The 2020 FDA draft DDI guidance for TPs

The 2020 FDA draft guidance on TP DDIs provided an update on US regulatory expectations around assessing therapeutic protein DDIs. Key highlights of the guidance include clarification of expectations for DDI assessment for drugs that are proinflammatory cytokines or cytokine modulators, as well as for TPs with alternative DDI mechanisms and ADCs (antibody-drug conjugates) as victim and perpetrator of interactions. The guidance clarified that the translation of in vitro data or animal data to humans for therapeutic protein DDIs has been limited (except for the use of in vitro DDI risk assessment for the small molecule component of ADCs). General recommendations for clinical trial designs to assess TP DDIs were provided, and the document shows that population PK or PBPK (physiologically-based pharmacokinetic) approaches might aid with characterizing TP DDIs.



FDA Draft Guidance, August 2020 https://www.fda.gov/media/140909/download

Figure 2: TP DDI decision tree per the FDA draft guidance

The 2019 publication that preceded the guidance (Jing et al, 2019), authored by FDA contributors, supplied a more detailed view of the 'landscape' and remains a useful resource on this topic. This publication documented that 'the concern for drug interactions appears to have remained relatively limited with TPs compared with small-molecule drugs.' Examples of drug labels (as of May 2019) where a more than 50% change in exposure of either the TP or the interacting drug was observed were peginterferon-α-2b, tocilizumab, glucarpidase, albiglutide, necitumumab, basiliximab, and palifermin. Effects larger than twofold were rare, and none resulted in a specific TP dose adjustment recommendation in the label. However, some labels did state that caution should be taken for interacting small molecule drugs when concomitantly used, typically those with narrow therapeutic indices.

Fast forward to 2022

The current landscape of TP DDI outcomes remains largely consistent with the findings of Jing et al. None of the recently approved TP DDI labels carry specific instructions for dose modification of the TP in section 7 of the USPI (US Package Insert). Actions relating to concomitant small molecule drugs or other TPs as a victim in Section 7 of TP USPIs and Drug Interactions section 4.5 of the EU (European Union) SmPC (summary of product characteristics) remain limited. However, USPIs for recently approved anti-cytokine monoclonal antibodies, satralizumab and benralizumab, carry DDI-related general informational language in USPI Pharmacokinetics section 12.3.

The FDA has also recently published a draft guidance focusing on the clinical pharmacology considerations including the DDI assessment of ADCs. For these drugs, a dose adjustment to match payload exposure may lead to reduced efficacy. Thus, labeling recommendations focus on whether a drug can be safely used concomitantly with the ADC and recommend monitoring for potentially increased toxicity, as in the USPIs for polatuzumab vedotin, enfortumab vedotin, and tisotumab vedotin. The risk of

victim and perpetrator effects should be addressed in vitro for the payload. When needed, victim in vivo DDI studies should be done with a focus on evaluating clinical concentrations of the payload. The FDA guidance recommends that characterizing the systemic exposure of the unconjugated payload, though possibly relatively low, is important for determining its DDI potential as a perpetrator.

