

Review Article

Unraveling the Dual Role of Voriconazole as an Antifungal Agent and Precursor to Squamous Cell Carcinoma

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Abstract

Voriconazole, a potent triazole antifungal medication, is extensively used to treat serious fungal infections in immunocompromised patients. Despite its efficacy, recent findings suggest a potential link between long-term voriconazole therapy and the development of squamous cell carcinoma (SCC). This review examines the dual role of voriconazole, emphasizing both its therapeutic benefits and carcinogenic risks. The pharmacodynamics of voriconazole involve the inhibition of ergosterol synthesis, crucial to fungal cell integrity. However, its metabolites, such as voriconazole-N-oxide, have been implicated in phototoxic reactions that lead to DNA damage and tumor formation. This is particularly significant in patients with prolonged drug exposure, such as organ transplant recipients, where increased SCC incidence has been observed. Clinical evidence and molecular studies suggest that voriconazole may disrupt key cellular pathways like the Hedgehog pathway, affecting epidermal differentiation and increasing cancer risk. Given these concerns, the necessity for careful therapeutic monitoring and patient education about potential risks is discussed. Alternative antifungal therapies and protective measures against phototoxic effects are also recommended as strategies to mitigate SCC risk. Future research should focus on understanding the mechanisms of voriconazole-induced carcinogenesis and refining patient management protocols. This review highlights the need for a balanced approach to voriconazole therapy, weighing its antifungal benefits against the risks of adverse dermatological outcomes.

Keywords

Antifungals, Squamous Cell Carcinoma, Voriconazole, Photocarcinogenesis

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1. Introduction

Voriconazole is a triazole antifungal medication known for its broad-spectrum activity against various pathogenic yeasts, dimorphic fungi, and opportunistic molds [1]. Utilized in the prophylaxis and treatment of invasive, life-threatening fungal infections in immunocompromised patients, voriconazole distinguishes itself from fluconazole with enhanced efficacy against *Aspergillus* spp., *Fusarium* spp., and *Scedosporium apiospermum* [1]. However, voriconazole's therapeutic efficacy faces significant interpatient variability stemming from factors such as age, genetics, and drug interactions, attributable to its nonlinear pharmacokinetics and extensive hepatic metabolism via the cytochrome P450 system (CYP) [2]. The drug's narrow therapeutic window necessitates vigilant therapeutic drug monitoring to optimize clinical efficacy while minimizing the risk of adverse effects, particularly when serum levels exceed 3-5 times the minimum threshold required for efficacy [2]. Moreover, long-term voriconazole treatment is associated with skin toxicity, prompting further investigation into its potential role in cutaneous malignancies [3].

With a globally rising incidence, squamous cell carcinoma (SCC) ranks as the second most prevalent cutaneous malignancy in the United States, following basal cell carcinoma (BCC) [4]. Cutaneous squamous cell carcinoma (cSCC) commonly presents as an erythematous, crusty, or scaly lesion on sun-exposed areas of the skin [4]. The primary risk factors associated with the development of SCC include prolonged exposure to ultraviolet (UV) radiation, genetic predisposition, and, more recently recognized, immunosuppression [5]. Additionally, cutaneous trauma and infections, including human papilloma virus (HPV), contribute to its pathogenesis [6]. While most cSCC lesions are manageable with excision, advanced cases exhibit a poor prognosis, with a 5-year survival rate below 40% [6]. The risk of metastasis for SCC is generally low; however, it increases in immunosuppressed patients such as organ transplant recipients [6]. These findings emphasize the importance of closely monitoring individuals undergoing prolonged voriconazole therapy, particularly those with compromised immune systems, for the occurrence of squamous cell carcinoma.

The interaction between voriconazole use and the development of cSCC presents a distinct clinical challenge, particularly among immunocompromised patients receiving prolonged therapy. Cases of cSCC emerging subsequent to photosensitivity reactions have been documented in recipients of stem cell or solid organ transplants undergoing voriconazole therapy for over 12 months [3]. Moreover, a case-control study among lung transplant recipients identified prolonged voriconazole use and residence in regions with increased exposure to UV light as independent risk factors for SCC development, highlighting the complex interplay between drug exposure and environmental factors [3]. Despite this recognition, the precise mechanism underlying voriconazole-induced cSCC remains elusive, necessitating further

research to inform clinical practice and ensure patient safety.

Given the rising global incidence of cSCC and the widespread utilization of voriconazole, elucidating their association and its implications for at-risk patients is paramount. Therefore, this review aims to synthesize existing literature concerning voriconazole's link to the development of cutaneous squamous cell carcinoma, providing insights into associated risks, molecular mechanisms, and best management practices. This effort seeks to enhance clinical care and ensure patient safety in this vulnerable population.

2. Materials and Methods

This narrative review was conducted using a search of databases such as PubMed, Google Scholar, and Web of Science, focusing on the pharmacodynamics of voriconazole, its association with SCC, and related clinical strategies. The search included terms such as "voriconazole," "squamous cell carcinoma," "immunosuppression," "antifungal therapy," and "drug-induced carcinogenesis." Inclusion criteria were based on the relevance to voriconazole's effects and SCC linkage. Articles discussing long-term effects, molecular mechanisms, and adverse outcomes associated with voriconazole were included. Data extraction was performed independently by two reviewers, focusing on duration of drug use, adverse effects, and outcomes related to SCC, with any discrepancies resolved through discussion.

