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Tyrosine Kinase 억제제와의 약물 상호작용이 약물 혈중농도 변화에 따라 부작용 발생에 미치는 영향: 메타분석 연구

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The Impact of Drug Interactions with Tyrosine Kinase Inhibitors on Adverse Event Development based on the changes of drug concentration level: Meta-analysis

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ABSTRACT

Background: Oral cancer drugs, particularly tyrosine kinase inhibitors (TKIs), are increasingly popular due to their convenience. However, they pose challenges like drug interactions, especially with medications like azole antifungals. While the FDA provides some guidance, more detailed information is needed to manage these interactions effectively. A meta-analysis was conducted to understand the impact of interactions between TKIs and azole antifungals on adverse events during clinical studies. **Methods:** A meta-analysis followed PRISMA guidelines. Data from PubMed, EMBASE, and references were searched until November 30, 2021. Inclusion criteria encompassed studies on TKI-antifungal interactions in English. Study selection and quality assessment were conducted by two independent investigators. **Results:** Out of 158 articles, 11 were selected for analysis. Combination therapy showed a slight increase in adverse events but was not statistically significant (OR 1.02, 95% CI 0.49-2.13, p=0.95). AUC and Cmax fold changes did not significantly impact adverse event development. Both itraconazole and ketoconazole showed no significant difference in adverse event development compared to TKI alone. **Conclusions:** Study finds TKI-DDI not significantly linked to AE increase; azole antifungal types not related to AE. Future DDI research crucial for drug development.

KEYWORDS: Antifungal agents, drug interactions, meta-analysis, tyrosine kinase inhibitors

As oral medication constitues 84% of the best-selling pharmaceutical products with an annual growth rate of 10%,[1)] the majority of new drugs treating cancers approved by the US Food and Drug Administration have been oral formulations as opposed to intravenous over the past few years.[2)] Increased use of oral anticancer therapies contributes to the alteration of the traditional hematology and oncology practice based on injectable treatment.[2)] As generally well tolerated drug, tyrosine kinase inhibitors (TKIs) make up large proportion of oral anticancer therapies.[3)] Through catalyzing phosphorylation, TKI is designed to inhibit the corresponding kinase including EGFR, ALK, ROS1, HER2, NTRK, VEGFR, RET, MET, MEK, FGFR, PDGFR, and KIT, which showed significant contribution to progress in cancer treatment.[4)] Although, as a convenient option for appropriate

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patients, TKI is preferably used, some alternative challenges such as significant drug-drug interactions (DDIs) are commonly faced with TKI than with injectable medications.[5] Potential issues for increasing toxicity and reduced efficacy if not managed appropriately, through assessing concomitant medications, real and potential DDIs should be addressed.[2] Although, according to previous study report, over 40% of patients experienced adverse effects caused by DDI with oral cancer therapies such as TKIs, clinical practice only relying on person experience with scarcity of guidance.[6] Still, FDA provides guidance for DDIs in clinical aspects during drug development, which did not provide detailed explanations of DDIs between investigational drugs and concomitant medication based on specific drugs.[7] However, only the guideline indicates sponsors should assess the DDI potential before investigational drug administered with concomitant medications such as antifungal agents to patients. Considering association between drug exposure such as increase of area under the curve (AUC) with CYP450 inhibitors and risk increase in study participants, especially combing with strong CYP450 inhibitors, azole antifungals,[8] sufficient DDI information even with healthy populations is necessary during drug development. Thus, to provide more empirical evidence using highly statistical power, the current study conducted meta-analysis to analyze the impact of DDI between TKIs and azole antifungal agents on developing adverse events based on concentrations such as maximum serum concentration (Cmax) or AUC during clinical studies.

Materials and Methods

A meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[9]

Data Sources and Search Strategy

Literature was searched using PubMed, EMBASE, and references from relevant studies until November 30, 2021. The database search was conducted using the search keywords “tyrosine kinase inhibitor”, “ tyrosine kinase”, “TKI”, “antifungal”, “itraconazole”, “ketoconazole” along with relevant Medical Subject Headings (MeSH) terms and marketed names of TKIs. The search strategy targeted published articles that evaluated the effects of drug interactions between TKIs and itraconazole or ketoconazole on pharmacokinetic/pharmacodynamics (PK/PD) levels and safety and was limited to full-text articles written in English (Supplementary table). In addition, the references of the collected articles and systematic reviews were manually searched to retrieve additional studies. Disagreements between investigators were re-solved through discussion.