Figure 3: DDI assessment for current FDA approved ADCs

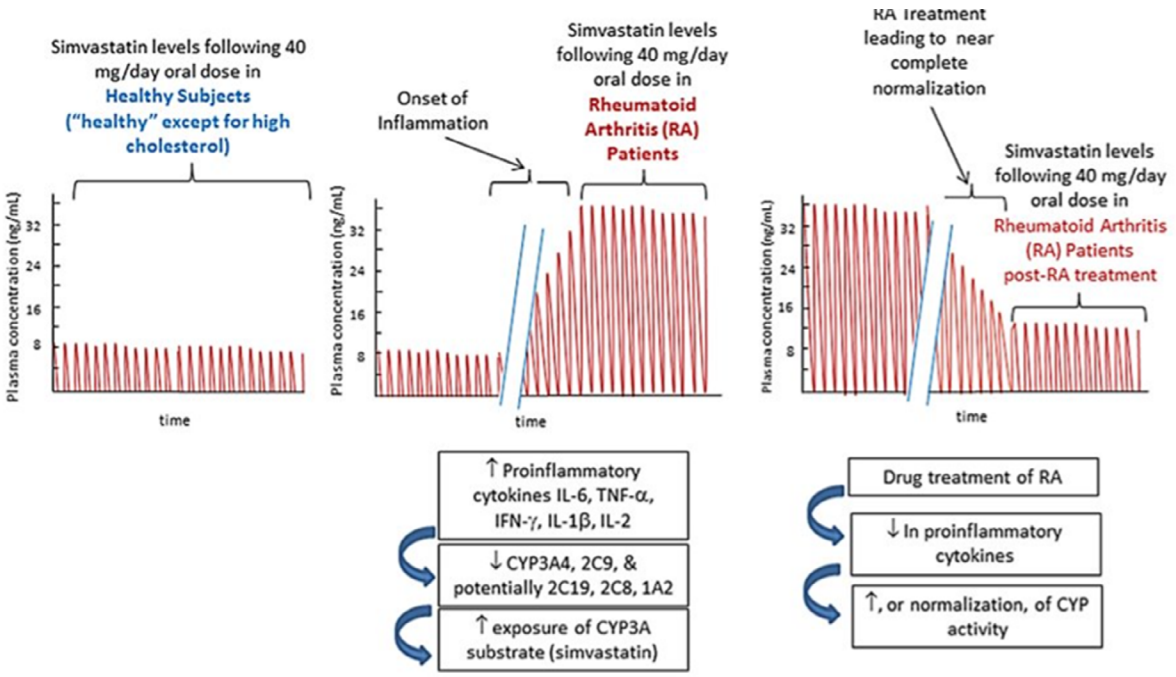
ADC	Clinical DDI assessment approach
Brentuximab vedotin	**Clinical DDI studies with strong CYP34A inhibitor and inducer, and sensitive CYP3A substrate**
Fam-Trastuzumab Deruxtecan	**Clinical DDI study with dual inhibitor of OATP1B/CYP3A and a strong CYP3A inhibitor**
Polatuzumab vedotin	No clinical DDI studies, PBPK, using supporting clinical DDI data with brentuximab vedotin
Enfortumab vedotin	No clinical DDI studies, review relied on clinical DDI data with brentuximab vedotin at initial approval, subsequent PBPK update
Tisotumab vedotin	No clinical DDI studies, review relied on clinical DDI data with brentuximab vedotin
Ado-Trastuzumab emtansine	No dedicated clinical DDI studies, exploratory assessment of the effect CYP3A inhibitors using data from phase 3 study, limited utility
Loncastuximab tesirine	No clinical DDI studies, effects of co-administered drugs assessed using PK and safety data collected in clinical studies
Gemtuzumab ozogamicin	No dedicated clinical DDI studies, effects of/on co-administered drugs assessed using PK data collected in supporting studies
Inotuzumab ozogamicin	No dedicated clinical DDI studies, PopPK-considered supportive only
Sacituzumab Govetican	No clinical DDI studies, review utilized indirect evidence of from UGT1A1 poor metabolizers
Belantamab mafodotin	No clinical DDI studies

The persistent effects by therapeutic proinflammatory cytokines, the slow restoration of drug metabolizing enzymes caused by cytokine modulators, and the transient effect of cytokine release

The EU SmPCs have generally similar wordings as their US counterparts. Interestingly the DDI-related language in the EU SmPC for satralizumab is stronger than that in the USPI in that it contains recommended actions relating to effects on concomitant small molecule drugs when starting or discontinuing satralizumab treatment, potentially suggesting some differences in the risk assessment of the IL-6 modulating effect between US and EU reviewers (further information below).

Development programs for proinflammatory cytokines and cytokine modulators continue to characterize the effect of their products on the activity of CYP (cytochrome P450) enzymes and effects on sensitive CYP substrates. Cytokine modulating treatments often restore enzyme expression along with obtaining efficacy on the inflammatory condition. The conceptual impact of such a change is summarized in Figure 4 below, using simvastatin (CYP3A substrate) as an example of a victim small molecule drug. These DDI studies need to be performed in patients and after a long treatment duration. Nested studies could be used for this purpose, including taking advantage of concomitant medications as DDI probes. There are now also many examples of cocktail DDI studies evaluating the effect of cytokine modulators, e.g., daclizumab (Tran et al, 2016), guselkumab (Zhu et al, 2020), risankizumab (Khatri et al, 2019) and tildrakizumab (Khaliljeh et al, 2018) on CYP substrates in various disease populations. As these effects usually can be considered normalization of enzyme activity, the clinical consequences of these interactions are limited to drugs subject to individual dose titration, where a re-titration may be necessary as the enzyme expression is restored.

