Received: 22 June 2017 | Revised: 4 August 2017 | Accepted: 30 August 2017

DOI: 10.1111/ajt.14500

ORIGINAL ARTICLE

AJT

Voriconazole and squamous cell carcinoma after lung transplantation: A multicenter study

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This study evaluated the independent contribution of voriconazole to the development of squamous cell carcinoma (SCC) in lung transplant recipients, by attempting to account for important confounding factors, particularly immunosuppression. This international, multicenter, retrospective, cohort study included adult patients who underwent lung transplantation during 2005-2008. Cox regression analysis was used to assess the effects of voriconazole and other azoles, analyzed as time-dependent variables, on the risk of developing biopsy-confirmed SCC. Nine hundred lung transplant recipients were included. Median follow-up time from transplantation to end of follow-up was 3.51 years. In a Cox regression model, exposure to voriconazole alone (adjusted hazard ratio 2.39, 95% confidence interval 1.31-4.37) and exposure to voriconazole and other azole(s) (adjusted hazard ratio 3.45, 95% confidence interval 1.07-11.06) were associated with SCC compared with those unexposed after controlling for important

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; D, donor; DDD, defined daily dose; HR, hazard ratio; IA, invasive aspergillosis; ICU, intensive care unit; ILD, interstitial lung disease; IPF, interstitial pulmonary fibrosis; LT, lung transplant, transplantation; R, recipient; Ref, reference category; SCC, squamous cell carcinoma.

confounders including immunosuppressants. Exposure to voriconazole was associated with increased risk of SCC of the skin in lung transplant recipients. Residual confounding could not be ruled out because of the use of proxy variables to control for some confounders. Benefits of voriconazole use when prescribed to lung transplant recipients should be carefully weighed versus the potential risk of SCC. EU PAS registration number: EUPAS5269.

KEYWORDS

antibiotic: antifungal, clinical research/practice, complication: malignant, health services and outcomes research, infection and infectious agents - fungal, infectious disease, lung disease, lung transplantation/pulmonology, patient safety

1 | INTRODUCTION

Skin cancer is the most common malignancy reported in recipients of solid organ transplants, with squamous cell carcinoma (SCC) of the skin being most frequently diagnosed.[1-3] The incidence of SCC in recipients of solid organ transplants is >65 times that of the general population but varies by organ transplant.[1,4] Risk factors for the development of SCC include prolonged exposure to sunlight, long duration of immunosuppressive therapy, infection with human papillomavirus, lower CD4 cell counts, and certain host factors, such as male sex, older age, white race, and Fitzpatrick skin types I to III.[4–6] The rates of all skin cancers among adult lung transplant (LT) recipients surviving 1, 5, and 10 years after transplantation have been reported to be 1.3%, 11.9%, and 20.8%, respectively.[7] LT recipients may be particularly vulnerable for developing SCC as a result of concurrent intensity of immunosuppression.[3]

Fungal infection is also an important complication for LT recipients, with 15% to 35% of patients being diagnosed with fungal infections, such as invasive aspergillosis (IA).[8] The treatment of IA in LT recipients generally involves minimizing immunosuppression, followed by early initiation of a suitable antifungal agent until resolution of the pulmonary lesions.[9]

Voriconazole (VFEND; Roerig, Pfizer, New York, NY) was approved in 2002 for the treatment of IA and other invasive fungal infections. Voriconazole was also recently approved for prophylaxis of invasive fungal infections in high-risk recipients of hematopoietic stem cell transplantations in the European Union and other countries. In addition to its approved indications, many transplant programs have implemented universal antifungal prophylaxis using voriconazole to prevent IA in recipients of LTs or heart-lung transplants.[10, 11] Data from a worldwide survey showed that voriconazole is the most widely prescribed antifungal agent for prophylaxis in LT recipients.[12, 13]

Single cases[14–16] and small case series[17, 18] of SCC in voriconazole-treated immunocompromised patients have been reported, including in recipients of solid organ transplants and those with hematologic malignancies or human immunodeficiency virus infection. The risk of SCC or nonmelanoma skin cancer with voriconazole exposure has been investigated in single-center, retrospective, observational case-control or cohort studies, primarily among recipients of LTs [19–24] but also in recipients of hematopoietic stem cell transplants.[25] Although most studies reported that exposure to voriconazole increased the risk of skin cancer, findings were not generally consistent, perhaps due to the differences in the exposure/endpoint assessments and/or analytical methods used. Also, some of the studies did not control for the presence of comorbidities or underlying conditions, sun exposure, or the use of potentially phototoxic concomitant medications, nor did they adequately account for immunosuppressives or antifungal agents, other than voriconazole, received by transplant recipients.

Given the limitations of the currently available data, the objective of this study was to assess the independent contribution of voriconazole to the development of SCC in LT or heart-lung transplant recipients, by accounting for important confounding factors, particularly comorbidities and the use of concomitant immunosuppressants and other azoles.

2 | METHODS

2.1 | Study design and patients

This multicenter, retrospective cohort study used patient-level data collected from 14 LT centers across 9 countries: United States, Canada, France, Germany, Italy, the Netherlands, Spain, Switzerland, and Australia. Consecutive patients aged ≥18 years who underwent single LT, double LT, or heart-lung transplantation at the participating study centers between January 1, 2005, and December 31, 2008, were eligible for inclusion (Figure 1). Patients with simultaneous or sequential abdominal organ transplant and those with a previous history of biopsy-confirmed SCC were excluded. The study protocol was approved by the University Health Network Research Ethics Board (REB No. 10-0622-AE) as the coordinating site and by institutional review boards and/or independent ethics committees at each site.

