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Occurrence of voriconazole-induced cutaneous squamous cell carcinoma in Japan: data mining from different national pharmacovigilance databases

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Long-term voriconazole use may increase the risk of cutaneous squamous cell carcinoma (cSCC), especially in immunocompromised patients. However, relatively little is known regarding voriconazole-induced cSCC in Japan. Thus, the purpose of this study was to evaluate the association between voriconazole use and cSCC in Japan using different national pharmacovigilance databases. First, using the Japanese Adverse Drug Event Report (JADER) database, we evaluated the association between voriconazole use and cSCC in Japan. Second, using the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database, we examined regional differences in the occurrence of voriconazole-induced cSCC between Japan and other countries. We calculated reporting odds ratios (RORs) as disproportionality analysis to evaluate voriconazole-induced cSCC. In this study, cases in which one or more of "Bowen's disease", "Carcinoma in situ of skin", "Keratoacanthoma", "Squamous cell carcinoma in skin", or "Squamous cell carcinoma" were reported as adverse events were considered to be cSCC cases. The analysis based on the JADER database showed an association between voriconazole use and cSCC in Japan, with a ROR (95% confidence interval) of 35.37 (25.60–48.87). Further, the analysis based on the FAERS database revealed that signals were detected in Japan as well as in Western countries and Australia. This study is the first in which the association between voriconazole use and cSCC in Japan is assessed using national pharmacovigilance databases. Healthcare providers need to be fully aware of the potential for cSCC development owing to voriconazole use and in all countries, including Japan, ensure careful follow-up of patients' skin.

1. Introduction

Non-melanoma skin cancer is one of the most prominent cancers in the world, and under this classification, cutaneous squamous cell carcinoma (cSCC) is the second most frequently encountered type (Caudill et al. 2022). In many countries, it has been observed that the incidence of cSCC increases with advancing age (Birch-Johansen et al. 2010; Rogers et al. 2010; Carsin et al. 2011; Hollestein et al. 2012). Additionally, cSCC is the most common type of skin cancer observed after transplantation, with a 65-fold increased incidence in organ transplant recipients (OTRs) relative to the general population (Bangash et al. 2012). The most important risk factor for cSCC is long-term exposure to solar ultraviolet (UV) radiation, which causes genetic and epigenetic alterations in keratinocytes (Park et al. 2020; Riihilä et al. 2021). The incidence rate of skin cancer considerably depends on skin phenotype and geographic variations. It is also well known that the incidence of skin cancer is significantly lower in non-Caucasian OTRs than their Caucasian counterparts (Chung et al. 2017). Thus, it is necessary to consider these factors when interpreting data related to skin cancer.

Voriconazole is a broad-spectrum triazole antifungal agent that is used to treat invasive fungal infections caused by Aspergillus, Candida, Fusarium, and Skedosporium species (Herbrecht et al. 2002). Further, owing to its broad antifungal spectrum, excellent oral bioavailability, and generally acceptable side effect profile, it is also used to prevent deep-seated fungal diseases in patients who have undergone hematopoietic stem cell transplantation (Wingard et al. 2010). However, it has been observed that it is associated with cutaneous toxicity, including photosensitivity, and its long-term use may increase the risk of cSCC, especially in immunocompromised patients (Williams et al. 2014). The mechanism underlying voriconazole-induced carcinogenesis possibly involves a multistep process that begins with acute and chronic phototoxicity, followed by actinic keratosis, and culminates in cSCC (Epaulard et al. 2013); however, the details in this regard are poorly understood. Additionally, the majority of reports on voriconazole-induced cSCC are based on studies conducted in Western countries and Australia (Williams et al. 2014; Epaulard et al. 2013; D'Arcy et al. 2020; Hamandi et al. 2018). Relatively little is known regarding the occurrence of cSCC in Japan. Reportedly, the use of hydrochlorothiazide, which causes photosensitivity like voriconazole, increases the risk of cSCC in Caucasian populations; however, Asians are less susceptible (Pottegård et al. 2019; Park et al. 2020). This could be attributed to the Fitzpatrick skin type III or IV in Asians, which has a relatively high melanin content; therefore, reducing their overall risk of skin cancer, compared with Caucasians. These results suggest that the risk of drug-induced cSCC may vary according to the Fitzpatrick skin type. However, it is still unknown whether this pattern also applies to voriconazole.