Figure 4: DDI mechanism mediated by normalization of proinflammatory cytokine levels in Rheumatoid Arthritis (RA)



Coutant and Hall, The Journal of Clinical Pharmacology / Vol 58 No 7 2018
Schmitt et al, Clinical Pharmacology & Therapeutics | Volume 89 Number 5 | May 2011

Of note, the possibility of transient cytokine release-related DDIs is being increasingly scrutinized with the development of drug classes leading to cytokine release syndrome (CRS), most notably CD3-engaging bispecific antibodies. FDA comments for such drug classes in early development frequently focus on understanding the duration and magnitude of cytokine release and incorporating safety assessment of any NTI (narrow therapeutic index), sensitive CYP substrates used in early phase clinical trials. However, given the transient nature of the cytokine release for such drugs, predominantly after the first or second dose of the drugs, DDIs that rise to the level of actionable labeling language appear limited. Among the labels for compounds which lead to transient cytokine release-related DDIs, the 'strongest' language to date appears to be in section 7 of the blinatumomab USPI. The blinatumomab label specifies the duration of the highest DDI risk and recommends monitoring for toxicities or drug concentrations and dose adjustment of the concomitant CYP450 substrate drugs as needed, especially NTI drugs. The FDA review for the recently approved CD3 engager tebentafusp shows the totality of evidence approach taken by the reviewers to assess the need of DDI perpetrator warnings low based on the transient nature of the cytokine release, the short half-life of tebentafusp, available safety in phase 3 in patients treated with NTI drugs and the prolonged monitoring of safety post-dose. Section 12.3 of the tebentafusp label documents a general note that elevation of certain proinflammatory cytokines may suppress CYP450 enzyme activities. Here, the EU SmPC again has somewhat stricter recommendations, recommending monitoring of the safety of NTI drugs 24 hours post-dose and dose adjustment of these if needed.

Other TP DDI mechanisms

Additional mechanisms of TP DDIs that have been observed to date include: DDIs due to altered physiological processes such a gastric emptying, drugs targeting the same target and impacting target biology (as observed between the anti-PCSK9 antibody evolocumab and high intensity statin regimens), drugs competing for recycling through FcRn receptor and thus non-target mediated elimination (for example when IVIG is used concomitantly with a monoclonal antibody) or via impacts on immunogenicity and consequent effect on drug elimination.

An example of a TP DDI due to direct alteration in metabolism is the interaction between glucarpidase (which is a carboxypeptidase that hydrolyzes folic acid and classical anti-folates such as methotrexate) and leucovorin (which is a derivative of folic acid used as an antidote to folic acid antagonists). Glucarpidase is used to reduce toxic plasma methotrexate concentration in patients with delayed methotrexate clearance. In patients with cancer receiving high-dose methotrexate and leucovorin rescue, glucarpidase administered 2 hours before leucovorin reduced (6S)-leucovorin AUC0-3h by 33% and Cmax by 52%. The glucarpidase (Voxraze) USPI therefore carries instructions to administer leucovorin at least 2 hours before or 2 hours after the glucarpidase dose when used concomitantly.

In addition to the PK-related TP DDIs described above, potential PD-related DDI mechanisms are also relevant to consider. These include:

- potentiation of adverse effects such as the increase in progressive multifocal leukoencephalopathy risk described in the natalizumab label when used concomitantly with immunosuppressors or Tumor Necrosis Factor-α inhibitors
- increase in the risk of clinically significant QTc interval prolongation when used concomitantly with other drugs known to prolong the QTc interval as in the label for inotuzumab ozogamycin.
- The effect on response to vaccines.

MIDD (Model-Informed Drug Development) approaches

Population PK approaches can be useful for investigating victim DDIs on therapeutic proteins. This was how the DDI between infliximab and methotrexate was discovered and can be a useful approach for investigating DDIs in the patient population with commonly prescribed concomitant medications. In addition, although inotuzumab ozogamicin is not currently approved for the B cell Non-Hodgkin's Lymphoma indication, based on population PK modeling inotuzumab ozogamicin clearance was observed to be decreased by 16% when co-administered with rituximab in B cell NHL patients. This is likely due to the diminished contribution of B cell-dependent clearance pathway to overall inotuzumab ozogamicin clearance, caused by rituximab-mediated depletion of B cells (Garrett et al, 2019).