2.2 | Exposure

Cumulative voriconazole exposure of ≥30 days, not necessarily consecutive, was considered clinically meaningful for the risk of SCC; the same criterion was applied to other azoles. Sensitivity analysis using a cumulative exposure of 1 day was also conducted. LT recipients with

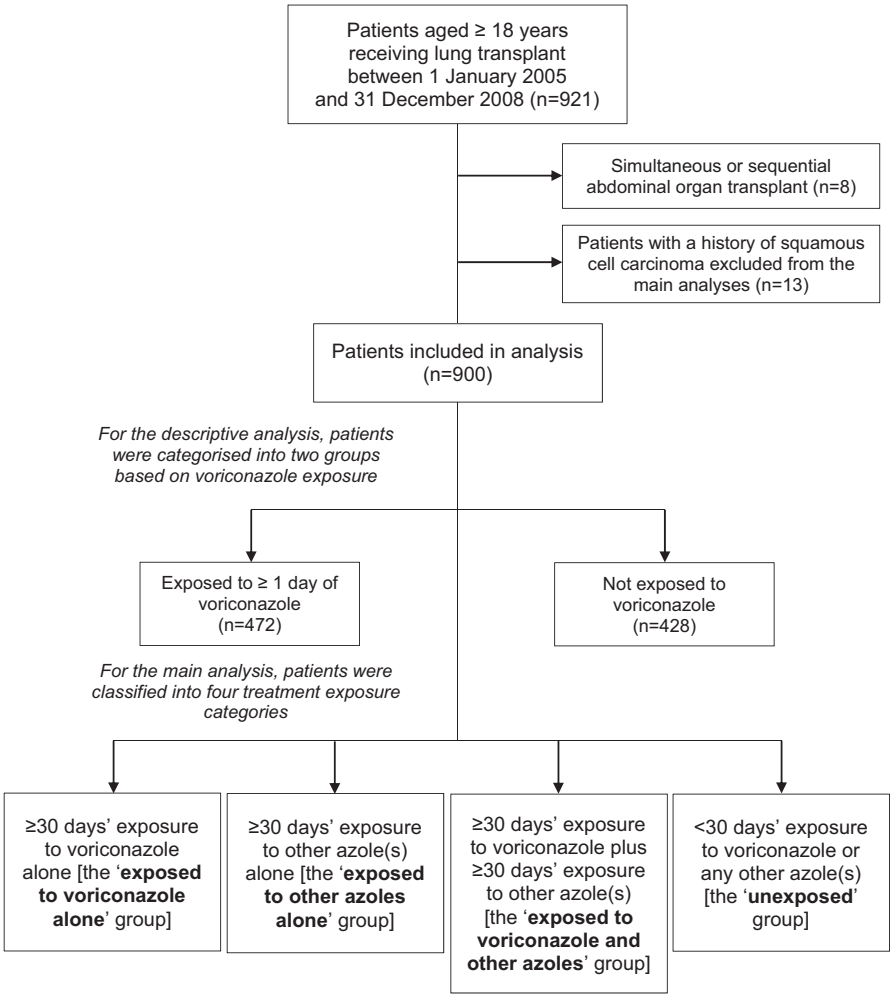

FIGURE 1 Eligibility in this study that evaluated the association between voriconazole exposure and squamous cell carcinoma in patients receiving a lung or heart-lung transplant and categorization of treatment exposure

any indication for voriconazole (or other azole) use, including prophylaxis, empiric treatment, or targeted treatment, were included. The "index date" was the date of LT. Exposures to voriconazole and other azoles were analyzed as time-dependent variables and measured as person-time of exposure (Appendix S1 illustrates determination of treatment exposure categories at each time point during follow-up, with the use of hypothetical examples). At each post-LT time point, time-dependent exposure was classified into 1 of 4 treatment categories:

1. Unexposed to any azole or exposed to some azole for <30 days (referred to as "unexposed")
2. Exposed to voriconazole for ≥30 days but not to any other azole for ≥30 days (referred to as "exposed to voriconazole alone")
3. Exposed to other azole(s) for ≥30 days but not to voriconazole for ≥30 days (referred to as "exposed to other azoles alone")
4. Exposed to voriconazole for ≥30 days as well as exposed to some other azole for ≥30 days [referred to as "exposed to voriconazole and other azole(s)"].

Finally, to assess the possibility that the risk of SCC may be dose dependent, we modelled exposure to voriconazole based on the mean cumulative daily dose, measured as "defined daily doses."[26]

2.3 | Covariates

Comprehensive data were collected on demographic and clinical characteristics including potential confounders and effect modifiers for SCC. In addition to the use of immunosuppressive agents post-LT and potentially phototoxic agents, data on whole blood concentrations of calcineurin inhibitors and number of episodes of elevated calcineurin inhibitor levels were collected (Appendix S2 presents all covariates and their transformation).

2.4 | Outcome assessment

The primary outcome was the first occurrence of biopsy-confirmed SCC during the follow-up period from the index date of LT. Recipients of LTs were followed from the index date to whichever of the following occurred first: SCC, death, last patient visit (based on documentation in the medical records), or December 31, 2012.

