P32. MECHANISMS AND CLINICAL SIGNIFICANCE OF PHARMACOKINETIC-BASED DRUG-DRUG INTERACTIONS WITH DRUGS APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION IN 2020

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ABSTRACT

Understanding the ADME processes involved in pharmacokinetic-based drug-drug interactions (DDIs) is critical to facilitate an optimal management of DDIs in the clinic.

Methods: In the present work, DDI data for small molecular drugs approved by the U.S. Food and Drug Administration (FDA) in 2020 (N = 40) were analyzed using the University of Washington Drug Interaction Database. The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the new drug application reviews. DDI study results from dedicated DDI clinical trials, pharmacogenetic studies, as well as physiologically-based pharmacokinetics (PBPK) modeling and simulations that functioned as alternatives to dedicated clinical studies were examined.

Results: About 180 positive clinical studies, defined as mean area under the curve ratios (AUCRs) ≥ 1.25 for inhibition DDIs or pharmacogenetic studies and ≤ 0.8 for induction DDIs, were then fully analyzed. Oncology was the most represented therapeutic area, including 30% of 2020 approvals. When new drugs were evaluated as victims of DDIs, inhibition and induction of CYP3A explained most of all observed clinical interactions (approximately 60% and 20%, respectively). Two oncology drugs, avapritinib and lonafarnib, were identified to be sensitive substrates of CYP3A, with AUCRs of 7.00 and 5.07 when co-administered with itraconazole (PBPK evaluation) and ketoconazole, respectively. Only one drug, relugolix, also for the treatment of cancer, was found to be a sensitive substrate of transporter, with an AUCR of 6.25 in the presence of erythromycin due to inhibition of P-gp. Ten drugs were found to be moderate sensitive substrates (AUCRs 2-5): fostemsavir (CYP3A), oliceridine (CYP2D6), ozanitib (BCRP), pemigatinib (CYP3A), pralsetinib (CYP3A), rimegepant (CYP3A), selpercatinib (CYP3A), tazemetostat (CYP3A), tucatinib (CYP2C8), and vibegron (P-gp). As precipitants, three drugs (all for chemotherapy) were considered strong inhibitors of enzymes (AUCR ≥ 5): cedazuridine for cytidine deaminase, lonafarnib for CYP3A, and tucatinib for CYP3A. No drug showed strong inhibition of transporters. Additionally, the following drugs were found to be moderate inhibitors: berotralstat (CYP2D6 and CYP3A), capmatinib (CYP1A2 and BCRP), osilodrostat (CYP1A2), and selpercatinib (CYP2C8). No strong or moderate inducer of enzymes or transporters was identified. As expected, all DDIs with AUCRs ≥ 5 or ≤ 0.2 (≥ 5-fold change) and almost all those with AUCRs of 2-5 and 0.2-0.5 (2- to 5-fold change) triggered dosing recommendations in the drugs' labels.

Conclusion: Overall, all 2020 drugs found to be either sensitive substrates or strong inhibitors of enzymes or transporters were oncology treatments, underscoring the need for effective DDI management strategies in cancer patients often receiving poly-therapy.

OBJECTIVES

- To review pharmacokinetic-based clinical DDI data available in the new drug application (NDA) reviews for drugs approved by the FDA in 2020.
- To understand main mechanisms that mediate interactions resulting in label recommendations.

METHODS

The University of Washington Drug Interaction Database was used to identify clinical DDI studies available for drugs approved by the FDA in 2020. The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the NDA reviews. DDI study results from dedicated DDI clinical trials, pharmacogenetic studies, as well as PBPK modeling and simulations that functioned as alternatives to dedicated clinical studies were examined. . Using available mean area under the time-plasma concentration curve ratios (AUCRs), all clinical studies with AUCRs ≥ 1.25 and ≤ 0.8 (i.e. positive DDI results) were analyzed. Applying the categorization recommended by the FDA, any drug interactions with AUC changes ≥ 5-fold (i.e., AUCRs ≥ 5 or ≤ 0.2), 2- to 5-fold (2 ≤ AUCR < 5 or 0.2 < AUCR ≤ 0.5), or 1.25- to 2-fold (1.25 ≤ AUCR < 2 or 0.5< AUCR ≤ 0.8) were considered strong, moderate, or weak drug interactions, respectively.