Some drug-induced adverse events are rare and may only be detected with prolonged observation. Further, the administration of voriconazole in actual clinical settings is complicated, and unlike clinical trials, in this setting, it is not restricted to a specific patient population. In recent years, as data science has developed, there has been considerable growth in big data research. Here, we aimed to evaluate the association between voriconazole use and cSCC in Japan using different national spontaneous reporting databases. First, we evaluated the association between voriconazole use and cSCC in Japan, using data from the Japanese Adverse Drug

Event Report (JADER) database, a national spontaneous reporting database in Japan. Second, we examined regional differences in the occurrence of voriconazole-induced cSCC between Japan and other countries, using data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database, which includes reports from the United States and many other countries, including Japan.

Table 1: Background data (sex and age) of cases with drug-induced cSCC registered in the JADER database

	Number of cases [%]	
	Voriconazole-induced cSCC (n = 44)	All drug-induced cSCC (n = 282)
Sex		
Male	32 [72.73]	188 [66.67]
Female	10 [22.73]	87 [30.85]
Unknown	2 [4.55]	7 [2.48]
Age		
40–49 years	3 [6.82]	19 [6.74]
50–59 years	5 [11.36]	38 [13.48]
60–69 years	14 [31.82]	86 [30.50]
70–79 years	12 [27.27]	71 [25.18]
≥ 80 years	8 [18.18]	38 [13.48]
Unknown/ others	2 [4.55]	30 [10.64]

Table 2: Background data (sex and age) of cases with voriconazole-induced cSCC registered in the FAERS database

	Number of casess [%] (n = 256)
Sex	
Male	151 [59.98]
Female	58 [22.66]
Unknown	47 [18.36]
Age	
< 10 years	10 [3.91]
10–19 years	31 [12.11]
20–29 years	13 [5.08]
30–39 years	6 [2.34]
40–49 years	24 [9.38]
50–59 years	55 [21.48]
60–69 years	41 [16.02]
70–79 years	11 [4.30]
≥ 80 years	4 [1.56]
Unknown	61 [23.83]

2. Investigations and results

In the JADER database, 282 drug-induced cSCC cases were recorded, and among these, the use of voriconazole was confirmed in 44 cases. Notably, for all these 44 cases, voriconazole was reported to be the suspect drug for cSCC. Further, voriconazole was the only suspect drug in 35 cases (79.55%) and in the nine remaining cases, other suspect drugs were also reported in addition to voriconazole. Specifically, in some cases, the concomitant use of immunosuppressive drugs, including tacrolimus (5 cases) or methotrexate (1 case), was also confirmed. Further, voriconazole-induced cSCC was more frequently reported in males and in patients with ages in the range 60–69 years. We also observed that all the drug-induced cSCC cases showed a very similar distribution pattern (Table 1). Disproportionality analysis based on the JADER database (cases, 44; non-case, 3647) showed an association between voriconazole use and cSCC, with reporting odds ratio (ROR) [95% confidence interval (CI)] of 35.37 [25.60–48.87]. In addition, analysis based on the FAERS database was conducted to examine regional differences in reporting. Particularly, in the FAERS database, there were 256 cases of voriconazole-induced cSCC, reported predominantly in males and in patients with ages in the range 50–59 years (Table 2). The majority of the reports (95 cases, 37.11%) corresponded to North America, followed by Europe (64 cases, 25.00%), Oceania (58 cases, 22.66%), and Asia (39 cases, 15.23%). Our results also indicated that more than three cases of voriconazole-induced cSCC were reported in nine countries (including Japan), and positive signals were detected in all of these nine countries (Table 3). Further, in Malaysia, voriconazole was the suspected drug in all the reported cSCC cases.