2.5 | Statistical analysis

Assuming an incidence of SCC in LT recipients unexposed to voriconazole of 5% and a voriconazole exposed:unexposed ratio of 1:2, at least 157 LT recipients in the voriconazole-exposed cohort and 314 LT

recipients in the unexposed cohort were needed to detect a relative risk of 2.5 with 80% power at a 5% significance level. As a single patient may have contributed to >1 exposure category, for the baseline descriptive analysis, LT recipients were categorized into 2 categories: ≥1 day of exposure to voriconazole and no exposure to voriconazole. Unadjusted incidence rates of SCC were estimated during the total person-time of observation for the 4 treatment exposure categories, as described earlier.

Multivariate Cox proportional hazards models using fixed and time-dependent exposure categories for voriconazole were developed to control for the effect of known and potential confounding covariates decided a priori (age, sex, immunosuppression regimen, mean cyclosporine level, mean tacrolimus level, sun exposure, history of malignancy pretransplantation, transplant rejection episodes, underlying disease). Separate adjusted multivariate Cox proportional hazards models were also developed to assess the potential time-dependent effect of dose (measured in defined daily doses) and duration of voriconazole on the risk of SCC. The assumption of proportionality was graphically examined using log (cumulative hazard) plots and scaled Schoenfeld residuals.

All data were analyzed by using StataMP 12.1 (StataCorp LP, College Station, TX).

3 | RESULTS

Nine hundred twenty-one consecutive patients aged ≥18 years were eligible for evaluation. Eight patients with simultaneous or sequential abdominal organ transplant were excluded, plus 13 patients with a pretransplantation history of SCC. Median follow-up time for the remaining patients (n = 900) from LT to the end of follow-up was 3.51 years (range, 1 day to 7.97 years). Of 900 LT recipients, 440 (48.9%) were from Europe, 430 (47.8%) were from North America, and 30 (3.3%) were from Australia. Overall, LT recipients had a median age of 53 years, 53.1% were male, and the primary indications for LT were chronic obstructive pulmonary disease (28.7%), interstitial pulmonary fibrosis (24.4%), and cystic fibrosis (22.3%).

Most LT recipients received a concomitant immunosuppressive regimen that included tacrolimus (70.7%) or a mycophenolate derivative (77.3%), and almost all (98.7%) had been exposed to corticosteroids. Forty-five percent (401 of 900) of LT recipients were exposed to voriconazole for ≥30 days, and approximately one-third were exposed to an azole other than voriconazole, including itraconazole (21.4%), fluconazole (5.8%), and posaconazole (4.6%). Table 1 summarizes LT recipients' demographic and clinical characteristics. Of 472 LT recipients with ≥1-day exposure to voriconazole, 301 (63.8%) received voriconazole for prophylaxis, 132 (28.0%) received voriconazole for directed or empiric treatment, and 39 (8.3%) received voriconazole for both prophylaxis and treatment. Overall, slightly higher proportions of LT recipients with ≥1-day exposure to voriconazole than no exposure to voriconazole were classified in geographical areas with medium and high exposure to sunlight (medium sun exposure 59.3% vs 54.9%, high

TABLE 1 Patient demographic characteristics, hospitalization details, comorbid conditions and immunosuppressive agents used by voriconazole exposure (≥1-day exposure to voriconazole versus no exposure to voriconazole) (N = 900)

	Voriconazole unexposed (no exposure to voriconazole) (n = 428)		Voriconazole exposed (≥1-day exposure to voriconazole) (n = 472)		All study patients (n = 900)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Demographic characteristics						
Age, y						
18-29	48	11.2	97	20.6	145	16.1
30-49	119	27.8	132	28	251	27.9
50-59	163	38.1	110	23.3	273	30.3
60-69	97	22.7	116	24.6	213	23.7
>70	1	0.2	17	3.6	18	2.0
Sex						
Male	218	50.9	260	55.1	478	53.1
Female	210	49.1	212	44.9	422	46.9
Occupation[a]						
Indoor	130	30.4	255	54	385	42.8
Outdoor	21	4.9	36	7.6	57	6.3
Mixed	277	64.7	181	38.3	458	50.9
Geographical location						
Australia	15	3.5	15	3.2	30	3.3
Canada	149	34.8	79	16.7	228	25.3
France	4	0.9	23	4.9	27	3.0
Germany	94	22	101	21.4	195	21.7
Italy	26	6.1	0	0.0	26	2.9
Netherlands	64	15	27	5.7	91	10.1
Spain	59	13.8	25	5.3	84	9.3
Switzerland	10	2.3	7	1.5	17	1.9
United States	7	1.6	195	41.3	202	22.4
Sun exposure[b]						
Low	172	40.2	159	33.7	331	36.8
Medium	235	54.9	280	59.3	515	57.2
High	21	4.9	33	7.0	54	6.0
Clinical characteristics						
LT type						
Double	332	77.6	379	80.3	711	79
Heart-lung	14	3.3	13	2.8	27	3.0
Single	82	19.2	80	17.0	162	18.0
Re-LT						
No	409	95.6	449	95.1	858	95.3
Yes	19	4.4	23	4.9	42	4.7
Underlying disease						
COPD	140	32.7	118	25	258	28.7

(Continues)

TABLE 1 (Continued)