3. Pharmacological Profile of Voriconazole

Voriconazole is a triazole antifungal agent, whose mechanism of action revolves around the inhibition of fungal ergosterol biosynthesis. Specifically, this antifungal decreases ergosterol through the inhibition of 14- α -lanosterol demethylation [7]. Ergosterol is a central component of the fungal cell wall, providing an ideal target for treatment of infection. The structure of voriconazole resembles that of fluconazole, however, the difference in structure is the substitution of a fluoropyrimidine group for the triazole moiety seen in fluconazole [7]. Though structurally similar to fluconazole, the spectrum of activity of voriconazole more closely resembles that of another antifungal, itraconazole [7]. Voriconazole has a broad spectrum of activity, making it an ideal medication for many yeasts and molds, including but not limited to *Aspergillus*, *Candida* and *Cryptococcus* [8, 9].

The pharmacokinetics of voriconazole are unique in that it has a saturable, nonlinear metabolism thought to be directly related to its metabolic clearance [7, 10]. Voriconazole has a good oral bioavailability at greater than 96% with maximum concentrations at one to two hours after dosing [11]. The

pharmacokinetics of voriconazole are heavily influenced by the cytochrome P450 enzymes, primarily by the CYP2C19 genotype with CYP2C9 and CYP3A4 also playing a role [7, 11]. However, this mostly poses significant difficulties in patients who are CYP2C19 poor metabolizers with highest risk in individuals of Asian descent [7]. Voriconazole's narrow therapeutic window makes clinical monitoring highly important when caring for patients on this medication, especially those with challenges in metabolism [12].

4. Voriconazole's Impact on Cellular Processes

Voriconazole has historically been studied for its impact on fungal inhibition, but more recent studies have worked to isolate its role in carcinogenesis. Voriconazole's role in cell cycle regulation and terminal differentiation is unique in comparison to other azole therapeutic agents [13]. This antifungal also has been shown to upregulate genes directly involved in cell division including those involved in chromosome condensation, DNA replication and checkpoint control [13]. In contrast, voriconazole down-regulates genes involved in terminal epithelial differentiation and protease inhibitor activity [13]. This impact on inhibiting terminal differentiation pathways has been shown to impact formation of granular and corneal epithelial layers, which are important for photo-protection [13]. Such findings underscore the complexity of voriconazole's action on cellular processes, primarily influenced by its distinctive structural composition.

A pivotal aspect of voriconazole's mechanism of action is its regulation of the FOXM1 tumorigenesis pathway, a critical factor in cell proliferation and commonly overexpressed in many epithelial cancers [13]. The emergent understanding of voriconazole's influence on carcinogenesis, drives the exploration into its potential implications for the development of cancers such as squamous cell carcinoma.

5. Linking Voriconazole to SCC

Squamous cell carcinoma arises from the uncontrolled growth of squamous cells in the epidermis and, though highly treatable when identified early, can metastasize and become fatal [6]. Notably, among its risk factors, immunosuppression stands out [5]. Recent epidemiological research has revealed a striking link between the prolonged use of voriconazole, a widely prescribed antifungal for immunocompromised individuals, and an increased likelihood of developing SCC [14, 15]. Specifically, an increased incidence of SCC has been documented among patients receiving extended voriconazole therapy, particularly those with lung conditions or hematologic malignancies [15-17]. Hamandi et al. conducted a retrospective study revealing that voriconazole treatment raises the risk of SCC development by 2.39 times compared to those unexposed to azole medi-

cations [16]. Additionally, Singer et al. identified a dose-dependent relationship between voriconazole use and SCC risk, with a noted increased of 5.6% for each 60-day interval of exposure at standard dosage, culminating in a 28% absolute risk increase for SCC five years post-transplant [14]. These findings indicate that prolonged voriconazole use is positively correlated with the risk of SCC, underscoring the importance of careful monitoring during long-term voriconazole treatment [15].

5.1. Photocarcinogenesis as a Key Mechanism

Photocarcinogenesis emerges as a primary molecular mechanism behind voriconazole-induced SCC. The interaction between voriconazole metabolites, such as voriconazole-N-oxide (VNO), which constitutes 72% of the drug's circulating metabolites in plasma, and UV-A-generated reactive oxygen species leads to significant epidermal DNA damage [18, 19]. Therefore, it is hypothesized that a greater accumulation of VNO could lead to increased voriconazole-associated cSCC [20]. Additionally, voriconazole activates the aryl hydrocarbon receptor (AhR) and upregulates COX-2 enzyme levels, which are crucial in the development of UV-related tumors. This carcinogenic process is thought to be initiated by voriconazole metabolite-induced photosensitivity or phototoxicity, with tumor progression potentially driven by the activation of the aryl hydrocarbon receptor nuclear translocator (ARNT) gene by AhR, or by immune dysregulation [18, 21, 22].

Interestingly, other antifungals within the same class, such as itraconazole and posaconazole, have been identified as inhibitors of the Hedgehog (Hh) signaling pathway [23, 24]. The Hh pathway is essential for regulating the proliferation and differentiation of adult stem cells, and its dysregulation has been linked to tumorigenesis, particularly in the case of BCC. However, recent studies, including a review of over 13,000 immunocompromised patients, indicate that long-term voriconazole use increases the risk of SCC, while no association has been observed with the development of BCC [15, 17].

Table 1. Comparison of Antifungal Agents.