Study Selection

The titles and abstracts of the retrieved articles were evaluated by two independent investigators to isolate potentially relevant articles. All randomized controlled trials (RCTs) evaluating PK/PD levels and frequency of adverse events comparing between TKIs with antifungals (referred as combined form) and TKIs alone (referred as single form). were selected. For inclusion, study treatment periods needed to be one week or longer and treatments had to be administered using TKIs and itraconazole (Sporanox®) or ketoconazole (Nizoral®). Also, patients in the finally included studies were healthy participants, and outcomes were limitedly included with AUC, Cmax levels, and number of people showing adverse events. Animal studies, studies with a sample size of fewer than five patients were excluded. Standalone published abstracts were excluded.

Data Extraction and Quality Assessment

Data extracted from the retrieved articles included publication year, type of intervention, type of patients, type of comparison, sample size, age of study population, targets of TKIs, phase of trials, NCT number, AUC,Cmax levels, and number of people showing adverse events.

Assessing the internal validity and quality of collected articles of data extracted was conducted by two investigators. The risk of bias of RCTs was assessed by the tool developed by the Cochrane Collaboration.[10] Confidence levels were evaluated by the effect estimates for each outcome.

Data Synthesis and Analysis

The current study assessed safety issues related to DDI of combined forms compared to single forms. The number of patients experiencing adverse events after using combined forms or single form during the trials. The overall effect size was expressed as odds ratio (OR) with corresponding 95% confidence interval (CI) for comparative studies and each intervention. Subgroup analysis was performed based on the different fold levels of AUC (<3 and ≥3), levels of Cmax (<3 vs ≥3), and types of antifungals. The I^2 statistic was used to evaluate heterogeneity among studies, and the percentile statistics were classified as low (<25%), medium (25-50%), or high (>50%). The

meta-analysis was conducted using Review Manager (RevMan, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study Selection

Through the database searches from PubMed and Embase, 158 potentially eligible articles were identified. After screening and identifying full-text articles, 11 articles[11-21] were finally included in the current analysis (Fig. 1).

Study Description

The characteristics of the included studies are described in Table 1. The total number of participants included in the current analysis was 478. Three studies[12,13,18] included in the current analysis used TKIs targeted at EGFR, and TKIs examined in three studies[13,16,17] were targeted at VEGFR. Eight studies[14,15,21] showed AUC fold change less than 3, and three studies[12,18,19] demonstrated AUC fold change over 3. For the Cmax fold change, 8 studies[11,13-17,20,21] demonstrated fold change less than 3, whereas other studies[12,18,19] showed more than 3 for the Cmax change. As comparators, four studies[11,13,15,18] combined itraconazole with TKIs, and other seven studies[12,14,16,17,19-21] evaluated ketoconazole combined with TKIs.

Overall adverse events development

Eleven studies[11-21] were included in the analysis to report overall differences in adverse events between groups treated by combination and single forms. Based on the comparison, combination form was related to slightly increase of adverse event developments although there was no statistical significance (OR 1.02 , 95% CI 0.49-2.13, p=0.95, Fig. 2), which were shown generally mild or no clinically relevant changes. The heterogeneity of the analysis for evaluating overall adverse event development between combination and single forms was moderately shown (I^2=50%, p=0.03).