Table 3: Signal detection for the association between voriconazole use and cSCC using data from the FAERS database

	Case	Non-case	ROR	95% CI
All	256	9684	42.46	37.40–48.21
North America	95	4412	47.31	38.48–58.16
United States	89	4251	48.12	38.87–59.57
Canada	6	143	37.94	16.58–86.83
Europe	64	2752	14.68	11.41–18.90
France	28	729	19.82	13.39–29.32
United Kingdom	27	710	28.77	19.37–42.74
Spain	3	257	7.49	2.36–23.79
Germany	3	178	7.14	2.27–22.46
Others	3			
Oceania	58	124	190.0	134.5–268.3
Australia	58	122	194.7	137.3–276.2
Asia	39	1802	45.98	32.50–65.04
Malaysia	24	10	18604	1060–326397
Japan	14	1063	27.80	15.89–48.64
Other	1			

CI, confidence interval; ROR, reporting odds ratio.

3. Discussion

In this study, we evaluated the association between voriconazole use and cSCC in Japan, using data from the JADER database, and further examined regional differences in the occurrence of voriconazole-induced cSCC between Japan and other countries using data from the FAERS database. Analysis based on the JADER database showed an association between voriconazole use and cSCC in Japan, and this observation was further corroborated by the results of analysis based on the FAERS data, which revealed three or more cases of voriconazole-induced cSCC in four continents and nine countries, with positive signal detected in all of the nine countries.

In Japan, cSCC is the second most common cutaneous malignancy after basal cell carcinoma. Further, some reports have indicated that in Japan, the age at diagnosis of cSCC is 80–89 years, and that cSCC incidence rates increase with advancing age (Ishii et al. 2013; Umezono et al. 2019). It has also been estimated that the incidence of cSCC by race is 17 to 360 per 100,000 in Caucasians, 2.6 to 2.9 per 100,000 in Asians, and 3 per 100,000 in blacks (Gloster et al. 2006). Furthermore, cSCC is the most frequently observed skin cancer after transplantation, with a 65-fold increased incidence in OTRs relative to the general population (Bangash et al. 2012). Additionally, keratinocyte carcinoma risk factors among OTRs include Caucasian origin (particularly for individuals with Fitzpatrick skin types I–III), residence in regions with high ambient UV

radiation, male sex, advanced age, history of skin cancer, and duration of immunosuppressive drug treatment (D'Arcy et al. 2020). It is also known that the incidence of skin cancer is significantly lower in non-Caucasian OTRs than Caucasian OTRs (Chung et al. 2017).

Long-term voriconazole use increases the risk of cSCC, especially in immunocompromised patients, mainly in Western countries and Australia (Williams et al. 2014; Epaulard et al. 2013; D'Arcy et al. 2020; Hamandi et al. 2018). In recent years, voriconazole-induced cSCC has been reported in Japanese patients (Ng et al. 2017; Sawada et al. 2020). Based on literature review and case reports from their institution, Ng et al. (2017) pointed out the rarity of the occurrence of cSCC in Asian hematopoietic stem cell transplantation recipients as well as the need for close dermatological surveillance of Asian patients on long-term voriconazole therapy; however, this information for Asians, including Japanese, remains limited. In this study, analysis using the JADER and FAERS databases revealed an association between voriconazole use and cSCC in Japan. Additionally, based on the JADER database, voriconazole-induced cSCC was more frequently reported in patients with ages between 60 and 69 years. Given that the overall age at diagnosis of cSCC peaks in the range 80–90 years (Ishii et al. 2013; Umezono et al. 2019), attention should be paid to the development of cSCC at a younger age in voriconazole users. The incidence rate of skin cancer greatly depends on skin phenotype and geographic variations. However, the analysis based on the FAERS database showed no regional differences in the occurrence of voriconazole-induced cSCC, suggesting that some drugs, including voriconazole, may not be affected by the Fitzpatrick skin type.

The mechanism underlying voriconazole-induced carcinogenesis possibly involves a multistep process that begins with acute and chronic phototoxicity, followed by actinic keratosis, and culminates in cSCC (Epaulard et al. 2013). Voriconazole exposure regulates specific cell cycles and terminal differentiation pathways in keratinocytes (Mansh et al. 2017). It has also been observed that voriconazole n-oxide, the major metabolite of voriconazole, facilitates UV-induced DNA damage and inhibits DNA repair (Ikeya et al. 2018). Additionally, voriconazole induces the upregulation of cyclooxygenase 2, which is associated with the aetiology of various tumours, including skin cancers (Ikeya et al. 2018).