Antifungal	SCC Risk	Mechanism of Action
Voriconazole	High	Inhibits ergosterol biosynthesis
Itraconazole	Lower	Inhibits Hh signaling pathway
Posaconazole	Lower	Inhibits Hh signaling pathway

5.2. Epidemiological Evidence

The occurrence of cutaneous SCC after voriconazole therapy has been well documented in immunocompromised patients. Recent meta-analyses and systematic reviews have

revealed an increased risk of SCC linked to voriconazole administration, particularly in recipients of lung or hematopoietic cell transplant, with prolonged exposure exacerbating this risk [15, 17]. Importantly, this association extends beyond immunocompromised individuals to include immunocompetent patients.

In a case presentation from 2022, a 42-year-old male presented with an exophytic, non-tender preauricular mass. Voriconazole was the only reported medication, taken daily for six years for pulmonary aspergillosis. Notably, he presented with eosinophilia, accelerated graying of hair, and diffuse actinic skin changes. Following wide local excision of the cSCC, voriconazole was discontinued, resulting in resolution of actinic skin changes and eosinophilia within the following three months [25]. Furthermore, a retrospective review also highlighted the susceptibility of pediatric patients to cutaneous malignancies associated with voriconazole treatment [26]. Among the 430 pediatric patients analyzed, all experienced a phototoxic reaction during voriconazole treatment, while four developed non-melanoma skin cancer [26]. Consistent with previous reports, cSCC has been observed in children aged 9-15 years old following 30-60 months of voriconazole therapy [27, 28]. These findings underscore the considerable risks associated with voriconazole therapy, particularly pronounced among immunosuppressed individuals. However, children and immunocompetent individuals are also susceptible to these adverse effects. In this section, authors are advised to provide a thorough analysis of the results and make comparisons with relevant literature, not a short summary or conclusion. Any future research directions could also be stated in the discussion.

5.3. Clinical Manifestations

Adverse dermatological reactions are observed in fewer than 10% of patients undergoing treatment with voriconazole [29]. These reactions are typically characterized by a sunburn-like response, leading to mild and non-tender skin rashes. However, in rare cases, severe conditions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis have been linked to the use of voriconazole [29]. Distinctively, voriconazole can induce photosensitivity reactions not commonly seen with other antifungals. These reactions can manifest as facial erythema, hyperpigmentation of the hands, exfoliative dermatitis, discoid lupus erythematosus, and pseudoporphyria [30, 31]. The photosensitivity associated with voriconazole has led to its identification as an independent risk factor for cutaneous malignancy, particularly in immunocompromised patients. In such cases, voriconazole-induced skin cancer has been reported to develop as soon as six months after initiation [26].

Cases of voriconazole-induced SCC have been associated with elevated serum eosinophil levels and have shown complete resolution upon discontinuation of the drug [32, 33].

This suggests a link between eosinophil levels and the drug's phototoxic effects. Therefore, monitoring eosinophil levels in patients receiving voriconazole therapy may serve as a potential approach to identify and mitigate risk. Moreover, research over the last decade has identified voriconazole-associated cSCC as not only more aggressive and multifocal compared to non-voriconazole-related cases, but also associated with a poorer prognosis [26, 28, 34, 35, 36]. This highlights the importance of cautious monitoring and management in this patient population.

6. Managing Voriconazole-Induced SCC

Management approaches for voriconazole-induced SCC typically involve a combination of surveillance, treatment, and preventive measures. These include early detection, prompt evaluation of suspicious lesions, modification or discontinuation of voriconazole, and early treatment of SCC itself such as surgical excision, topical treatment with imiquimod or 5-fluorouracil, photodynamic therapy, radiation therapy or systemic therapy as needed. Dermatologic evaluations should be performed at regular intervals, with a focus on early detection of SCC or precursor lesions such as actinic keratoses. Any new or changing skin lesions should be promptly evaluated by a dermatologist, and biopsies may be necessary to confirm the diagnosis of SCC or other skin malignancies. In cases where voriconazole-induced SCC is suspected or confirmed, the decision to discontinue or modify voriconazole therapy should be made in consultation with infectious disease specialists and oncologists. Alternative antifungal agents, such as itraconazole or posaconazole, may be considered based on the patient's clinical condition and the risk-benefit profile of continued voriconazole therapy. Previous studies have shown itraconazole to be highly effective for fungal prophylaxis in lung transplant recipients [44]. However, while some studies have shown similar efficacy when comparing voriconazole to itraconazole for antifungal prophylaxis and treatment options, others have argued that voriconazole is more efficacious [45, 46, 47]. Notably, neither itraconazole nor posaconazole was associated with risk of SCC [48]. However, both were linked to basal cell carcinoma risk, though the association did not strengthen with cumulative use [17]. Given the considerations surrounding voriconazole's risks and benefits, it is paramount for healthcare providers to carefully weigh the individual patient's risk of developing SCC against the need for effective antifungal prophylaxis, ensuring a personalized approach to their treatment plan. Moreover, patients with a history of voriconazole-induced SCC require long-term follow-up care, including regular dermatologic evaluations and surveillance for recurrence or development of new skin lesions. Close monitoring is essential due to the potential for recurrence and the increased risk of subsequent skin malignancies in these patients.

Diagnosing and managing voriconazole-induced cutaneous

SCC presents several challenges in immunocompromised patients where these reactions can mimic other conditions like graft-versus-host-disease [27]. Additionally, the early age of onset and brief duration of immunosuppression before skin cancer development in voriconazole-treated patients deviate from typical SCC incidence patterns after immunosuppression, making diagnosis more complex [27]. A recent case report illustrated this complexity, detailing a patient on voriconazole therapy who presented with a hyperkeratotic lesion initially diagnosed as actinic keratosis [37]. However, histological examination revealed vascular invasive SCC, occurring just one year after initiating voriconazole therapy. While clinical and dermoscopic findings may suggest cSCC, histopathological examination remains the gold standard, underscoring the importance of timely biopsy for appropriate management decisions. Managing voriconazole-induced cSCC poses further challenges, as clinicians must weigh the risk of fungal exacerbation against malignancy development. Additionally, ensuring patient adherence to strict photoprotective measures and periodically reassessing the need for long-term voriconazole use adds to management challenges. Collaborative efforts across specialties are crucial to address these challenges effectively and ensure optimal patient outcomes.