Characteristic	Voriconazole unexposed (no exposure to voriconazole) (n = 428)		Voriconazole exposed (≥1-day exposure to voriconazole) (n = 472)		All study patients (n = 900)	
	n	%	n	%	n	%
IPF	99	23.1	121	25.6	220	24.4
Cystic fibrosis	69	16.1	132	28	201	22.3
α_1-Antitrypsin	29	6.8	18	3.8	47	5.2
Primary pulmonary hypertension	14	3.3	14	3.0	28	3.1
Bronchiolitis obliterans	11	2.6	8	1.7	19	2.1
Scleroderma	9	2.1	10	2.1	19	2.1
Sarcoidosis	7	1.6	9	1.9	16	1.8
ILD	6	1.4	3	0.6	9	1.0
Other	44	10.3	39	8.3	83	9.2
Immune disorder[c]						
No	420	98.1	465	98.5	885	98.3
Yes	8	1.9	7	1.5	15	1.7
Other cancer pre-LT[d]						
Yes	2	0.5	0	0.0	2	0.2
No	426	99.5	472	100	898	99.8
Dialysis 30 days post-LT						
No	414	96.7	459	97.2	873	97
Yes	14	3.3	13	2.8	27	3.0
Transplant rejection episodes						
0	240	56.1	213	45.1	453	50.3
1-2	136	31.8	184	39	320	35.6
3-4	41	9.6	46	9.7	87	9.7
>4	11	2.6	29	6.1	40	4.4
Neutropenia episodes[e]						
0	183	42.8	157	33.3	340	37.8
1-2	140	32.7	152	32.2	292	32.4
3-4	63	14.7	63	13.3	126	14
>4	42	9.8	100	21.2	142	15.8
Diabetes post-LT						
No	332	77.6	328	69.5	660	73.3
Yes	83	19.4	122	25.8	205	22.8
Missing	13	3.0	22	4.7	35	3.9
CMV						
D^-R^-	84	19.6	105	22.2	189	21.0
D^+R^+	112	26.2	142	30.1	254	28.2
D^-R^+	102	23.8	86	18.2	188	20.9
D^+R^-	67	15.7	101	21.4	168	18.7
Missing	63	14.7	38	8.1	101	11.2
Days in hospital at the time of LT						
1-14	62	14.5	71	15.0	133	14.8
15-30	151	35.3	191	40.5	342	38.0
>30	157	36.7	153	32.4	310	34.4
Missing	58	13.6	57	12.1	115	12.8
Days in ICU at the time of LT						
1-14	34	7.9	148	31.4	182	20.2
15-30	19	4.4	62	13.1	81	9.0
>30	41	9.6	105	22.2	146	16.2
Missing	334	78.0	157	33.3	491	54.6
Immunosuppressive agents						
Alemtuzumab	0	0.0	126	26.7	126	14.0
Anti-thymocyte globulin	10	2.3	27	5.7	37	4.1
Basiliximab	192	44.9	105	22.2	297	33.0
Daclizumab	2	0.5	4	0.8	6	0.7
Other or multiple agents	4	0.9	3	0.6	7	0.8
None	219	51.2	133	28.2	352	39.1
Missing	9	2.1	78	16.5	87	9.7
Supratherapeutic CNI episodes[f]						
0	195	45.6	206	43.6	401	44.6
1-2	162	37.9	190	40.3	352	39.1
3-4	43	10	54	11.4	97	10.8
>4	28	6.5	22	4.7	50	5.6
Steroid mean daily dose (mg per day)						
<10	132	30.8	185	39.2	317	35.2
10-20	196	45.8	202	42.8	398	44.2
>20	100	23.4	85	18.0	185	20.6
Immunosuppression[g]						
Cyclosporine use						
No	149	34.8	233	49.4	382	42.4
Yes	279	65.2	239	50.6	518	57.6
Tacrolimus use						
No	173	40.4	91	19.3	264	29.3
Yes	255	59.6	381	80.7	636	70.7
Steroid use						
No	11	2.6	1	0.2	12	1.3
Yes	417	97.4	471	99.8	888	98.7
Mycophenolate use						
No	139	32.5	65	13.8	204	22.7
Yes	289	67.5	407	86.2	696	77.3

(Continues)

TABLE 1 (Continued)

(Continues)

TABLE 1 (Continued)

Characteristic	Voriconazole unexposed (no exposure to voriconazole) (n = 428)		Voriconazole exposed (≥1-day exposure to voriconazole) (n = 472)		All study patients (n = 900)	
	n	%	n	%	n	%
Azathioprine use						
No	228	53.3	335	71	563	62.6
Yes	200	46.7	137	29	337	37.4
Sirolimus use						
No	413	96.5	421	89.2	834	92.7
Yes	15	3.5	51	10.8	66	7.3
Everolimus use						
No	391	91.4	442	93.6	833	92.6
Yes	37	8.6	30	6.4	67	7.4
Potentially phototoxic drug exposure						
Phototoxic drug use[h]						
No	327	76.4	345	73.1	672	74.7
Yes	101	23.6	127	26.9	228	25.3

CMV, cytomegalovirus; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; D, donor; ICU, intensive care unit; ILD, interstitial lung disease; IPF, interstitial pulmonary fibrosis; LT, lung or heart-lung transplantation; R, recipient.

[a]Subjectively classified according to whether subject would spend majority of time indoors/outdoors/mixed.

[b]According to respective study center's geographical location by latitude: low (>45° latitude), medium (35-45° latitude), high (<35° latitude).

[c]Includes rheumatoid arthritis, systemic lupus erythematosus, Henoch-Schönlein purpura, and psoriasis.

[d]Not including squamous cell carcinoma, basal cell carcinoma, and melanoma.

[e]Absolute neutrophil counts <500 cells/mm^3.

[f]Elevated CNI levels were defined as cyclosporine trough >350 μg/L or tacrolimus trough >20 μg/L.

