

A multi-step voriconazole-related phototoxic pathway may lead to skin carcinoma: results from a French nationwide study

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Summary

A call for notification allowed identifying 19 patients with skin carcinoma(s) during/after voriconazole therapy. The likelihood of voriconazole involvement in the carcinoma onset was determined "high" in 15 cases. A multi-step sequence (phototoxicity, keratosis, carcinoma) was observed in 14 patients.

Abstract

Background. Voriconazole long-term therapy is suspected to induce cutaneous squamous cell carcinomas (SCC), as suggested by 18 case reports worldwide and three retrospective studies.

Methods. To better characterize the natural history of these potentially voriconazole-associated tumors, a nationwide call for notification of skin cancers and other skin lesions observed between 2002 and 2012 in patients treated by voriconazole was launched in France. A multidisciplinary committee evaluated voriconazole involvement in each case.

Results. Nineteen SCC were reported. The committee determined the likelihood of voriconazole involvement as “high” in 15 cases, “intermediate” in 2, and “low” in 2. In the 17 patients with high/intermediate likelihood of voriconazole involvement, the mean time between voriconazole initiation and SCC diagnosis was 39 ± 18 months (range 28-84), and was shorter in transplant recipients (35 vs. 45 months, $p < 0.05$). Cumulative mean duration of voriconazole therapy at SCC diagnosis was 35 months (range 7-63). A multi-step process was noted in 14/17 patients: acute phototoxicity during the first year of voriconazole therapy (mean time 6 months, range 0-18), actinic keratosis (AK) of the same sun-exposed skin area in the second/third year (mean 30 months, range 11-57), followed by SCC during the third year or later. Five cases of AK without SCC and 37 cases of other skin lesions were also reported.

Conclusions. Our study suggests that long-term voriconazole prescription may be associated with a multi-step phototoxic process involving acute skin lesions followed by AK then by SCC. Discontinuation of voriconazole should be strongly considered in patients experiencing chronic phototoxicity.

Introduction

Voriconazole is a triazole anti-fungal agent which received FDA and EMA (European Medical Agency) approvals in 2002. It has been recommended as the first line therapy for invasive aspergillosis in USA [1] and Europe [2], and is also widely used for secondary anti-*Aspergillus* prophylaxis [3]. It is also currently used for the treatment of candidemia in non-neutropenic patients, severe invasive *Candida* spp. infections resistant to fluconazole, and *Scedosporium* spp. [4] and *Fusarium* spp. [5] infections.

However, several adverse effects may limit the use of voriconazole. Hepatotoxicity and reversible visual disorders received major attention, but prescribers were less aware of phototoxic effects. Isolated clinical cases and small series with acute or subacute erythema, blisters, pseudoporphyria, and cheilitis have been indeed reported; these lesions often healed when voriconazole was discontinued [6]. In addition, a total of 18 patients who presented with skin squamous cell carcinoma (SCC) while receiving long-term voriconazole therapy has also been notified [7-13]. Between 2010 and 2012, 3 retrospective studies identified voriconazole as an independent risk factor for SCC in lung transplant recipients [14-16], and a simulation model extrapolated that in this population 46% of patients continuously receiving voriconazole would develop SCC after 5 years, compared with 18% in patients not receiving voriconazole [17]. The European summary of product characteristics has recently been modified to mention this risk [18]. However, no consensus exists concerning the link between voriconazole prescription and SCC onset, and no guidelines have been issued.

We conducted a retrospective study to evaluate the natural history and the frequency of voriconazole-associated SCC in France.

Patients and methods

A call for notifications of voriconazole-associated skin reactions was sent by e-mail twice (February-March 2011, December 2011) to members of concerned, ie, French scientific societies (Infectious Diseases, Dermatology, Transplantation, Hematology, Bone-Marrow Transplantation and Cellular Therapy, Pharmacology, Pediatric Immuno-Hematology, Hereditary Immuno-Deficiency Reference Center) and to physicians participating to the French pharmacovigilance network. A similar call was made during the French Congress of Infectious Diseases in June 2011 and in various French meetings of dermatology and photobiology between December 2010 and January 2012. Physicians were asked to notify every acute or chronic skin and/or lip non-malignant manifestation if it occurred when patients were receiving voriconazole, and every skin cancer that developed in patients who were either currently or in the past receiving voriconazole. Notification was made to a dedicated e-mail address, or by fax.