This study has several limitations. First, the dose and duration of voriconazole treatment could not be evaluated owing to missing information in many cases recorded in the JADER database. These are important factors to be considered in voriconazole-induced cSCC (D'Arcy et al. 2020). However, many voriconazole-induced cSCC cases recorded in the JADER database were prescribed voriconazole for bronchopulmonary aspergillosis (data not shown). Further, in this study, it was not possible to evaluate the detailed time-to-onset of cSCC. This notwithstanding, it is understandable that voriconazole was used for a long period. Second, it is impossible to calculate the incidence of adverse events in studies that involve the use of a spontaneous report database. Therefore, the impact of voriconazole on cSCC occurrence is unknown. This is a common limitation in many studies in which the spontaneous reporting database is used. Third, unfortunately, no race- or skin phenotype-related information was recorded in the JADER or FAERS databases. Therefore, we calculated RORs by continents or countries to assess geographic variations. Fourth, reports in which regional differences in the occurrence of cSCC were examined using the FAERS database are scarce (Nomura et al. 2015). Thus, further research is needed to validate these results. VigiBase, which is the biggest adverse event report database in the world, is also used to investigate regional differences (Wakao et al. 2019). However, it can only be accessed free of charge by the authorities/national centres (the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan) of WHO international drug monitoring system member countries.

In conclusion, this study is the first in which the association between voriconazole use and cSCC occurrence in Japan is assessed using the national pharmacovigilance databases analysis strategy. Despite the limitations inherent to the databases used, the study revealed an association between voriconazole use and cSCC occurrence in Japan. This implies that in Japan, healthcare providers need to be fully aware of the potential for cSCC development owing to voriconazole use and ensure careful follow-up of patients' skin.

4. Experimental

We conducted a disproportionality analysis using the JADER or FAERS databases. Data from the JADER database were obtained from the PMDA website (https://www.pmda.go.jp/index.html), while data from the FAERS database were obtained using the OpenVigil 2.1 Medical Dictionary for Regulatory Activities (MedDRA) platform (Böhm R et al. 2016). Specifically, in this study, data from the JADER and FAERS databases corresponding to the April 2004 to March 2021 period were used.

Further, the case/non-case method was used to estimate the disproportionality between the expected and reported cases for a given drug of interest or a pharmacological class as a whole and a specific adverse event, according to the data recorded in the specific database (van Puijenbroek et al. 2002). Reports including the adverse events of interest, were considered "cases", while the remainder were considered as "non-cases". Furthermore, in this study, the drug of interest was voriconazole, and the adverse event of interest was cSCC ("Bowen's disease (Preferred terms (PT) code: 10006059", "Carcinoma in situ of the skin (PT code: 10007390)", "Keratoacanthoma (PT code: 10023347)", "Squamous cell carcinoma of skin (PT code: 10041834)", or "Squamous cell carcinoma (PT code: 10041823")) in MedDRA version 24.0. In other words, cases in which one or more of "Bowen's disease", "Carcinoma in situ of skin", "Keratoacanthoma", "Squamous cell carcinoma in skin", or "Squamous cell carcinoma" were reported as adverse events were considered to be cSCC cases. The ROR (van Puijenbroek et al. 2002) was used to evaluate the association between the drug and the adverse event. Additionally, we defined the signals as positive when the lower limit of the 95% CI of the ROR was > 1. It is not possible to calculate ROR values from two-by-two contingency tables that contains zero in one of the columns; therefore, we performed the Haldane-Anscombe 1/2 correction in such cases.

Further, OpenVigil 2.1 has a built-in ability to filter reporter countries, allowing users to limit their analysis to continents or countries according to their interests and also calculate ROR for a limited area, instantly. This function was used to examine regional differences between Japan and other countries with respect to the occurrence of voriconazole-induced cSCC based on FAERS data.

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