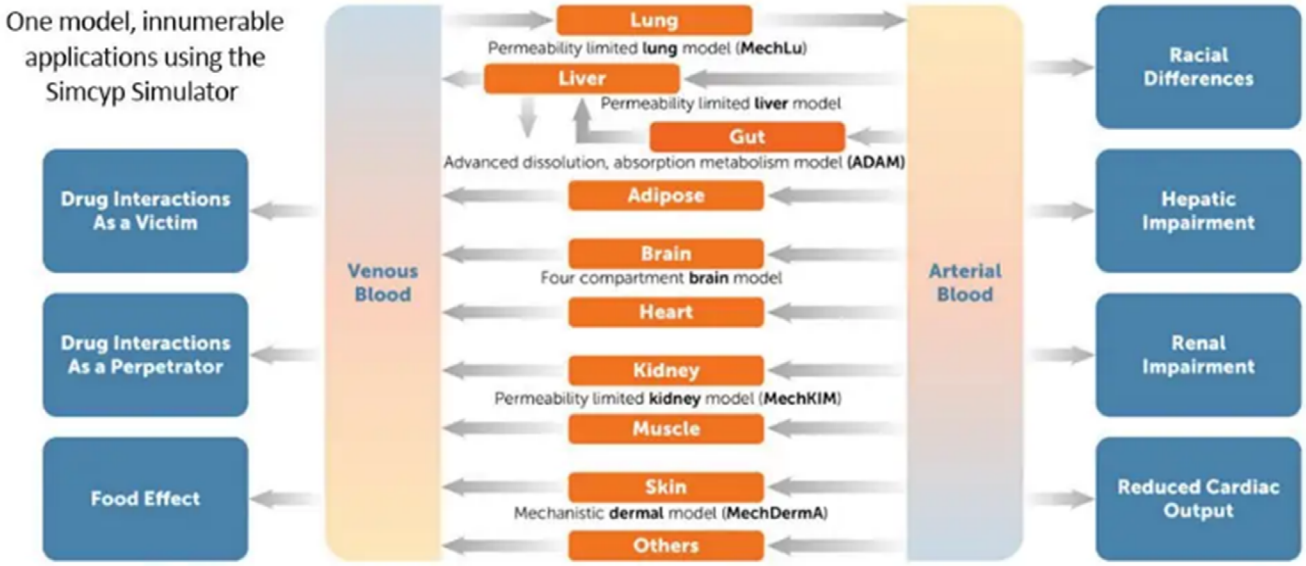
In contrast to population PK, PBPK models are aimed to be built bottom up with physiological data to generate a virtual population and information on the absorption, distribution, metabolism, and elimination of a drug to allow a priori predictions. PBPK modeling has been used to predict the impact of IL-6 and IL-6 modulators on the clearance of small molecule drugs (Machavaram et al, 2013). Clinical consequences of the target IL-6 suppression of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A were simulated from in vitro CYP suppression using a PBPK approach, predicting weak DDI effect restoring these enzyme activities in patients with chronically elevated IL-6 levels. Even at high IL-6 concentration, only weak (CYP2C9, CYP2D6) or moderate (CYP2C19, CYP3A4) CYP suppression was simulated by a PBPK model, informed by in vitro suppression data of CYP activity. Predicted AUC-ratios ranged from no interaction for the CYP1A2 substrate caffeine to 2.30 for the CYP3A substrate simvastatin (Machavaram et al, 2019).

A PBPK model was developed for the bispecific antibody blinatumomab that causes a transient elevation of IL-6 and other cytokines within the first 48 h after dosing. The model predicted that CYP3A, CYP1A2, and CYP2C9 activity returned to baseline one week after blinatumomab treatment, meaning the DDI potential lasted for less than one week when a small molecule drug such as simvastatin (CYP3A), midazolam (CYP3A), theophylline (CYP1A2), caffeine (CYP1A2), or S-warfarin (CYP2C9) was co-administered (Xu et al, 2015). The use of PBPK modeling is mentioned in the drug label for blinatumomab. A second example for which the impact of cytokine elevation on CYP enzymes was predicted by a PBPK model is teclistamab.