[g]Patients receiving at least 1 dose were classified as being exposed.

[h]Includes doxycycline, hydroxychloroquine, nifedipine, diltiazem, glyburide, naproxen, piroxicam, and isotretinoin.

sun exposure 7.0% vs 4.9%). Phototoxic reactions were recorded in 15 LT recipients overall, all of whom were exposed to voriconazole.

3.1 | Incidence of SCC

Of the 900 LT recipients, 55 developed SCC. Median age was 58 years (range, 18-75 years), most were male (62%), and the majority had undergone double LT (78%) and had been diagnosed with interstitial pulmonary fibrosis (40%) or chronic obstructive pulmonary disease (29%). Median time from LT to development of SCC was 3.3 years (interquartile range 1.8-4.2 years). The crude incidence rate (per 1000 person-years) of SCC was 33.4 in the exposure to voriconazole alone category, 21.7 in the exposure to voriconazole and other azole(s) category, 10.4 in the exposure to other azoles alone category, and 13.1 in the unexposed category. Overall, a gradual increase in incidence rate of SCC was observed with increase in time since LT in the unexposed, voriconazole alone, and other azole alone exposure categories (Table 2).

3.2 | Voriconazole exposure and other risk factors for SCC

At the univariate level (Table 3), exposure to voriconazole alone was associated with an increased risk for SCC compared with unexposed (hazard ratio [HR] 2.55, 95% confidence interval [CI] 1.42-4.60). An increasing risk of SCC was observed with increasing age. A "dose-response relationship" was observed between exposure to sunlight and SCC. LT recipients with medium sunlight exposure (HR 3.37, 95% CI 1.42-8.0) and high sunlight exposure (HR 4.40, 95% CI 3.50-23.49) were at higher risk for SCC compared with recipients with low sunlight exposure. A history of malignancy before LT was also associated with SCC (HR 22.06, 95% CI 9.97-48.81). With regard to immunosuppressive agents, exposure to alemtuzumab (HR 2.44, 95% CI 1.23-4.80), cyclosporine/azathioprine (HR 7.11, 95% CI 1.56-32.50), and tacrolimus/mycophenolate (HR 4.35, 95% CI 1.00-18.99) was each significantly associated with the risk of SCC at the univariate level. No patients exposed to antithymocyte globulin developed SCC.

In a multivariable model analyzing voriconazole, other azoles, and immunosuppressive agents as time-dependent covariates, exposure to voriconazole alone (adjusted HR 2.39, 95% CI 1.31-4.37) and exposure to voriconazole and other azole(s) (adjusted HR 3.45, 95% CI 1.07-11.06) compared with unexposed were associated with SCC after controlling for confounders (Table 4). Those exposed to other azoles alone did not demonstrate an increased hazard for SCC compared with unexposed individuals alone (adjusted HR 0.80, 95% CI 0.26-2.49).

3.3 | Effect of dose, duration, and indication of voriconazole exposure on the risk of SCC

A multivariable model adjusting for potential confounders suggested that an increase in the mean daily exposure to voriconazole equal to 1 defined daily dose (400 mg daily) increased the risk of SCC by 2.70-fold (adjusted HR 2.70, 95% CI 1.53-4.78) in LT recipients. In addition, the cumulative duration of both voriconazole and other azole(s) exposure and the risk of SCC were modeled in a separate multivariable model adjusting for potential confounders. Compared with unexposed to any azole, cumulative voriconazole exposure of >180 days (adjusted HR 3.52, 95% CI 1.59-7.79) was associated with a higher risk of SCC. The model did not suggest an increased risk of SCC with increasing duration of other azoles (Table 4).

4 | DISCUSSION

This multicenter, retrospective, cohort study suggests a 2.4-fold increased risk of SCC in LT recipients exposed to voriconazole

TABLE 2 Incidence rate (per 1000 person-years) of squamous cell carcinoma by 4 treatment exposure categories: overall and by time since lung transplantation

Characteristic	Unexposed, person-y	Exposure to voriconazole alone, person-y	Exposure to other azole alone, person-y	Exposure to voriconazole and other azole(s) , person-y
Overall incidence rate (No. SCC cases/person-y)				
All patients	13.1 (17/1299)(17/1299)	33.4 (28/837)	10.4 (5/481)	21.7 (5/230)
Incidence rate by time since LT (No. SCC cases/person-y)				
Year 1 post-LT	2.4 (1/415)	4.4 (1/227)	0 (0/118)	34.2 (1/29)
Year 2 post-LT	4.3 (3/698)	20.3 (9/444)	4.2 (1/238)	10.4 (1/96)
Year 3 post-LT	7.5 (7/934)	17.8 (11/618)	8.9 (3/336)	12.6 (2/158)
Year 4 post-LT	8.9 (10/1126)	28.1 (21/749)	9.7 (4/413)	24.6 (5/203)
Year 5 post-LT	9.1 (11/1209)	33.7 (27/802)	8.9 (4/447)	22.9 (5/219)
Year 6 post-LT	11.1 (14/1266)	34.0 (28/824)	10.7 (5/468)	22.1 (5/226)
Year 7 post-LT	13.1 (17/1294)	33.6 (28/834)	10.5 (5/478)	21.7 (5/230)

LT, lung or heart-lung transplantation; SCC, squamous cell carcinoma.

compared with those unexposed, after controlling for important confounding variables. The study findings corroborate previous studies examining the association between voriconazole exposure and SCC or nonmelanoma skin cancer and suggest a dose-response relationship (ie, increasing dose or duration of voriconazole increases the risk of SCC). This risk increased to 3.5-fold when LT recipients were exposed to voriconazole for a cumulative period of >180 days compared with those unexposed and to 2.7-fold for every 400-mg increase in the mean daily dose. LT recipients receiving prophylaxis had a longer duration of exposure compared with those receiving treatment only and were at an increased hazard for SCC.