6.1. Genetic Factors Influencing SCC Risk

Genetic factors, alongside immunosuppression, contribute to the development of cutaneous SCC. Specifically, variations in CYP enzymes play a significant role. Individuals with homozygous polymorphisms in the CYP2C19 gene exhibit poor metabolism of voriconazole, resulting in serum levels two to five times higher than those observed in individuals without this polymorphism [38]. This effect is more prevalent in Asian populations, where 20-30% are homozygous poor metabolizers, in contrast to 2-3% in white populations [38]. This indicates a potentially higher risk of voriconazole toxicity among Asian populations.

More recent studies have focused specifically on the role of the CYP2C19 *17 allele, associated with ultra-rapid metabolism. Individuals carrying this allele exhibit a 74% increased risk for SCC, likely due to elevated concentrations of voriconazole's metabolite, VNO [20]. Interestingly, the *17 allele of CYP2C1 is more common in Europeans and Africans, but rare in Asians. These results suggest that, in the context of voriconazole treatment, carriers of the *17 allele might face an increased risk of SCC. Together, these underscore the critical role of CYP2C19 genetic variations in influencing the outcomes of voriconazole treatment, including the potential for toxicity and the risk of developing cSCC [39]. Given these insights, genetic screening for the CYP2C19 genotype emerges as a valuable tool in assessing patient suitability and risk associated with voriconazole therapy.

Table 2. Risk Factors for SCC in Voriconazole-Treated Patients.

Risk Factor	Description
Genetic Predisposition	Variations in CYP2C19 affecting metabolism; CYP2C19 *17 allele linked to higher SCC risk
Treatment Duration	Longer duration increases SCC risk, especially notable in transplant recipients
UV Exposure	Living in regions with higher UV exposure adds to the SCC risk when using voriconazole

6.2. Considerations for Patient Selection

Furthermore, certain non-modifiable risk factors, such as fair skin, male sex, and advanced age, necessitate careful consideration in patient selection, particularly in the post-transplant setting where the risk of SCC is already elevated. Additionally, biomarkers associated with voriconazole toxicity can provide insights into an individual's risk profile for SCC. For instance, Hoenig et al. highlighted the association between body mass index (BMI) and toxic plasma concentrations of voriconazole, proposing dosing adjustments based on ideal or adjusted body weight to mitigate risk [40]. Moreover, chronic inflammation has been implicated in predisposing individuals to tumorigenesis, with evidence suggesting that voriconazole metabolism may be impaired in inflammatory states, thereby increasing drug exposure and potential toxicity [41, 42]. In light of these insights, a comprehensive assessment that includes genetic screening, evaluation of non-modifiable risk factors, and consideration of biomarkers for voriconazole toxicity is essential for optimizing patient outcomes.

6.3. Surveillance Strategies for Voriconazole-Treated Patients

Surveillance strategies for voriconazole-treated patients are essential to monitor for potential side effects and complications associated with both voriconazole therapy and its association with the development of squamous cell carcinoma. A comprehensive approach involves several key aspects, including regular follow-up, routine monitoring for side effects, ophthalmologic monitoring, liver function examination, renal function examination, educational resources, communication, multidisciplinary collaboration, patient counseling, and adherence monitoring.

Patients treated with voriconazole should undergo regular follow-up appointments with their healthcare provider, including dermatologists and oncologists, as early detection of squamous cell carcinoma is key. Monitoring for drug-related side effects is crucial as well, as voriconazole can induce a plethora of side effects including visual disturbances, hepatotoxicity, neurotoxicity, and skin reactions. Patients need to be educated about these potential side effects and instructed to report any new or worsening symptoms promptly. Since

voriconazole is known for ocular side effects like visual disturbances, photopsia, and changes in color vision, ophthalmologic evaluations, including visual acuity testing and fundoscopic examination, are recommended, especially for patients on long-term voriconazole therapy. Further research is warranted to identify if these ophthalmological effects are related to squamous cell carcinoma of the eyelid, as SCC has been identified as the second most common eyelid malignancy [43].

Additionally, the regular monitoring of liver function tests is crucial due to the risk of hepatotoxicity associated with voriconazole therapy. Elevated liver enzymes may necessitate dose adjustments or discontinuation of the drug. Although renal toxicity is less common with voriconazole, periodic monitoring of renal function is important, especially in patients with pre-existing renal impairment or those receiving concomitant nephrotoxic medications.

Education on sun avoidance and sun-protective measures is imperative for patients on photosensitizing medication like voriconazole. However, studies have highlighted a concerning gap in patient education and referral to dermatology. Several studies have shown that only about one-quarter of patients who experienced phototoxic reactions were informed about sun protection, and even fewer received dermatology referrals [26]. This oversight is particularly concerning for patients with fair skin or undergoing prolonged immunosuppression, who are at higher risk for cutaneous malignancies. Early dermatological intervention is crucial to identify and manage any adverse skin reactions associated with voriconazole use. Thus, enhancing patient education and implementing surveillance strategies are vital aspects of patient care for those receiving voriconazole treatment. Patients receiving voriconazole therapy should be educated about the importance of sun protection measures, including the use of broad-spectrum sunscreen, protective clothing, and avoiding excessive sun exposure. Minimizing UV radiation exposure can help reduce the risk of developing SCC and may also prevent worsening of existing lesions. Additionally, patients should receive educational materials about the signs and symptoms of squamous cell carcinoma risk, potential drug side effects, and the importance of adherence to treatment and follow-up appointments in regular visits to their dermatologist.

