UNDERSTANDING THE ROLE OF CYP3A IN THE METABOLISM OF KINASE INHIBITORS MARKETED IN THE PAST DECADE TO BETTER MANAGE THE RISK OF CLINICAL DRUG-DRUG INTERACTIONS

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Abstract

Kinase inhibitors (KIs) are among the most represented therapeutic areas for novel drugs approved in recent years. In the present analysis, drug metabolism data for all KIs approved in the US since 2011 were reviewed. Mechanistic clinical drug interaction studies with CYP3A perpetrators were fully analyzed using the Drug Interaction Database (DIDB®, https://www.druginteractionsolutions.org/). The mechanism(s) and clinical relevance of these interactions were characterized based on information available in the new drug application reviews. A total of 67 KIs were approved in 2011-2022. *In vitro* data suggest that CYP3A participates in the metabolism of 63 drugs (94%). Among them, 57 drugs had clinical interaction data with strong CYP3A inhibitors and/or inducers indicating a significant contribution of CYP3A in the drugs' metabolism (AUCRs ≥ 1.25 for inhibition studies or ≤ 0.80 for induction studies), 4 drugs had only *in vitro* data, without clinical evaluation, and for 2 drugs, the contribution of CYP3A was minimal (AUCR < 1.25). Among the clinical substrates (N = 57), 11 drugs were identified to be sensitive substrates (AUCRs ≥ 5 co-administered with the strong CYP3A inhibitors itraconazole or ketoconazole), namely ibrutinib (AUCR = 23.93), abemaciclib (AUCR = 15.73), avapritinib (AUCR = 10.66), midostaurin (AUCR = 10.42), bosutinib (AUCR = 8.60), mobocertinib (AUCR = 8.43), infigratinib (AUCR = 7.22), cobimetinib (AUCR = 6.70), entrectinib (AUCR = 6.04), zanubrutinib (AUCR = 5.58), acalabrutinib (AUCR = 5.00). Seventeen drugs were found to be moderate sensitive substrates of CYP3A, with AUCRs of 2-5 when co-administered with a strong CYP3A inhibitor. All drugs were also found to be sensitive to CYP3A induction (AUCRs 0.04-0.44 in the presence of rifampin, a strong CYP3A inducer), except encorafenib, for which the sensitivity to induction had not yet been evaluated (post-marketing commitments). As expected, most of the drugs exhibited higher sensitivity to induction than inhibition possibly due to the contribution of additional enzymes induced by rifampin. Label recommendations were available for all moderate sensitive and sensitive substrates, with recommendations for most drugs to avoid concomitant use with strong CYP3A inhibitors (N = 20, 71%) or strong CYP3A inducers (N = 26, 93%). Interestingly, 19 out of 22 weak sensitive substrates (AUCRs 1.25-2 in the presence of a strong CYP3A inhibitor) also had label recommendations regarding concomitant use with strong CYP3A inhibitors, likely explained by the narrow therapeutic index of KIs. In addition, among the 63 drugs that were metabolized by CYP3A *in vitro*, 49 (78%) were also substrates of P-gp *in vitro*, confirming the significant overlap in substrate specificity. On the other hand, as perpetrators, 15 of the drugs examined also inhibited CYP3A *in vivo*, with ceritinib, idelalisib, ribociblib, and tucatinib being strong inhibitors. Overall, our extensive review of KIs marketed in the past decade confirm the predominant role of CYP3A in the disposition of these drugs. Clinical investigations with marker compounds were critical to understand mechanistically the risk of CYP3A-related drug interactions and develop effective mitigation strategies.

Objectives

- To review pharmacokinetic-based DDI data for all KIs approved in the US from 2011 to 2022, with particular emphasis on mechanistic DDI studies with CYP3A perpetrators
- To understand the mechanisms and clinical relevance of these interactions

Methods

- Certara Drug Interaction Database (DIDB; www.druginteractionsolutions.org) was used to identify relevant DDI data. The mechanism(s) and clinical relevance of the 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.
- 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.