Interestingly, in a related application to understand disease-drug interaction, the ability of PBPK to predict cytokine effects was utilized in the first wave of the COVID-19 pandemic to successfully predict the effect of a cytokine storm on lopinavir/ritonavir exposure in patients with a severe disease progression. Based on the PBPK analysis, dosing adjustment was not deemed necessary for lopinavir or ritonavir, but it raised caution for narrow therapeutic index drugs (Stader et al, 2022).

In all described cases, PBPK models were developed for IL-6, which is the most potent suppressor of the majority of CYP enzymes as suggested by in vitro data. In vivo, the effect is likely driven by a combination of different cytokines. However, in vitro the results of IL-6 alone or in combination with other cytokines lead to similar results. Thus, a recent analysis concluded that IL-6 is sufficient to be incorporated into a PBPK model (Chen et al, 2022).

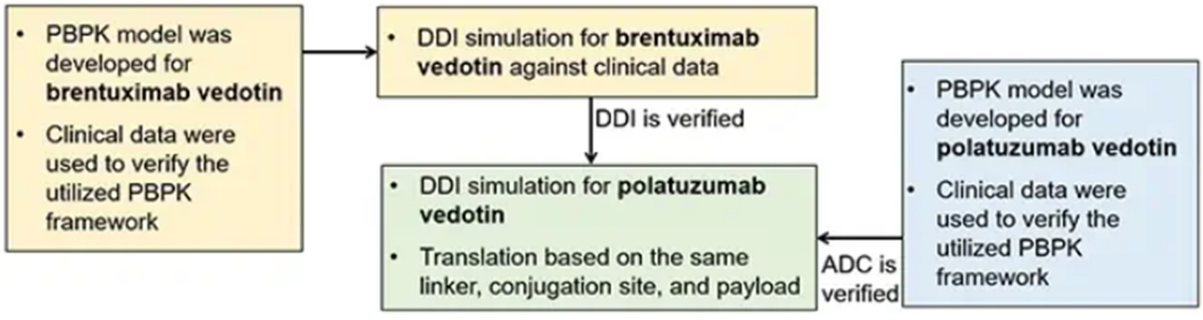
Figure 5: General PBPK applications



In addition to cytokine-mediated DDIs, PBPK modeling could also be used to simulate other DDIs between therapeutic proteins. Firstly, the impact of an anti-FcRn antibody (e.g., rozanolixizumab) on endogenous IgG and other administered monoclonal antibodies (mAbs) could be simulated by a PBPK model. Secondly, the competition of two mAbs binding to the same target or the antagonistic effect of one drug on the target of a mAb could be predicted by a mathematical model. PBPK has also been used to support DDI labeling language in the polatuzumab vedotin USPI relating to the impact of strong CYP3A inducers and inhibitors on concentrations of the small molecule MMAE payload and the effect of the ADC on sensitive CYP3A substrates without clinical studies. This analysis leveraged clinical DDI information available as part of the brentuximab vedotin program, which also contains an MMAE payload. Similarly, PBPK was also used to support a labeling update regarding DDI effects with dual P-gp and strong CYP3A4 inhibitor and inducers as well as sensitive substrates in the enfortumab vedotin USPI.

Generally, regulatory acceptance of predicting DDIs with small molecule drugs by a PBPK model is evolving, including cytokine-mediated TP DDIs and potential interactions with the payload of an ADC. For other TP DDIs, the PBPK approach can be considered as exploratory or supportive.

Figure 6: PBPK modeling approach used for polatuzumab vedotin



Samineni, D., et al., J Clin Pharmacol, 2020.

The case example of sartralizumab nicely illustrates how modeling and simulation approaches can be used to provide an integrated assessment of both victim and perpetrator DDI risk, and clinical consequences of altered exposures of the TP as a victim. Satralizumab is designed to block IL-6R signaling and hence would normalize CYP levels. A population PK approach was used in both adult and adolescent patients to investigate the effect of several covariates including commonly used anti-inflammatory co-medications on satralizumab PK (via impact on immunogenicity), and to predict receptor occupancy outcomes based on the target-mediated clearance of the molecule. Exposure-response analyses were used for safety, QTc, PD, and efficacy correlation to support the consequent assessment of altered satralizumab exposure.