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RESULTS

A total of 40 small new molecular entities (NMEs) were approved by the FDA in 2020. Antineoplastic agents were found to be the most represented therapeutic area, comprising 30% of all approved drugs (Figure 1). Among the 12 oncology drugs, eight were kinase inhibitors, highlighting the continuous major role of this therapeutic class in cancer therapy.

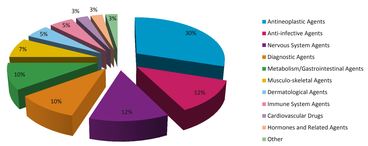

Figure 1. Therapeutic classes of drugs (small molecules) approved by the FDA in 2020

NMEs as substrates

- There were about 110 positive interaction studies where NMEs were the substrates (or victim drugs). Inhibition and induction of cytochrome P450 (CYP) 3A explained most of these interactions.
- Based on the results of mechanistic studies with clinical index inhibitors, three drugs were identified as sensitive substrates: avapritinib and lonafarnib for CYP3A, and relugolix for P-glycoprotein (P-gp) (Table 1).
- Regarding moderate inhibition, 10 drugs were found to be moderate sensitive substrates (AUCRs 2-5) based on inhibition or pharmacogenetic results: fostemsavir (CYP3A), oliceridine (CYP2D6), ozanitib (BCRP), pemigatinib (CYP3A), pralsetinib (CYP3A), rimegepant (CYP3A), selpercatinib (CYP3A), tazemetostat (CYP3A), tucatinib (CYP2C8), and vibegron (P-gp).
- Most of DDIs with AUC changes ≥ 2-fold led to specific label recommendations when concomitantly administered with known inhibitors or inducers, while for DDIs with AUC changes < 2-fold less than half led to clinical recommendations.

Table 1. Drug interactions with AUC changes ≥ 5-fold, NMEs as substrates

NME	Therapeutic Class	Precipitant	AUCR	Enzyme/Transporter Primarily Involved	Label Recommendation
inhibition DDIs with AUCRs ≥ 5					
avapritinib	Anti-neoplastic Agents	itraconazole	7.90 (PBPK)	CYP3A	avoid strong CYP3A inhibitors
relugolix	Anti-neoplastic Agents	erythromycin	6.25	P-gp[a]	avoid oral P-gp inhibitors;if unavoidable, separate dose of at least 6 h
lonafarnib	Other	ketoconazole	5.07	CYP3A[b]	contraindicated with strong or moderate CYP3A inhibitors; avoid weak CYP3A inhibitors, if unavoidable, reduce dose of lonafarnib; monitor for adverse reactions, such as arrhythmias and events such as syncope and heart palpitations
induction DDIs with AUCRs ≤ 0.2					
lonafarnib	Other	rifampin	0.02	CYP3A[b]	contraindicated with strong or moderate CYP3A inducers
avapritinib	Anti-neoplastic Agents	rifampin	0.08	CYP3A	avoid strong CYP3A inducers
selpercatinib	Anti-neoplastic Agents	rifampin	0.13	CYP3A[b]	avoid strong CYP3A inducers
pemigatinib	Anti-neoplastic Agents	rifampin	0.15	CYP3A[b]	avoid strong CYP3A inducers
fostemsavir	Anti-infective Agents	rifampin	0.18 (temsavir)	CYP3A[b]	contraindicated with strong CYP3A inducers
rimegepant	Migraine Treatments	rifampin	0.20	CYP3A4[b]	avoid strong or moderate CYP3A4 inducers

[a] Inhibiton of CYP3A may be also involved. However, compared to the DDI study result with CYP3A inhibitors, the increase in relugolix exposure is likely primarily driven by the increase in oral bioavailability due to inhibition of intestinal P-gp efflux by erythromycin. A post-marketing commitment was issued to conduct a pharmacokinetic study to evaluate the effect of P-gp inhibitors administered after relugolix to further inform dosing strategy. [b] *In vitro*, the NME was a substrate of P-gp. Inhibition or induction of P-gp may also contribute to the NME exposure change.