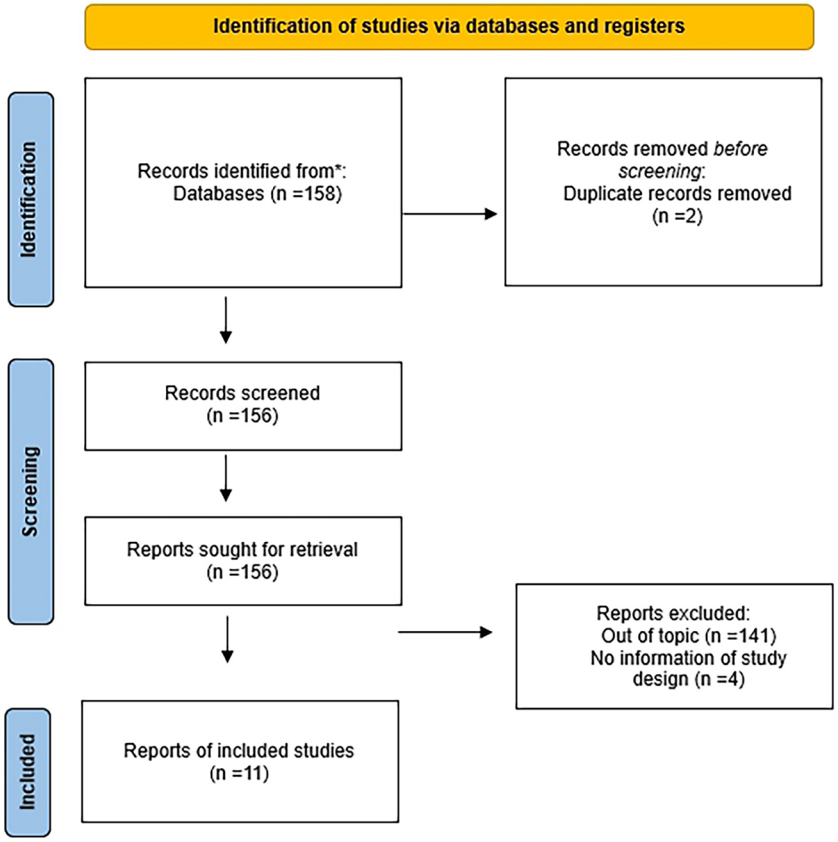

Fig. 1. Flow chart describing systemic research and study selection process

Table 1. Baseline characteristics of included studies

Study name	Study design	Primary targets	Patients number-Safety		Intervention	Control	Fold change	
			Intervention	Control			C_{max}	AUC
Poggesi *et al*. 2019 (11)	RCT	FGFR	17	19	Erdaftinib+Itraconazole	Erdaftinib	1.05	1.34
Abbas *et al.* 2011 (12)	RCT	EGFR	23	22	Neratinib+Ketoconazole	Neratinib	3.63	5.16
Martin *et al.* 2011 (13)	RCT	VEGFR-2/EGFR	15	15	Vandetanib+Itraconazole	Vandetanib	0.99	1.14
Dutreix *et al.* 2004 (14)	RCT	ABL/BCR-ABL/ARG	14	14	Imatinib+Ketoconazole	Imatinib	1.29	1.38
Dymond *et al.* 2017 (15)	Partially randomized	MEK1/2	24	26	Selumetinib+Itraconazole	Selumetinib	1.18	1.49
Pithavala *et al.* 2012 (16)	RCT	VEGFR1-3	29	32	Axitinib+Ketoconazole	Axitinib	1.50	2.06
Shumaker *et al.* 2015 (17)	RCT	VEGFR1-3	18	18	Lenvatinib+Ketoconazole	Lenvatinib	1.21	1.16
Liu *et al.* 2021 (18)	RCT	EGFR-2	18	18	Pyrotinib+Itraconazole	Pyrotinib	3.71	11.12
Sonnichsen *et al.* 2011 (19)	RCT	Src/Abl	24	24	Bosutinib+Ketoconazole	Bosutinib	5.18	8.64
Narasimhan *et al.* 2013 (20)	RCT	BCR/ABL	23	23	Ponatinib+Ketoconazole	Ponatinib	1.46	1.78
Li *et al.* 2018 (21)	RCT	FLT3	31	31	Quizartinib+Ketoconazole	Quizartinib	1.16	1.94

AUC, area under the curve; Cmax, maximum serum concentration; EGFR, Epidermal growth factor receptor FGFR, fibroblast growth factor receptor; MEK, Mitogen-activated protein kinase kinase RCT, randomized clinical trial; VEGFR, Vascular Endothelial Growth Factor;