Considering that the diagnosis of skin cancer (in our cases squamous cell carcinoma) relies on precise pathology criteria, we did not ask every reporting physician to provide histologic material to re-assess the diagnosis first made by the local experienced pathologist.

Pertinent data were then anonymously collected from medical record review or interview of reporting clinicians, including information on co-prescriptions of phototoxic drugs (e.g., fluoroquinolones, cyclins, amiodarone, phenothiazine, retinoids, non-steroidal anti-inflammatory drugs) and of azathioprine, past history of skin disease, and Fitzpatrick phototype. Each case was reviewed by a multidisciplinary committee including physicians from concerned medical societies (2

dermatologists, 1 kidney transplant physician, 1 bone-marrow transplant physician, 1 pediatric immunologist, 1 physician from the pharmacovigilance network, 2 infectious disease physicians) to assess the likelihood of voriconazole involvement.

Criteria for skin cancers, actinic keratosis (AK) and other skin manifestations are detailed below:

a) *Skin cancers*. The criteria for skin cancers relied upon i) the phototoxic process likely to be involved and ii) the course of the 18 cases previously published of patients developing SCC after long-term use of voriconazole. The likelihood of voriconazole involvement was classified according to the following criteria:

- 1) onset in the same area of acute or subacute phototoxic events, *then* actinic keratosis (AK), *then* skin cancer;
- 2) onset of multiple malignant lesions in a short time lapse (6 months);
- 3) only acute phototoxicity *or* AK noted before skin cancer onset.

The likelihood was classified “high” if at least one of the criteria 1 and 2 was noted, “intermediate” if only the criterion 3 was noted, and otherwise “low”.

b) *Actinic keratosis (AK)*. The likelihood of voriconazole involvement was classified according to the following criteria:

- 1) onset of acute or subacute phototoxic events during voriconazole therapy in the same area before the onset of AK;
- 2) decrease and/or healing of AK after voriconazole discontinuation;
- 3) age of less than 50 (as age is a risk factor for AK in the general population and AK are rare before 60 years of age [19]).

The likelihood was classified “high” if the criteria 1 and/or 2 were noted, “intermediate” if only criterion 3 was noted, and otherwise “low”.

c) *Other skin manifestations*. The likelihood of voriconazole involvement was classified according to the following criteria:

- Positive criteria
 - Obvious phototoxic mechanism (e.g., lesions occurred after sun exposure, and/or limited to photo-exposed area);
 - Healing after voriconazole discontinuation;
 - No prescription of other phototoxic drug(s) with a consistent timing.
- Negative criteria
 - Clear lack of healing after voriconazole discontinuation.

Likelihood was considered “high” if 3 positive criteria were noted, or 2 positive criteria without negative criteria; “intermediate” if 1 positive criteria was noted, or 2 positive criteria with the negative criteria; and “low” in other cases.

The Log rank test was used to compare the time between voriconazole initiation and SCC diagnosis in different groups. The Mann-Whitney test was used to compare non-parametric continuous variables. Spearman's rank test was used to determine the dependence between two variables.

Results

Sixty-one cases of voriconazole-associated skin manifestations were directly reported to the study committee by 45 clinicians from 34 medical institutions in France between March 2011 and November 2012. Reported cases occurred between 2003 and 2012. No center reported more than 5 cases.

SCC and AK

Nineteen cases of skin cancer were reported; all were SCC, with no melanoma or other carcinoma. Six of these cases had already been partially published [8, 11, 13].

The likelihood of voriconazole involvement was considered “high” in 15 cases, “intermediate” in 2 cases, and “low” in 2 cases (one patient with vulvar SCC after 9 months of voriconazole without skin lesion and one patient aged 75 with only one AK and one SCC after 1 year of voriconazole).