While voriconazole effectively decreases morbidity and mortality of fungal infections, its association with accelerated SCC should not be understated and warrants further investigation to identify population-level risk, improve the availability of data, and investigated causal mechanisms behind this association [49]. Close communication and collaboration between the patient's oncologist, dermatologist, infectious disease specialist, and primary care provider are essential for comprehensive care and early detection of complications. Implementing these surveillance strategies enables healthcare providers to effectively monitor voriconazole-treated patients with squamous cell carcinoma, detect potential complications early, and optimize patient outcomes.

7. Future Directions

Future research efforts exploring voriconazole-induced squamous cell carcinoma necessitates a multidimensional approach to unravel the multifaceted interactions that predispose immunocompromised patients to this malignancy. A priority lies in conducting comprehensive molecular studies aimed at uncovering the specific mechanisms through which voriconazole influences cellular pathways and DNA repair mechanisms, potentially precipitating carcinogenic processes. Such studies are essential for understanding the direct impact of voriconazole at the molecular level and its contribution to the pathogenesis of SCC.

Concurrently, there is an imperative need for extensive epidemiological research to more accurately quantify the risk associated with voriconazole therapy. These studies should consider a wide range of variables, including the dosage and duration of voriconazole treatment, genetic predispositions of the individuals, and environmental factors like UV radiation exposure. A nuanced understanding of these variables will greatly enhance our ability to predict and manage the risk of SCC in patients undergoing voriconazole therapy.

In addition to molecular and epidemiological research, the exploration of alternative antifungal treatments that pose a lower risk of SCC while effectively combating fungal pathogens is crucial. This includes the development of novel antifungal agents or the modification of existing medications to reduce phototoxic effects without sacrificing their antifungal efficacy. Comparative studies focusing on the SCC risk between voriconazole and other antifungal agents will be instrumental in guiding clinical practice towards safer therapeutic options.

Advancements in genetic screening for susceptibility to voriconazole-induced toxicity could facilitate a more individualized approach to antifungal therapy, particularly for at-risk demographic groups such as middle-aged to elderly males, who are also predisposed to chronic pulmonary aspergillosis. This tailored strategy could significantly reduce the incidence of SCC among patients requiring antifungal treatment.

Furthermore, the efficacy of preventive measures, including rigorous photoprotection and regular dermatological screenings, in minimizing the risk of SCC in voriconazole-treated patients warrants thorough investigation. Such strategies could prove to be effective in mitigating the development of SCC, emphasizing the importance of proactive measures in patient care.

Lastly, longitudinal cohort studies assessing the incidence and risk factors for voriconazole-induced SCC are essential for a comprehensive understanding of the implications of voriconazole therapy. Evaluating the time of onset of SCC during or after voriconazole therapy, along with an in-depth examination of risk factors such as skin type, previous skin cancer diagnoses, and race, will provide critical insights. These studies are vital for developing safe treatment protocols and timelines for voriconazole therapy, thereby optimizing patient outcomes while minimizing the risk of SCC. Through

a concerted effort in these research domains, the medical community can strive towards a more informed and safer use of voriconazole in vulnerable patient populations.

8. Conclusion

Voriconazole, a widely used antifungal agent, has been shown to be associated with an increased risk of developing cSCC. This link between the antifungal agent and the development of cSCC presents a significant challenge in clinical practice. Genetic factors and molecular mechanisms shown to modulate the progression of voriconazole-induced cSCC include upregulation of cellular pathways involved in tumorigenesis, phototoxicity, and genetic polymorphisms of CYP2C19 enzymes, however the exact pathogenesis remains unclear.

The complexity of diagnosing and managing voriconazole-induced cSCC emphasizes the need for multidisciplinary collaboration and regular dermatological surveillance in patients receiving both short-term and prolonged voriconazole therapy. Regular follow-up, monitoring for drug-related side effects, and patient education on sun protection can mitigate the long-term effects of voriconazole use. Dermatologic surveillance strategies for voriconazole-induced cSCC may involve early detection through prompt evaluation of suspicious lesions, modification or discontinuation of voriconazole, and adjustment of treatment modalities based on patient response to therapy.

Further research focused on the pathogenesis of voriconazole-induced SCC, biomarkers for predicting SCC risk, and the development of alternative antifungal agents with lower carcinogenic potential will provide further insights to guide patient care. By addressing these research gaps and utilizing a multidisciplinary approach to care, therapeutic management can be optimized and the risk of voriconazole-induced cSCC development mitigated, ultimately improving outcomes for patients requiring antifungal therapy.