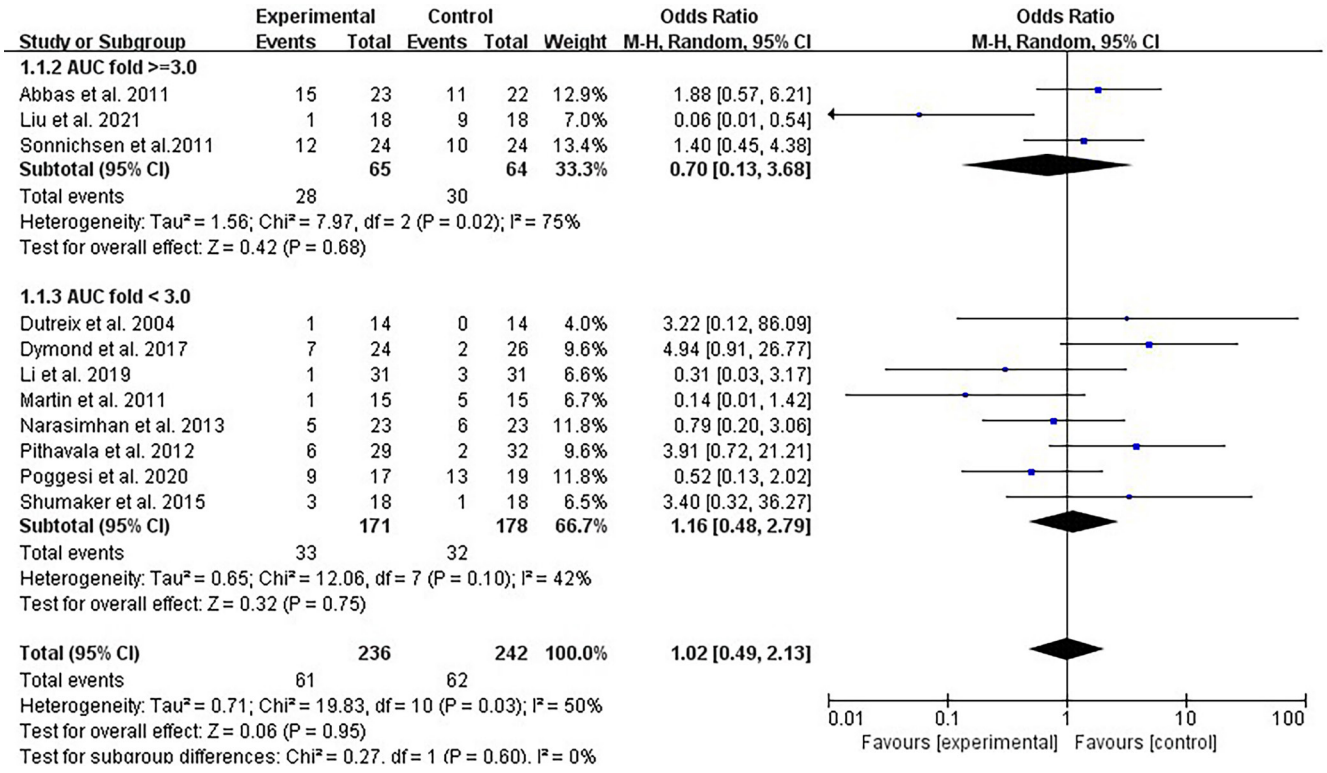

Fig. 2. Comparison of adverse event development based on AUC fold change

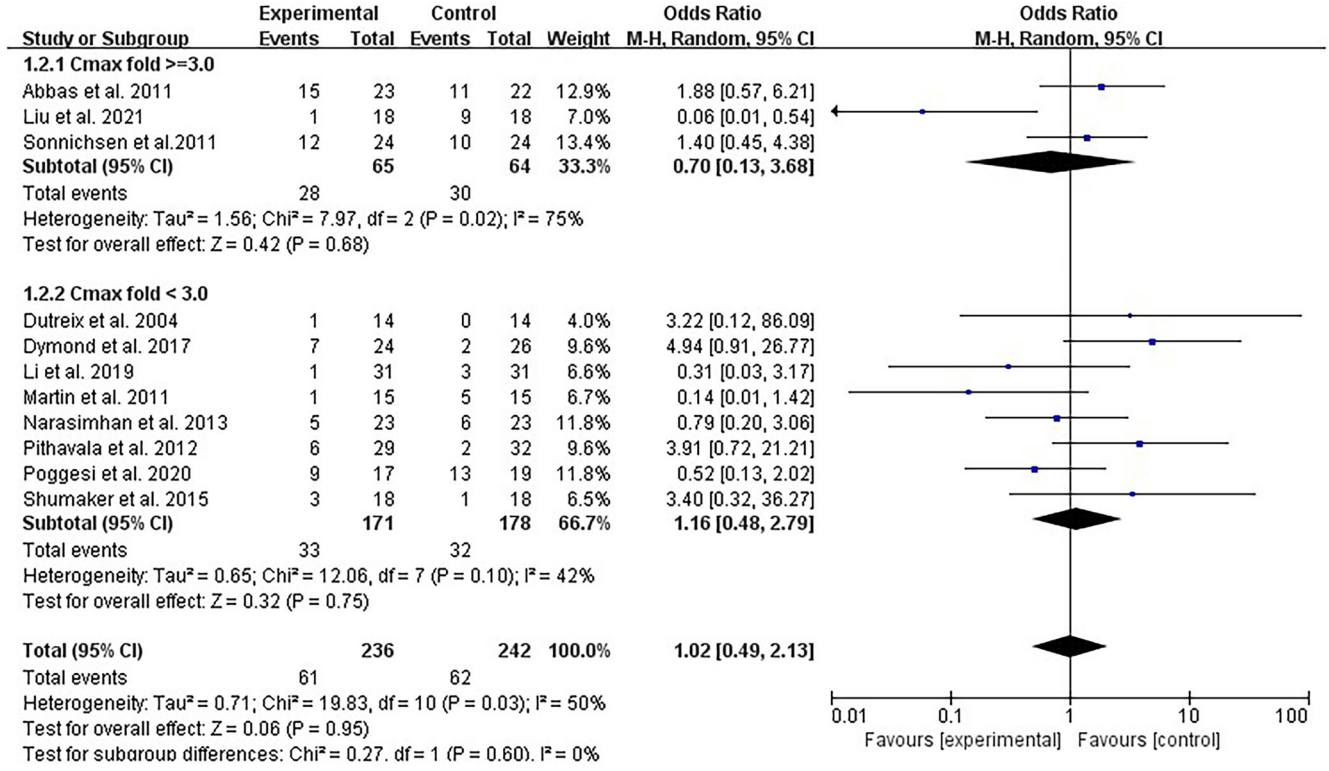

Fig. 3. Comparison of adverse event development based on Cmax fold change

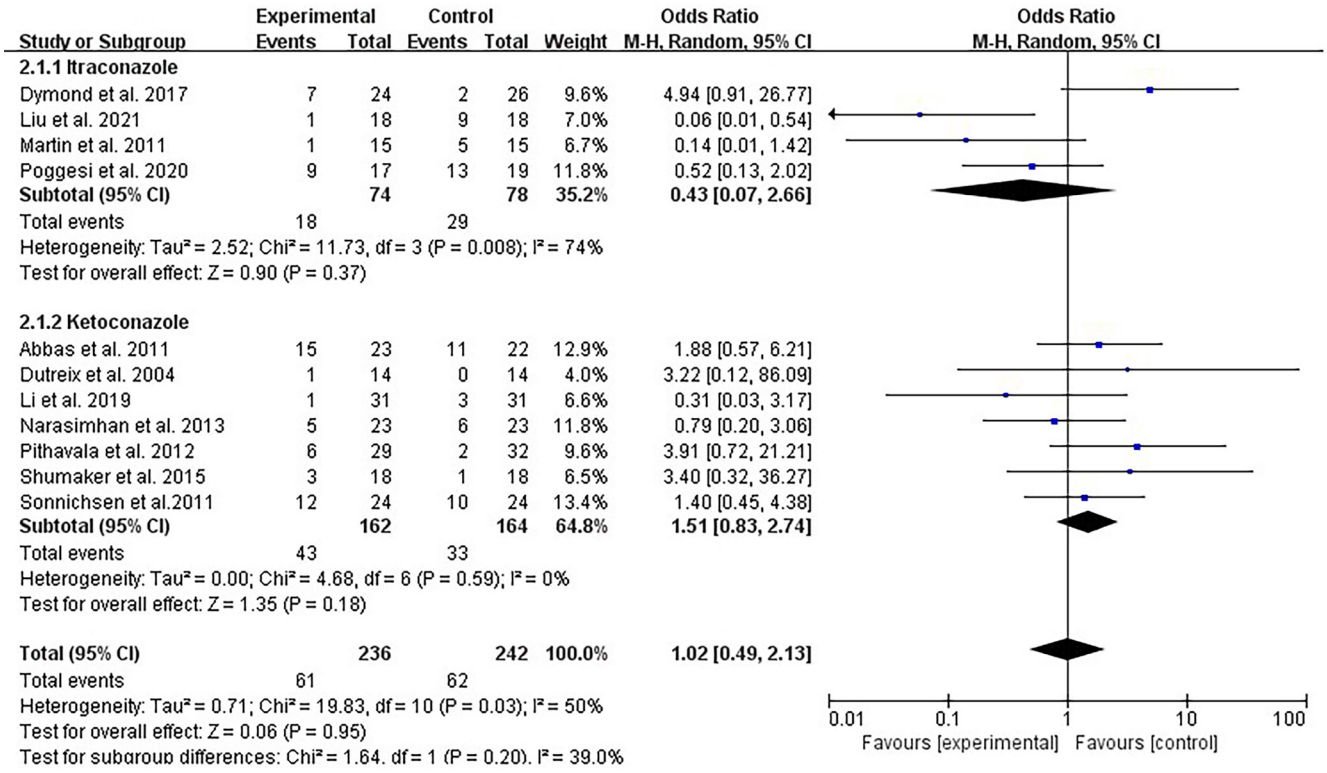

Fig. 4. Comparison of adverse event development based on the types of antifungals

Adverse event development according to AUC fold change levels

Based on the AUC fold change levels, Eight studies[14,15,21] showed AUC fold change less than 3, and three studies[12,18,19] demonstrated AUC fold change over 3For the subgroup analysis with studies showing AUC fold change level over 3, there was not significant increase of adverse events developments in people with combination forms (OR 0.70, 95% CI 0.13-3.68, p=0.68, Fig. 2). Other levels of AUC fold change was not also associated with