The impact of voriconazole exposure on the risk of SCC in LT recipients has been suggested in several epidemiologic studies[19–24]; however, this is the first multicenter study, and largest study overall, that has attempted to control for the potential confounding effect of immunosuppression and exposure to sunlight. Incidence of SCC varies across studies depending on the study methodology used, including follow-up time, but also likely as a result of varying patient demographic and clinical characteristics, including the use of different immunosuppression protocols during distinct transplantation eras. A retrospective cohort study by Singer and coworkers evaluated 327 LT recipients during 20 years and reported a crude incidence of 16.5% in patients exposed to voriconazole compared with 11.8% among those unexposed, with an overall median time from LT to SCC diagnosis of 3.6 years.[22] This study also suggested that any exposure to voriconazole was associated with a 2.6-fold increase in the risk of cutaneous SCC adjusted for age, sex, and race (HR 2.62, 95% CI 1.21-5.65), consistent with our finding of increased risk for SCC[22]; however, importantly, this did not account for the type or the duration or intensity of immunosuppression.

A single-center retrospective cohort study of 455 LT recipients showed that voriconazole exposure was associated with risk of SCC, adjusted for age, sex, and race (adjusted HR 1.73, 95% CI 1.04-2.88).[20] In contrast to our study, they were unable to account for voriconazole exposure during hospitalization, nor did they control for the type and intensity of immunosuppression, all of which may have biased their estimate.[20]

Although exposure to voriconazole was associated with an increased risk of SCC, our study also suggests a potential dose-response relationship. Evidence from a retrospective cohort study suggests that longer duration of voriconazole therapy, but not cumulative dose, is an independent risk factor for SCC (odds ratio 1.8, 95% CI 1.3-2.6).[19]Rather than cumulative dose, the present study modeled the mean cumulative dose as the summary exposure measure in an effort to better specify the intensity of voriconazole therapy.[27] Two other studies provide opposing evidence, with both reporting that neither increasing voriconazole duration nor increasing mean cumulative dose was associated with increased risk of skin cancer.[21, 27] Although both included measures of immunosuppression use, one of the studies failed to account for duration of use [27] and the other used a large prescription claims database, which did not contain data on voriconazole use during hospitalization, to inform both voriconazole exposure and the outcome of nonmelanoma skin cancer.[21] The final model in the present study not only accounted for both inpatient/outpatient exposure to voriconazole and individual immunosuppressive agents, including dose and duration, but also controlled for other patient-specific indicators of immunosuppression, including episodes of rejection and neutropenia and calcineurin inhibitor whole blood concentrations, which tend to demonstrate a high degree of both interpatient and intrapatient variability that may not correlate with dose administered.[28]

Although the means by which voriconazole may lead to the development of SCC has not been fully elucidated, it has been proposed that voriconazole itself, or one of its metabolites, may cause ultraviolet-induced DNA damage or disrupt mechanisms used to repair damaged DNA.[20] This process may initially present clinically as photosensitivity or phototoxicity, followed by the development of a cutaneous malignancy in some patients, perhaps accelerated by intense immunosuppression or other immune impairment.[29, 30] Thus far, the association

TABLE 3 Univariate analyses evaluating the association between 4 treatment exposure categories and the risk of squamous cell carcinoma in patients receiving a lung or heart-lung transplant (N = 900)

Characteristics	HR	95% CI Lower	95% CI Upper	*P*-value
Treatment exposure categories				
Unexposed	Ref			
Exposure to voriconazole alone	2.55	1.42	4.60	.002
Exposure to other azole alone	0.73	0.27	1.98	.541
Exposure to voriconazole and other azole(s)	1.47	0.53	4.05	.455
Age, y				
18-29	Ref			
30-49	6.66	0.88	50.70	.067
50-59	9.22	1.25	68.20	.030
≥60	15.04	2.05	110.08	.008
Sex				
Female	Ref			
Male	1.49	0.86	2.56	.153
Race/ethnicity				
Other	Ref			
White	2.08	0.30	14.52	.459
Missing	1.51	0.22	10.50	.674
Occupation[a]				
Indoor	Ref			
Outdoor	1.57	0.69	3.56	.281
Mixed	0.46	0.26	0.83	.009
Chemical exposure[b]				
No	Ref			
Yes	0.69	0.21	2.25	.537
Geographical location				
Spain	Ref			
Australia	24.8	3.17	193.21	.002
Canada	5.73	0.75	43.65	.092
France	-	-	-	-
Germany	1.68	0.15	18.41	.673
Italy	-	-	-	-
Netherlands	4.56	0.51	40.6	.174
Switzerland	-	-	-	-
United States	19.5	2.63	144.84	.004
Sun exposure[c]				
Low	Ref			
Medium	3.37	1.42	8.0	.006
High	4.40	3.50	23.49	<.001
LT type				
Heart-lung	Ref			
Double	1.44	0.19	10.82	.724
Single (right or left)	1.80	0.22	14.41	.581
Re-LT				
No	Ref			
Yes	0.41	0.59	2.84	.366
Underlying disease				
Cystic fibrosis	Ref			
COPD	3.08	1.04	9.10	.041
α_1-Antitrypsin	3.37	0.76	14.99	.111
IPF	6.20	2.15	17.91	.001
Primary pulmonary hypertension	4.82	1.08	21.55	.039
Scleroderma	5.69	1.00	32.44	.050
Other	2.97	0.80	11.08	.105
Immune disorder[d]				
No	Ref			
Yes	1.13	0.19	6.83	.897
Other cancer pre-LT[e]				
No	Ref			
Yes	22.06	9.97	48.81	<.001
Dialysis 30 days post-LT				
No	Ref			
Yes	-	-	-	-
Transplant rejection episodes				
0	Ref			
1-2	1.59	0.91	2.79	.107
3-4	0.84	0.32	2.22	.722
>4	-	-	-	-
Neutropenia episodes[f]				
0	Ref			
1-2	0.92	0.48	1.77	.800
3-4	0.66	0.26	1.65	.371
>4	1.39	0.69	2.78	.354
Diabetes post-LT				
No	Ref			
Yes	0.66	0.32	1.36	.26
CMV				
D^-R^-	Ref			
D^+R^+	0.73	0.33	1.60	.431
D^-R^+	1.10	0.52	2.34	.805
D^+R^-	1.11	0.52	2.41	.785