Abbreviations

SCC	Squamous Cell Carcinoma
cSCC	Cutaneous Squamous Cell Carcinoma
BCC	Basal Cell Carcinoma
UV	Ultraviolet
CYP	Cytochrome P450
AhR	Aryl Hydrocarbon Receptor
Hh	Hedgehog

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Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Herbrecht, R. (2004). Voriconazole: therapeutic review of a new azole antifungal. Expert review of anti-infective therapy, 2(4), 485–497. <https://doi.org/10.1586/14787210.2.4.485>
- [2] Mikulska, M., Novelli, A., Aversa, F., Cesaro, S., de Rosa, F. G., Girmenia, C., Micozzi, A., Sanguinetti, M., & Viscoli, C. (2012). Voriconazole in clinical practice. Journal of chemotherapy (Florence, Italy), 24(6), 311–327. <https://doi.org/10.1179/1973947812Y.0000000051>
- [3] Clancy, C. J., & M. Hong Nguyen. (2011). Long-Term Voriconazole and Skin Cancer: Is There Cause for Concern? Current Infectious Disease Reports, 13(6), 536–543. <https://doi.org/10.1007/s11908-011-0220-x>

- [4] Combalia, A., Carrera, C. (2020). Squamous Cell Carcinoma: An Update on Diagnosis and Treatment. *Dermatology practical & conceptual*, 10(3), e2020066. <https://doi.org/10.5826/dpc.1003a66>
- [5] Waldman, A., & Schmults, C. (2019). Cutaneous Squamous Cell Carcinoma. *Hematology/oncology clinics of North America*, 33(1), 1–12. <https://doi.org/10.1016/j.hoc.2018.08.001>
- [6] Howell, JY, Ramsey, ML. Squamous Cell Skin Cancer. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441939/>
- [7] Greer N. D. (2003). Voriconazole: the newest triazole anti-fungal agent. *Proceedings (Baylor University. Medical Center)*, 16(2), 241–248. <https://doi.org/10.1080/08998280.2003.11927910>
- [8] Cecil, J. A., & Wenzel, R. P. (2009). Voriconazole: a broad-spectrum triazole for the treatment of invasive fungal infections. *Expert review of hematology*, 2(3), 237–254. <https://doi.org/10.1586/ehm.09.13>
- [9] Theuretzbacher, U., Ihle, F., & Derendorf, H. (2006). Pharmacokinetic/pharmacodynamic profile of voriconazole. *Clinical pharmacokinetics*, 45, 649–663. <https://doi.org/10.2165/00003088-200645070-00002>
- [10] Schulz, J., Kluwe, F., Mikus, G., Michelet, R., & Kloft, C. (2019). Novel insights into the complex pharmacokinetics of voriconazole: a review of its metabolism. *Drug Metabolism Reviews*, 51(3), 247–265. <https://doi.org/10.1080/03602532.2019.1632888>
- [11] Geist, M. J., Egerer, G., Burhenne, J., Riedel, K. D., Weiss, J., & Mikus, G. (2013). Steady-state pharmacokinetics and metabolism of voriconazole in patients. *The Journal of antimicrobial chemotherapy*, 68(11), 2592–2599. <https://doi.org/10.1093/jac/dkt229>
- [12] Mushtaq, M., Fatima, K., Ahmad, A., Mohamed Ibrahim, O., Faheem, M., & Shah, Y. (2023). Pharmacokinetic interaction of voriconazole and clarithromycin in Pakistani healthy male volunteers: a single dose, randomized, crossover, open-label study. *Frontiers in pharmacology*, 14, 1134803. <https://doi.org/10.3389/fphar.2023.1134803>
- [13] Mansh, M., Ing, L., Dimon, M., Celli, A., Mauro, T. M., & Arron, S. T. (2017). Voriconazole exposure regulates distinct cell-cycle and terminal differentiation pathways in primary human keratinocytes. *The British journal of dermatology*, 176(3), 816–820. <https://doi.org/10.1111/bjd.14838>
- [14] Singer, J. P., Boker, A., Metchnikoff, C., Binstock, M., Boettger, R., Golden, J. A., Glidden, D. V., & Arron, S. T. (2012). High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. *The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation*, 31(7), 694–699. <https://doi.org/10.1016/j.healun.2012.02.033>
- [15] Tang, H., Shi, W., Song, Y., & Han, J. (2019). Voriconazole exposure and risk of cutaneous squamous cell carcinoma among lung or hematopoietic cell transplant patients: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, 80(2), 500–507. e10. <https://doi.org/10.1016/j.jaad.2018.08.010>
- [16] Hamandi, B., Fegbeutel, C., Silveira, F. P., Verschuuren, E. A., Younus, M., Mo, J., Yan, J., Ussetti, P., Chin-Hong, P. V., Sol é A., Holmes-Liew, C. L., Billaud, E. M., Grossi, P. A., Manuel, O., Levine, D. J., Barbers, R. G., Hadjiladis, D., Aram, J., Singer, L. G., & Husain, S. (2018). Voriconazole and squamous cell carcinoma after lung transplantation: A multicenter study. *American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 18(1), 113–124. <https://doi.org/10.1111/ajt.14500>
- [17] D'Arcy, M. E., Pfeiffer, R. M., Rivera, D. R., Hess, G. P., Cahoon, E. K., Arron, S. T., Brownell, I., Cowen, E. W., Israni, A. K., Triplette, M. A., Yanik, E. L., & Engels, E. A. (2020). Voriconazole and the Risk of Keratinocyte Carcinomas Among Lung Transplant Recipients in the United States. *JAMA dermatology*, 156(7), 772–779. <https://doi.org/10.1001/jamadermatol.2020.1141>
- [18] Ikeya, S., Sakabe, J. I., Yamada, T., Naito, T., & Tokura, Y. (2018). Voriconazole-induced photocarcinogenesis is promoted by aryl hydrocarbon receptor-dependent COX-2 up-regulation. *Scientific reports*, 8(1), 5050. <https://doi.org/10.1038/s41598-018-23439-7>
- [19] Ramsay, H. M., Fryer, A. A., Reece, S., Smith, A. G., & Harden, P. N. (2000). Clinical risk factors associated with nonmelanoma skin cancer in renal transplant recipients. *American journal of kidney diseases: the official journal of the National Kidney Foundation*, 36(1), 167–176. <https://doi.org/10.1053/ajkd.2000.8290>
- [20] Williams, K., & Arron, S. T. (2016). Association of CYP2C19 *17/*17 Genotype With the Risk of Voriconazole-Associated Squamous Cell Carcinoma. *JAMA dermatology*, 152(6), 719–720. <https://doi.org/10.1001/jamadermatol.2016.0351>
- [21] Epaulard, O., Leccia, M. T., Blanche, S., Chosidow, O., Mamzer-Bruneel, M. F., Ravaud, P., Thiebaut, A., Villier, C., & Lortholary, O. (2011). Phototoxicity and photocarcinogenesis associated with voriconazole. *Medecine et maladies infectieuses*, 41(12), 639–645. <https://doi.org/10.1016/j.medmal.2011.09.016>
- [22] Epaulard, O., Villier, C., Ravaud, P., Chosidow, O., Blanche, S., Mamzer-Bruneel, M. F., Thiébaut, A., Leccia, M. T., & Lortholary, O. (2013). A multistep voriconazole-related phototoxic pathway may lead to skin carcinoma: results from a French nationwide study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 57(12), e182–e188. <https://doi.org/10.1093/cid/cit600>
- [23] Chen, B., Trang, V., Lee, A., Williams, N. S., Wilson, A. N., Epstein, E. H., Jr, Tang, J. Y., & Kim, J. (2016). Posaconazole, a Second-Generation Triazole Antifungal Drug, Inhibits the Hedgehog Signaling Pathway and Progression of Basal Cell Carcinoma. *Molecular cancer therapeutics*, 15(5), 866–876. <https://doi.org/10.1158/1535-7163.MCT-15-0729-T>