adverse event development differences between groups dosed by combination and single forms (p>0.05). In addition, there was no significant differences of adverse event developments among subgroups (I^2=0%, p=0.60).

Adverse event development according to Cmax fold change levels

Three studies[12,18,19] were involved in the subgroup showing 3 or more of Cmax fold change whereas, nine studies[11,13-17,20,21] were shown the Cmax fold change less than 3 (Fig. 3). For the subgroup analysis with studies showing Cmax fold change ≥3, there was no significant differences developing adverse events between combination and single form use (OR 0.70, 95% CI 0.13 to 3.68, p=0.68). Consistently, for the subgroup analysis with studies showing Cmax fold change less than 3, adverse event developments were not significantly affected by the types of dosing forms such as combination and single (OR 1.16, 95% CI 0.48 to 2.79, p=0.75).

Adverse event development according to the types of antifungals

In the current analysis, four studies[11,13,15,18] evaluated adverse events comparing TKIs with itraconazole to TKIs alone (Fig. 4). Whereas, antifungals combined in seven studies[12,14,16,17,19-21] were ketoconazole. For studies used with itraconzole as antifungals, adverse event development was not significantly increased in the group of combining TKIs and itraconzole (OR 0.43, 95% CI 0.07 to 2.66, p=0.37). In addition, for the ketoconazole, it was consistently shown that there was no difference of adverse event development between groups used with TKIs and ketoconazole and TKI alone (OR 1.51, 95% CI 0.83 to 2.74, p=0.18).There were no subgroup differences observed based on the discrepancies of antifungals (I^2=39.0%, p=0.20).