(Continues)

(Continues)

TABLE 3 (Continued)

Characteristics	HR	95% CI Lower	95% CI Upper	*P*-value
Days in hospital at the time of LT				
1-14	Ref			
15-30	0.48	0.24	0.94	.033
>30	0.42	0.20	0.87	.020
Days in ICU at the time of LT				
1-14	Ref			
15-30	0.56	0.21	1.51	.252
>30	0.40	0.17	0.98	.045
IL-2 antagonist				
No	Ref			
Yes	0.67	0.38	1.20	.176
Alemtuzumab				
No	Ref			
Yes	2.44	1.23	4.80	.010
Antithymocyte globulin use				
No	Ref			
Yes	-	-	-	-
Supratherapeutic CNI episodes[g]				
0	Ref			
1-2	0.69	0.37	1.30	.253
3-4	1.30	0.64	2.66	.463
>4	1.18	0.42	3.32	.752
Steroid mean daily dose (mg per day)				
<10	Ref			
10-20	1.17	0.66	2.08	.587
>20	1.34	0.54	3.31	.524
Cyclosporine use				
No	Ref			
Yes	0.64	0.38	1.08	.094
Tacrolimus				
No	Ref			
Yes	1.04	0.58	1.86	.898
Steroid use				
No	Ref			
Yes	-	-	-	-
Mycophenolate				
No	Ref			
Yes	0.60	0.35	1.04	.067
Azathioprine				
No	Ref			
Yes	1.21	0.71	2.07	.49
Sirolimus				
No	Ref			
Yes	1.37	0.53	3.57	.518
Everolimus				
No	Ref			
Yes	-	-	-	-
Immunosuppression regimen[h]				
Cyclosporine/mycophenolate	Ref			
Cyclosporine/azathioprine	7.11	1.56	32.50	.011
Tacrolimus/mycophenolate	4.35	1.00	18.99	.05
Tacrolimus/azathioprine	4.51	0.88	23.04	.07
Rapamycin	4.32	0.81	23.07	.086
Other	1.69	0.39	7.44	.485
Phototoxic drug[i]				
No	Ref			
Yes	0.68	0.35	1.31	.247

Exposures to voriconazole, other azoles, and immunosuppressive agents were analyzed as time-varying covariates.

CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; D, donor; HR, hazard ratio; ICU, intensive care unit; IL, interleukin; IPF, interstitial pulmonary fibrosis; LT, lung or heart-lung transplantation; R, recipient; Ref, reference category.

[a]Subjectively classified according to whether subject would spend majority of time indoors/outdoors/mixed.

[b]Includes insecticides/herbicides/fungicides, petroleum/diesel/tar products, dry cleaning agents, asbestos, and fiberglass.

[c]According to respective study center's geographical location by latitude: low (>45° latitude), medium (35-45° latitude), and high (<35° latitude).

[d]Includes rheumatoid arthritis, systemic lupus erythematosus, Henoch-Schönlein purpura, and psoriasis.

[e]Not including squamous cell carcinoma, basal cell carcinoma, and melanoma.

[f]Absolute neutrophil counts <500 cells/mm^3.

[g]Elevated CNI levels were defined as cyclosporine trough >350 μg/L or tacrolimus trough >20 μg/L.

[h]Combined immunosuppressive agents are usually prescribed. CNIs, including cyclosporine and tacrolimus, have been the cornerstones of an immunosuppressive regimen, which usually includes ≥2 additional agents, almost always glucocorticoids, and a purine antagonist (mycophenolic acid or azathioprine). Sirolimus (rapamycin) has been used as a substitute for CNIs. The choice of agents is often immunosuppressive protocol driven but is usually adapted to each recipient's risk profile or intolerance to 1 of these agents.