The 17 patients (3 female and 14 male patients) with “intermediate” and “high” likelihood of voriconazole involvement were 49 ± 14 years old (21 to 79) (figure 1a) when voriconazole was initiated. Thirteen were immunocompromised (4 hematopoietic stem cell transplant recipients, 3 lung transplant recipients; chronic lymphoid leukemia, common variable immunodeficiency, AIDS, idiopathic CD4⁺ T lymphopenia, treated granulomatosis with polyangiitis (ex-Wegener’s granulomatosis), and treated sarcoidosis in one patient respectively). The remaining four patients presented with various lung diseases (emphysema, chronic obstructive pulmonary disease, bronchiectasis, and past surgery for a lung cancer). Fitzpatrick phototype was reported for 13 patients: 1 case of phototype I, 6 cases of phototype II, 5 cases of phototype III, 1 case of phototype IV. Only one of the patients had received azathioprine (for granulomatosis with polyangiitis). None of the patients received other long-term phototoxic medication.

Among these 17 patients, the first SCC was diagnosed 46 ± 18 months after voriconazole initiation (range 28 to 84 months, median 39 months). The median time between voriconazole initiation and SCC diagnosis was shorter in the 7 transplant recipients than in the other patients (35.0 vs. 45.2 months, $p < 0.05$) (figure 2). There was no statistical correlation between patient age and onset of SCC. Voriconazole use was intermittent in 6 patients between its initiation and SCC diagnosis; in the 17 patients, the cumulative duration of voriconazole therapy before SCC diagnosis was 35 ± 13 months (range 7 to 63 months, median 35 months). It should be noted that the

median time between voriconazole initiation and SCC diagnosis was longer in patients with an intermittent voriconazole course (63.8 months vs. 36.6 months, $p=0.02$).

A succession of skin lesions was reported in 14/17 patients. Acute and chronic erythema of sun-exposed areas was initially observed, usually during the first year of voriconazole administration (median 6 months, range 0-18 months in 9 patients with a precise date of onset). AK were then observed on the same skin area(s), usually in the second or third year of voriconazole administration (median 30 months, range 11-57 months in 9 patients with a precise date of onset). One or more SCC was subsequently diagnosed following AK lesions, during (as mentioned) the third year of voriconazole administration or later.

In 9/17 patients, more than 1 SCC was diagnosed either simultaneously or during the 6 months following the first diagnosis of SCC. Two patients (one lung transplant recipient and one patient with common variable immunodeficiency) presented with 17 and 20 SCC lesions, respectively.

It is also noteworthy that scalp SCC were reported in 10/17 patients; it was not possible to determine if these patients had alopecia. Scalp is not a frequent localization of in situ skin carcinoma [20] and may therefore be an important feature of voriconazole-associated SCC. The numbers of patients who demonstrated a multistep process, multiple SCC lesions, and/or scalp involvement are shown in figure 3.

All patients underwent surgery for their SCC. Nine patients required more than one surgical procedure because of local SCC relapse or diagnosis of new SCC lesions. One lung transplant recipient experienced multiple and relapsing scalp SCC with

non-resectable cervical lymph node metastasis, and required chemotherapy; he died of febrile neutropenia.

Five other patients developed multiple AK of sun-exposed area without SCC during the study period (2 patients with cystic fibrosis, 1 HIV-positive patient, 1 patient with acute leukemia, 1 hematopoietic stem cell transplant recipient). AK diagnosis was made 11, 22, 54, 65, and 80 months after the initiation of voriconazole therapy; voriconazole involvement was considered “high” in 3 cases, “intermediate” in 1 and “low” in 1. In 3 cases, acute phototoxicity was noted before the onset of AK. Moreover, a reversal of AK was noted after voriconazole discontinuation in 1 case; this reversal of AK was also noted in 3 cases of patients with SCC.