- [24] Kim, D. J., Kim, J., Spaunhurst, K., Montoya, J., Khodosh, R., Chandra, K., Fu, T., Gilliam, A., Molgo, M., Beachy, P. A., & Tang, J. Y. (2014). Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 32(8), 745–751. <https://doi.org/10.1200/JCO.2013.49.9525>
- [25] Parza, K., Singh, P., Cvinar, J., Zimmerman, T., Watson, B., & Faris, M. (2022). Voriconazole Induced Cutaneous Squamous Cell Carcinoma in an Immunocompetent Patient. *Cureus*, 14(5), e25508. <https://doi.org/10.7759/cureus.25508>
- [26] Sheu, J., Hawryluk, E. B., Guo, D., London, W. B., & Huang, J. T. (2015). Voriconazole phototoxicity in children: a retrospective review. *Journal of the American Academy of Dermatology*, 72(2), 314–320. <https://doi.org/10.1016/j.jaad.2014.10.023>
- [27] Cowen, E. W., Nguyen, J. C., Miller, D. D., McShane, D., Arron, S. T., Prose, N. S., Turner, M. L., & Fox, L. P. (2010). Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *Journal of the American Academy of Dermatology*, 62(1), 31–37. <https://doi.org/10.1016/j.jaad.2009.09.033>
- [28] Wong, J. Y., Kuzel, P., Mullen, J., Lien, D., Mahmood, M., Conrad, C., & Fiorillo, L. (2014). Cutaneous squamous cell carcinoma in two pediatric lung transplant patients on prolonged voriconazole treatment. *Pediatric transplantation*, 18(6), E200–E207. <https://doi.org/10.1111/ptr.12320>
- [29] Malani, A. N., & Aronoff, D. M. (2008). Voriconazole-induced photosensitivity. *Clinical medicine & research*, 6(2), 83–85. <https://doi.org/10.3121/cmr.2008.806>
- [30] Kwong, W. T., & Hsu, S. (2007). Pseudoporphyria associated with voriconazole. *Journal of drugs in dermatology: JDD*, 6(10), 1042–1044.
- [31] Vandecasteele, S. J., Van Wijngaerden, E., & Peetermans, W. E. (2004). Two cases of severe phototoxic reactions related to long-term outpatient treatment with voriconazole. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*, 23(8), 656–657. <https://doi.org/10.1007/s10096-004-1176-7>
- [32] Grzegorzczak, B., & Murata, Y. (2014). Peripheral eosinophilia and eosinophilic colitis during long-term azole therapy for pulmonary aspergillosis. *JMM case reports*, 1(4), e004135. <https://doi.org/10.1099/jmmcr.0.004135>
- [33] Vishnubhotla, P., Ibrahim, R. B., Abidi, M. H., & Chandrasekar, P. H. (2004). Fever and eosinophilia associated with voriconazole. *The Annals of pharmacotherapy*, 38(5), 900–901. <https://doi.org/10.1345/aph.1D404>
- [34] Brunel, A. S., Fraisse, T., Lechiche, C., Pinzani, V., Maubousin, J. M., & Sotto, A. (2008). Multifocal squamous cell carcinomas in an HIV-infected patient with a long-term voriconazole therapy. *AIDS (London, England)*, 22(7), 905–906. <https://doi.org/10.1097/QAD.0b013e3282f706a9>
- [35] Vanacker, A., Fabr  G., Van Dorpe, J., Peetermans, W. E., & Maes, B. (2008). Aggressive cutaneous squamous cell carcinoma associated with prolonged voriconazole therapy in a renal transplant patient. *American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 8(4), 877–880. <https://doi.org/10.1111/j.1600-6143.2007.02140.x>
- [36] McCarthy, K. L., Playford, E. G., Looke, D. F., & Whitby, M. (2007). Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 44(5), e55–e56. <https://doi.org/10.1086/511685>
- [37] Sawada, Y., Nakai, Y., Yokota, N., Habe, K., Hayashi, A., & Yamana, K. (2020). Voriconazole-Induced Squamous Cell Carcinoma after Hematopoietic Stem Cell Transplantation Showing Early-Stage Vascular Invasion. *Dermatopathology (Basel, Switzerland)*, 7(3), 48–52. <https://doi.org/10.3390/dermatopathology7030008>
- [38] Br ggemann, R. J., Alffenaar, J. W., Blijlevens, N. M., Billaud, E. M., Kosterink, J. G., Verweij, P. E., & Burger, D. M. (2009). Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 48(10), 1441–1458. <https://doi.org/10.1086/598327>
- [39] Blue, E. D., Freeman, S. C., Lobl, M. B., Clarey, D. D., Fredrick, R. L., Wysong, A., & Whitley, M. J. (2022). Cutaneous Squamous Cell Carcinoma Arising in Immunosuppressed Patients: A Systematic Review of Tumor Profiling Studies. *JID innovations: skin science from molecules to population health*, 2(4), 100126. <https://doi.org/10.1016/j.xjidi.2022.100126>
- [40] Hoenigl, M., Duettmann, W., Raggam, R. B., Seeber, K., Troppan, K., Fruhwald, S., Pruellner, F., Wagner, J., Valentin, T., Zollner-Schwetz, I., W fler, A., & Krause, R. (2013). Potential factors for inadequate voriconazole plasma concentrations in intensive care unit patients and patients with hematological malignancies. *Antimicrobial agents and chemotherapy*, 57(7), 3262–3267. <https://doi.org/10.1128/AAC.00251-13>
- [41] Kosmidis, C., Mackenzie, A., Harris, C., Hashad, R., Lynch, F., & Denning, D. W. (2020). The incidence of cutaneous squamous cell carcinoma in patients receiving voriconazole therapy for chronic pulmonary aspergillosis. *Naunyn-Schmiedeberg's archives of pharmacology*, 393(11), 2233–2237. <https://doi.org/10.1007/s00210-020-01950-x>
- [42] Miller, M. A., & Lee, Y. M. (2020). Applying Pharmacogenomics to Antifungal Selection and Dosing: Are We There Yet? *Current fungal infection reports*, 14(1), 63–75. <https://doi.org/10.1007/s12281-020-00371-w>
- [43] Donaldson, M. J., Sullivan, T. J., Whitehead, K. J., & Williamson, R. M. (2002). Squamous cell carcinoma of the eyelids. *The British journal of ophthalmology*, 86(10), 1161–1165. <https://doi.org/10.1136/bjo.86.10.1161>
- [44] Shitrit, D., Ollech, J. E., Ollech, A., Bakal, I., Saute, M., Sahar, G., & Kramer, M. R. (2005). Itraconazole prophylaxis in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. *The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation*, 24(12), 2148–2152. <https://doi.org/10.1016/j.healun.2005.05.003>