A discussion based on IL-6 literature data in the target population as well as observed DDI effects by the IL-6 modulators tocilizumab, sarilumab, and sirukumab was used to contextualize the magnitude of the DDI effect in the proposed patient population. A PBPK approach was also applied to support the cytokine-mediated perpetrator DDI predictions (Machavaram et al, 2019), but this high-regulatory impact application was not considered sufficiently qualified by EU regulators and considered exploratory by the FDA. Due to identified uncertainties, a cautious approach was taken by the EU regulators adding a warning for use of NTI substrates of CYP450 3A4, 1A2, 2C9 or 2C19 into the SmPC. The US labeling is less conservative. The Japanese label includes the result of the modeled change in IL-6 concentrations, induced by satralizumab, to conclude that no clinically significant effect is expected on the pharmacokinetics of co-administered drugs. The example demonstrates the ability of the PBPK approach to simulate PK scenarios in different ethnic groups.

Conclusions

DDI risk assessment is an important consideration in TP drug development. A case-by-case, risk-based, and fit-for-purpose assessment approach should be planned. MIDD approaches including population PK, exposure-response, and PBPK can support efficient drug development strategies for addressing the risk of perpetrator and victim drug interactions of therapeutic proteins

Author Biographies

Eva Gil Berglund

Eva is a pharmacist by training and has a PhD in Clinical Pharmacology, both from Uppsala University, Sweden. She has been a Clinical Pharmacology reviewer at the Swedish Medical Products Agency for over 20 years and a Senior Expert for 12 years, working with all types of molecules in marketing applications, clinical trials and scientific advice procedures in the EMA Network of National agencies. Eva has been working in all therapeutic areas and has extensive knowledge in antivirals, antibiotics, CNS active drugs, oncology, rheumatology, inhalation products etc.

Eva has been Rapporteur and actively involved in drafting of several EU Clinical Pharmacology guidance documents (drug-drug and drug-food interactions, PBPK, pediatrics, pharmacogenetics, etc.), in inter-regional harmonization activities and in the work of EMA working parties Pharmacokinetics Working Party and Paediatrics Working Party. Eva joined Certara in 2019 and provides her Clinical Pharmacology experience and Regulatory strategy knowledge in GAP analyses, regulatory stress tests and mock meetings, regulatory interactions, filing and clin pharm response support, pediatric submissions (PIP, PSP, new indications). Her inspiration is scientific development and its practical application, optimizing drug development, pushing regulatory science forward, and improving patient access to efficacious and safe drugs.

Felix Stader

Felix Stader is a Senior Research Scientist at Certara UK. He studied biology and pharmaceutical science in Muenster (Germany) and did his PhD in Basel (Switzerland) about HIV drug pharmacokinetics and drug-drug interaction magnitudes in the elderly by using PBPK modeling. At Certara UK, Felix worked extensively on the biologics models of the Simulator including antibody-drug conjugates and the possibility to simulate therapeutic protein disposition in pediatrics. Additionally, Felix has broad experience in developing population and compound files.

Khaled Benkali

Dr. Khaled Benkali joined Certara as a Director, Clinical Pharmacology in February 2020. He is a pharmacist and completed his training with a Master of Science and a PhD in pharmacology and holds an executive MBA. Khaled brings a strong business acumen and strategic perspective acquired through 10 years in the pharmaceutical industry, at Galderma and Pierre Fabre, successively. During this period, he participated actively in the development and successful approval of several dermatological drugs. Khaled participated to the development of new chemical entities and monoclonal antibodies. He had also an extensive exposure to in-licensing opportunities and interactions with regulatory bodies, a good understanding of M&S (popPK, PBPK) and their applications to support drug development.

Krithika Shetty

Krithika joined Certara in 2021 having previously been an Oncology Clinical Pharmacology Reviewer at the FDA for 3 years where she contributed to scientific review of numerous regulatory submissions across all phases from INDs to BLA/NDA submissions. Prior to that, Krithika was at Novartis for 3.5 years where she focused on the DMPK and early clinical development of biologics. Krithika has a degree in Pharmacy from the Birla Institute of Technology and Science (BITS) in Pilani, India, and a PhD in Pharmaceutical Sciences from the State University of New York in Buffalo, US.

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