Other skin lesions

Non-malignant skin manifestations (without association with SCC) with available pertinent data were reported in 37 other patients. The likelihood of voriconazole involvement was considered “low” in 2 cases, “intermediate” in 3 cases, “high” in 29 cases, and indeterminate in the remaining 3 cases.

The age at the time of initial voriconazole treatment of the 32 patients (11 female and 21 male patients) with “intermediate” and “high” voriconazole involvement ranged between 3 and 77 years (mean 26 ± 20) ($p=0.001$ for the difference with SCC patients) (figure 1b). Twelve patients were less than 15 years of age. Three were transplant recipients (hematopoietic stem cells, lung, liver), 5 had chronic granulomatous disease, 10 had hematologic malignancies, 1 had STAT3-Deficient Hyper IgE Syndrome, 1 had Evans syndrome; 9 others had cystic fibrosis, and 3 had other chronic lung diseases.

These 32 patients experienced acute or subacute phototoxic events: erythema and blisters (5), erythema and cheilitis (6), erythema and lentigos (3), erythema alone

(15), cheilitis alone (1), and pseudoporphyria (2). The mean time between voriconazole initiation and first skin phenomenon occurrence was 3.5 months (107 days, range 14 to 421 days) when documented (n=23). A precisely timed sun exposure was associated with the onset of lesions (e.g., immediately after a soccer match) in 11 cases. Voriconazole was discontinued in 22/32 cases, with a rapid improvement of skin lesions in 18 cases (including cases with a switch to posaconazole (n=6) or itraconazole (n=3)). In other cases, skin improvement was either slower (n=3) or not documented (n=1). In 10 cases, voriconazole therapy was maintained with photoprotection.

Discussion

The authors of several case reports, small series, and pharmacovigilance reports have documented voriconazole phototoxicity since its launching a decade ago [6]. In vitro absorbance studies [21] suggest that voriconazole and/or its N-oxide primary metabolite are chromophores, generating phototoxic reactions responsible for acute and chronic skin lesions (erythema, blisters, lentigo, photo-aging) and lip lesions (cheilitis). These lesions may occur in about 8% of patients receiving voriconazole [6]. Interference with retinoid metabolism may also explain these events, the risk of which may potentially be enhanced by vitamin A supplementation [22].

The long-term phototoxic consequences of voriconazole therapy are still poorly known, particularly concerning the risk of SCC. A potential phototoxicity-related carcinogenic effect of voriconazole has been suggested i) by previous reports of patients who presented with AK and SCC when voriconazole was given for years, and ii) by the healing of AK and interruption of SCC development after voriconazole discontinuation in some cases [11]. Our nationwide study was designed to better

understand the natural history of voriconazole-associated SCC, whatever the underlying disease.

The major information provided by our series is that most patients with such SCC experienced skin lesions consistent with a multi-step photo-induced malignant process: erythema of the photo-exposed areas in the first year, followed by AK in the second/third year, and SCC in the third/fourth year. Given the lack of concomitant other phototoxic medication with a consistent timing, this strongly suggests that voriconazole phototoxicity is responsible for a carcinogenic effect. As far as we know, such a drug-induced pathogenic process has never been described in humans. It is likely that in patients presenting with AK without SCC, this process was also ongoing, but the patients were reported at an earlier stage. The fact that a reversal of most AK was observed in 4 patients after voriconazole discontinuation also suggests that voriconazole is responsible for the different steps of this process, from the acute phototoxic events to the SCC.

Other synergistic mechanisms may obviously promote the onset of SCC, such as immunosuppression, which probably accounts for the shorter period between voriconazole initiation and SCC diagnosis in solid organ and allogeneic hematopoietic stem cell transplant recipients. However, voriconazole-induced skin cancers differ from those observed in organ transplant recipients. Indeed, in these patients, skin cancers (including SCC but also basal cell carcinoma) rarely affect the scalp without alopecia [20], usually appear later after transplantation [23], and are usually preceded by warts and not only AK (with a clear influence of the type, number, and course duration of immunosuppressive drugs). Moreover, our results clearly emphasize that immunocompetent patients are also at risk of voriconazole-

associated SCC, indicating that immunosuppression is not required for this multi-step carcinogenic process to occur.