Results

- A total of 67 KIs were approved from 2011 to 2022, and 56 (89%) are oncology drugs (**Figure 1**).
- 63 KIs (94%) had *in vitro* evidence of CYP3A contribution to their metabolism, including 49 drugs (78%) which were also substrates of P-gp *in vitro*.
- 57 of the 63 *in vitro* substrates of CYP3A had clinical drug interaction data with CYP3A strong inhibitors and/or inducers yielding AUCRs ≥ 1.25 for inhibition studies or ≤ 0.80 for induction studies:
  - 11 were identified as CYP3A **sensitive substrates**, with AUCRs ≥ 5 when co-administered with strong CYP3A inhibitors (**Table 1**).
  - 17 were **moderate sensitive substrates** of CYP3A, with AUCRs of 2-5 when co-administered with a strong CYP3A inhibitor.
  - Among the 28 sensitive and moderate sensitive CYP3A substrates, 27 were also evaluated with rifampin, a strong CYP3A inducer, and 21 (78%) showed higher sensitivity to induction than inhibition (**Figure 2**).
- Label recommendations were available for all sensitive and moderate sensitive substrates, but also for 19 out of 22 (86%) **weak sensitive substrates,** which is likely explained by the narrow therapeutic index of KIs.
- When considered as perpetrators, 15 drugs were found to be inhibitors of CYP3A, including 4 being **strong inhibitors** (ceritinib, idelalisib, ribociblib, and tucatinib).

Table 1. KIs identified as CYP3A sensitive substrates

KI	Max AUCR	Inhibitor	Label Recommendation
abemaciclib*	15.73 (PBPK)	ketoconazole	**avoid** ketoconazole; **reduce dose** with other strong and moderate CYP3A inhibitors
acalabrutinib*	5.00	itraconazole	**avoid** strong CYP3A inhibitors; **dose adjustments** may be recommended
avapritinib	10.66 (PBPK)	itraconazole	**avoid** strong CYP3A inhibitors
bosutinib*	8.60	ketoconazole	**avoid** moderate or strong CYP3A inhibitors
cobimetinib*	6.70	itraconazole	**avoid** moderate or strong CYP3A inhibitors
entrectinib	6.04	itraconazole	**avoid** moderate or strong CYP3A inhibitors; **reduce dose** if unavoidable
ibrutinib	23.93	ketoconazole	**modify dose** with CYP3A inhibitors
infigratinib*	7.22	itraconazole	**avoid** moderate or strong CYP3A inhibitors
midostaurin	10.42	ketoconazole	consider **alternative therapies** that do not strongly inhibit CYP3A4; **monitor** for increased risk of adverse reactions
mobocertinib*	8.43	itraconazole	**avoid** strong CYP3A inhibitors
zanubrutinib*	5.58 (PBPK)	ketoconazole	**modify dose** with moderate or strong CYP3A inhibitors

* also a P-gp substrate *in vitro*

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- CYP3A plays a major role in the disposition, metabolizing *in vitro* 63 of the 67 (94%) KIs approved in 2011-2022.
- Nearly 80% of the KIs metabolized by CYP3A were also P-gp substrates *in vitro.*
- Among the 57 KIs identified as clinical substates of CYP3A, 88% have label recommendations related to the co-administration of CYP3A perpetrators.

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Additional Figures

Figure 1. Number of KIs approved from 2011 to 2022 (N = 67, including 56 oncology drugs)

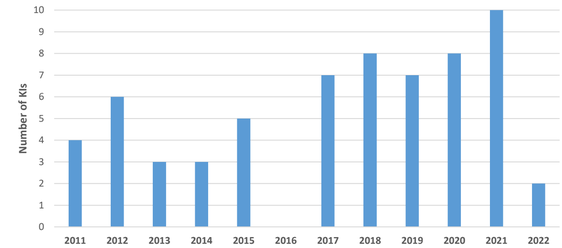

Figure 2. Inhibition and induction results of CYP3A sensitive and moderate sensitive substrates (N = 27)