- [45] Pióro, A., Latos, M., Urlik, M., Stącel, T., Gawęda, M., Pandel, A., Przybyłowski, P., Knapik, P., & Ochman, M. (2022). Antifungal Prophylaxis and Treatment Among Lung Transplant Recipients in Early Postoperative Stage: A Single-Center Study. *Transplantation proceedings*, 54(4), 1104–1108. <https://doi.org/10.1016/j.transproceed.2022.02.015>
- [46] Husain, S., Paterson, D. L., Studer, S., Pilewski, J., Crespo, M., Zaldonis, D., Shutt, K., Pakstis, D. L., Zeevi, A., Johnson, B., Kwak, E. J., & McCurry, K. R. (2006). Voriconazole prophylaxis in lung transplant recipients. *American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 6(12), 3008–3016. <https://doi.org/10.1111/j.1600-6143.2006.01548.x>
- [47] Cadena, J., Levine, D. J., Angel, L. F., Maxwell, P. R., Brady, R., Sanchez, J. F.,... & Restrepo, M. I. (2009). Antifungal prophylaxis with voriconazole or itraconazole in lung transplant recipients: hepatotoxicity and effectiveness. *American Journal of Transplantation*, 9(9), 2085-2091. <https://doi.org/10.1111/j.1600-6143.2009.02734.x>
- [48] Kolaitis, N. A., Duffy, E., Zhang, A., Lo, M., Barba, D. T., Chen, M., Soriano, T., Hu, J., Nabili, V., Saggar, R., Sayah, D. M., DerHovanessian, A., Shino, M. Y., Lynch, J. P., 3rd, Kubak, B. M., Ardehali, A., Ross, D. J., Belperio, J. A., Elashoff, D., Saggar, R., ... Weigt, S. S. (2017). Voriconazole increases the risk for cutaneous squamous cell carcinoma after lung transplantation. *Transplant international: official journal of the European Society for Organ Transplantation*, 30(1), 41–48. <https://doi.org/10.1111/tri.12865>
- [49] Williams, K., Mansh, M., Chin-Hong, P., Singer, J., & Arron, S. T. (2013). Voriconazole-associated cutaneous malignancy: A literature review on Photocarcinogenesis in organ transplant recipients. *Clinical Infectious Diseases*, 58(7), 997-1002. <https://doi.org/10.1093/cid/cit940>