RESULTS

NMEs as precipitants

- There were only 10 moderate-to-strong drug interactions involving NMEs as precipitants, and all were related to inhibition, with no strong or moderate inducer of enzymes or transporters identified. Inhibition of CYP3A explained about half of the interactions. A total of seven drugs were involved, with more than half indicated for cancer treatment. All interaction results led to label recommendations to mitigate the risk of DDI in clinical settings.
- Three drugs were considered strong inhibitors of enzymes (victim drug AUCR ≥ 5): cedazuridine for cytidine deaminase, lonafarnib for CYP3A, and tucatinib for CYP3A (Table 2).
- The following drugs were found to be moderate inhibitors: berotralstat (CYP2D6 and CYP3A), capmatinib (CYP1A2 and BCRP), osilodrostat (CYP1A2), and selpercatinib (CYP2C8).
- There were 55 studies showing weak inhibition or induction. Similarly to the substrate studies, only 40% of these interactions were considered clinically relevant. About a third of these weak interactions were mediated by drug transporters, involving P-gp, BCRP, OATP1B1/1B3, OCT2, and MATE1/2-K.

Table 2. Drug interactions with AUC changes ≥ 5-fold, NMEs as precipitants

NME	Therapeutic Class	Substrate	AUCR	Enzyme/Transporter primarily Involved	Label Recommendation
cedazuridine	Anti-neoplastic Agents	decitabine	12.00	cytidine deaminase	avoid co-administration of cedazuridine and decitabine with drugs that are metabolized by cytidine deaminase
lonafarnib	Other	midazolam	7.39	CYP3A	contraindicated with midazolam, lovastatin, simvastatin, and atorvastatin; avoid other sensitive CYP3A substrates, if unavoidable, monitor for adverse reactions and reduce the dose of those sensitive CYP3A substrates; for certain CYP3A substrates where minimal concentration changes may lead to serious or life-threatening toxicities, monitor for adverse reactions and reduce the dose of the CYP3A substrate
tucatinib	Anti-neoplastic Agents	midazolam	5.74	CYP3A	avoid CYP3A substrates where minimal concentration changes may lead to serious or life-threatening toxicities; if unavoidable, reduce dose of the CYP3A substrate

CONCLUSIONS

The present analysis evaluated mechanisms involved in pharmacokinetic-based clinical drug interactions with a focus on those triggering label recommendations that involve drugs approved by the FDA in 2020.

As victims of DDIs:
- Inhibition and induction of CYP3A explained most of all observed clinical interactions.
- Three drugs, avapritinib (CYP3A), lonafarnib (CYP3A), and relugolix (P-gp), were identified to be sensitive substrates.
- Ten drugs were found to be moderate sensitive substrates of CYP2C8, CYP2D6, CYP3A (N = 6), P-gp, and BCRP.

As precipitants of DDIs:
- Three drugs were considered strong inhibitors of enzymes (AUCR ≥ 5): cedazuridine for cytidine deaminase, lonafarnib for CYP3A, and tucatinib for CYP3A.
- No drug showed strong inhibition of transporters.
- Four drugs were found to be moderate inhibitors (AUCRs 2-5) of CYP1A2, CYP2C8, CYP2D6, CYP3A, and BCRP.
- No strong or moderate inducer of enzymes or transporters was identified.

All DDIs with AUC changes ≥ 5-fold and almost all those with AUC changes 2- to 5-fold triggered dosing recommendations in the drugs' labels.

REFERENCES

1. NDA reviews from Drugs@FDA. Website: https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed 2020.