It is noteworthy that patients presenting with SCC had received long-term voriconazole therapy (median cumulative duration 35 months). Such schedules are usually used for secondary prophylaxis in persistently immunocompromised patients infected with a voriconazole-susceptible mold; however, no precise guidelines have addressed this complex situation.

Several phototoxic drugs have been associated with the onset of SCC. The conjunction of 8-methoxypsoralen and ultraviolet-A light is associated with a risk of SCC correlated to the number of courses [24]. Hydrochlorothiazide has also been associated with a greater risk of SCC [25] and AK [26], but the effect of such drugs was detectable only in large series. Fluoroquinolones are known photogenotoxic agents, inducing DNA damage such as cyclobutane thymine dimers [27]. In an animal model of long-term oral intake of lomefloxacin in association with UV irradiation, all animals had developed SCC between 16 and 24 weeks [28]. Such fluoroquinolone-associated SCC have not been reported in humans, possibly because of the usually short course prescription. Photocarcinogenesis may also be promoted by other mechanisms. For example, cyclosporine A and azathioprine reduce DNA repair of lesions induced by UV radiations [29]. Further studies should be performed to determine voriconazole-induced phototoxicity and photocarcinogenesis.

Our study also stresses the need to define involvement criteria for skin carcinogenicity. In addition to exposed/non-exposed studies and case-controls studies, which require large population samples, reporting cases highly evocative of drug-induced malignant process is crucial to understand the natural history of such

diseases and to assess drug responsibility. For voriconazole, the great variety of phototoxic events (erythema, blister, cheilitis, lentigo, photo-aging) and the multistep process for KA and SCC helped to elaborate the phototoxicity-based criteria.

Our retrospective study had several limitations. It was most certainly not exhaustive, since it relied on reports of cases having occurred during the past decade at a country basis. It is indeed doubtful that only 19 patients in the voriconazole-treated population were diagnosed with SCC during this period. Cases more strongly associated with other unusual features (such as prominent phototoxicity) may have been preferentially reported. These cases however help to define the described multi-step process; however, i) they may not be representative of all voriconazole-associated SCC, and ii) they do not allow concluding that all SCC in voriconazole-treated population are directly induced by voriconazole per se. Moreover, clinicians may have not declared some cases, particularly in transplant recipients, assuming that SCC were only related to iatrogenic immunosuppression in this population. A prospective study might bring more robust data; however, it is likely that long-term prescription of voriconazole in patients experiencing long-term phototoxicity, such as observed in the cases reported here, will be much less frequent now that i) alternative therapeutic options are available and ii) concerns about voriconazole photocarcinogenicity render unethical such long-term prescription in such patients. Data from future prospective studies may therefore bring interesting data on the long-term risk of SCC associated with voriconazole, but probably not on the multi-step process clearly observed here.

Conclusion

Our study suggests that voriconazole may be responsible for a multi-step process beginning with acute and chronic phototoxicity, followed by AK, and finally skin SCC, especially if voriconazole therapy is maintained. Strict photoprotection is mandatory for all patients receiving voriconazole; voriconazole replacement by another triazole must be discussed in case of acute phototoxicity. Voriconazole must be stopped in patients with chronic phototoxicity, and a long-term dermatologic follow-up of skin lesions is required even after voriconazole withdrawal.

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Conflict of interest:

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Figure Legends

Figure 1

Age distribution in patients with SCC (a) or with phototoxicity without SCC or AK (b) (patients with “high” and “intermediate” likelihood of voriconazole involvement).

Figure 2

Time between voriconazole initiation and SCC diagnosis in transplant recipients (bold line) and non-transplant patients (thin line) patients with “high” and “intermediate” likelihood of voriconazole involvement), $p < 0.05$.

Figure 3

Characteristics of the 15 SCC cases with a high likelihood of voriconazole involvement. The number of patients concerned by the main features (multi-step process, multiplicity of SCC lesions, scalp involvement) is mentioned at each intersection.