Discussion

The current meta-analysis showed that the increase of TKI

exposure combined with azole antifungal agent use was not significantly associated with increase in AE development. In the process of drug development, drug-drug interaction (DDI) studies provide important information related to participants' safety. Unintentional and mismanaged DDIs are a common reason for preventable adverse events. Previously, telaprevir carries a black-box warning for potentially lethal skin reactions, which precluded it use in healthy-volunteer DDI studies.[22] Along with unfortunate incidents such as multiple market withdrawals and the rapid accumulation of scientific knowledge that has improved the understanding of DDI mechanisms and awareness of DDI risks, regulatory agencies have frequently updated their guidances on drug interaction studies. Although these guidances are directed for studies performed for drugs under development, their concepts can be applied to drugs on the market as well. Despites of the importance of current guidances approaches of DDI studies should be more specific according to the individual study combinations. Since clinical DDI studies performed in healthy volunteers are considered as golden standard,[23] insignificant AE developing from combining TKI with azole antifungals such as ketoconazole or itraconazole from our results could provide important safety information for designing the next clinical trials.

Furthermore, even ketoconazole is considered a model drug to evaluate CYP inhibition on the pharmacokinetics of oral drugs metabolized by CYP enzyme, but, based on the results of current study, ketoconazole is not acted as strong inhibitor increasing AUC over 5- fold change as indicated in the current guideline. Furthermore, combining TKI with azole antifungal therapies such as ketoconazole or itraconazole, based on the current outcome, is not significantly related to increment of safety concerns. A study indicated, although intensity of inhibitors of CYP enzymes have been informed to design DDI clinical studies, pharmacological metabolic process should be more specified and focused on inter-individual variability and drug properties.[23] Furthermore, if the index inhibitor inhibits several enzymes and/or transporters, the observed effects on victim drug pharmacokinetics cannot be attributed to a single pathway without further studies.[23] Therefore, not only model drugs evaluating CYP inhibition such as ketoconazole, more clinical DDI studies of TKIs with moderate, weak, and nonselective inhibitors are also needed.

In addition, the current study showed that TKI combination with azole antifungals such as ketoconazole and itraconazole was not significantly associated with AE increments in healthy volunteers. Itraconazole was identified as CYP3A inhibitors that satisfy the requirements for safety, potency, and selectivity, which was considered to indirect representative of the worst-case DDI scenario. Recommendations of FDA limited use of ketoconazole because of the risk of hepatotoxicity, adrenal insufficiency in DDI studies also caused more itraconazole use in DDI studies. However, concerns remain regarding of decreased cardiac contractility[24] and, to clarify victim drugs, at least two-week daily dosing[22] could be the reasons to, still, propose ketoconazole as a model drug of clinical DDI studies.

The current study has several limitations. First, the current study did not include clinical studies with patient populations. However, clinical DDI studies with healthy volunteers are considered as golden standard, based on the current outcome, we expect more future studies evaluating DDI studies with patients. Second, the study did not evaluate other types of anticancer therapies except for TKIs. Although, for evaluating DDI in humans, oral anticancer therapies such as TKIs should be assessed with oral azole antifungals, considering the importance of safety information in DDI studies, we expect more other types of DDI studies will be performed in the future. Finally, In this study, we focused solely on ketoconazole and itraconazole as azole antifungals for drug interaction evaluation. As a recommended alternative antifungal to ketonazole regarding as a model drug in drug interaction study, several previous indicated itraconazole for the best practice.[22,23] Thus, in the current study only included these azole antifungals for evaluation. However, we expect more antifungals will be evaluated in various settings.

Conclusion

The current study showed that the impact of DDI with TKI was not significantly associated with AE increment, and the types of azole antifungals were not related to AE development. To provide more evidence for drug development, various DDI studies in clinical settings should be performed as future studies.

Conflict of Interest

The authors have no conflicts of interest to declare with regards to the contents of this study.

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