[i]Includes doxycycline, hydroxychloroquine, nifedipine, diltiazem, glyburide, naproxen, piroxicam, and isotretinoin.

between voriconazole plasma concentrations and phototoxicity has been poorly studied, with limited reports of phototoxic skin reactions due to voriconazole being described as idiosyncratic.[15–17] Optimizing voriconazole dosing for an individual can be challenging as a result of considerable interpatient and intrapatient variability in plasma concentrations.[31] Nonetheless, there have been recommendations published with respect to a possible upper limit for therapeutic drug levels in an

TABLE 4 Cox proportional hazards models for the relation between voriconazole exposure and the risk of squamous cell carcinoma of the skin

Model	HR	95% CI	*P*-value
Full cohort, un-adjusted, time-dependent covariates			
Unexposed	Ref		
Exposure to voriconazole alone	2.55	1.42-4.60	.002
Exposure to other azole alone	0.73	0.27-1.98	.541
Exposure to voriconazole and other azole(s)	1.47	0.53-4.05	.455
Full cohort, adjusted, time-dependent covariates[a]			
Unexposed	Ref	-	-
Exposure to voriconazole alone	2.39	1.31-4.37	.005
Exposure to other azole alone	0.80	0.26-2.49	.698
Exposure to voriconazole and other azole(s)	3.45	1.07-11.06	.038
Full cohort, adjusted, time-dependent covariate[a]			
Mean voriconazole daily dose (per 1 DDD increment)[b]	2.70	1.53-4.78	.001
Full cohort, adjusted, time-dependent covariates, by duration[a]			
No exposure to any azole	Ref		
Exposure to voriconazole 1-90 days	0.45	0.10-2.10	.311
Exposure to voriconazole 91-180 days	2.23	0.94-5.30	.070
Exposure to voriconazole >180 days	3.52	1.59-7.79	.002
Exposure to other azole 1-90 days[c]	-	-	-
Exposure to other azole 91-180 days	1.59	0.35-7.34	.551
Exposure to other azole >180 days	1.12	0.24-5.30	.887
Full cohort, adjusted, time-dependent covariates, by indication[a]			
Unexposed	Ref		
Prophylaxis alone	2.77	1.53-5.00	.001
Treatment alone	1.16	0.50-2.67	.727
Prophylaxis and treatment	2.37	0.55-10.11	.244

CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; Ref, reference category.

[a]Adjusted for age, sex, immunosuppression regimen, mean cyclosporine level, mean tacrolimus level, sun exposure, history of malignancy pretransplantation, transplant rejection episodes, and underlying disease.

[b]DDD (voriconazole, 1 DDD = 0.4 g).

[c]No events occurred for this group.

effort to minimize the risk of other drug-related toxicities.[32–34] Further investigation is needed to determine whether therapeutic drug monitoring may help mitigate the risk of SCC.

Despite the strengths of this study, including a large and generalizable cohort of LT recipients and accounting for important confounding factors, limitations did still exist, including the retrospective observational nature of the dataset and the potential for inaccuracies in medical records. Given that proxy variables were used to control for confounding (ie, immunosuppressive agents in the absence of a comprehensive measure of immune status; geographical location/latitude of LT center in the absence of individual-level data on exposure to sunlight in medical charts), residual confounding due to these factors cannot be completely ruled out. Further, because immunosuppression and sun exposure are center and region-specific, it is difficult to separate the effect of center practices versus geographic location. Caution should be exercised when generalizing the findings to more-diverse populations (ie, all voriconazole-treated patient populations) given that patients with LT are a special patient population with unique factors that make them more susceptible to SCC of the skin.

In summary, this study using real-world data from across Europe, North America, and Australia suggests that voriconazole is associated with an increased risk of SCC in LT recipients and that this risk increases with increasing dose or duration of voriconazole. There is currently no universally accepted recommendation for an optimal antifungal prophylactic strategy in LT recipients. Voriconazole has been shown to decrease morbidity and mortality in a variety of clinical circumstances, including primary treatment of IA in LT recipients[9]; however, voriconazole's association with an increased risk in SCC in susceptible LT recipients should be weighed carefully with its benefits in preventing or treating invasive fungal infections. Further, LT recipients who require prolonged voriconazole prophylaxis or treatment should be counselled regarding sun avoidance and sunscreen and have close dermatologic follow-up.

ACKNOWLEDGMENTS

We thank Dr John Orazem for advice on data analysis, Dr Quazi Ataher for help in data interpretation and critical review of the draft manuscript, and Dr Marcia Ruiz, Ken Schanbacher, Yinka Akinlolu, and Rhea Pavan for research coordination and support. Medical writing support was provided by Martin Bell at Complete Medical Communications and was funded by Pfizer. *Sources of support: This study was sponsored by Pfizer.*

DISCLOSURE

The authors of the manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Drs Shahid Husain, Lianne G. Singer, and Bassem Hamandi are employees of University Health Network, University of Toronto, Ontario, Canada, which received financial support from Pfizer in connection with the study and development of the manuscript. Dr Fernanda P. Silveira is an employee of the University of Pittsburgh, Pittsburgh, PA, USA, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer

in connection with the study and development of the manuscript. Dr Amparo Solé is an employee of the University Hospital La Fe, University of Valencia, Valencia, Spain, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Denis Hadjiliadis is an employee of the University of Pennsylvania, Philadelphia, PA, USA, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Piedad M. Ussetti is an employee of the Hospital Puerta de Hierro, Madrid, Spain, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Christine Fegbeutel is an employee of the Hanover Medical School, Hanover, Germany, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Erik A. Verschuuren is an employee of the University Medical Centre Groningen, University of Groningen, Groningen, Netherlands, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Peter V. Chin-Hong is an employee of the University of California San Francisco, San Francisco, CA, USA, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Chien-Li Holmes-Liew is an employee of the Royal Adelaide Hospital, Adelaide, Australia, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Eliane M. Billaud is an employee of APHP Hopital Européen G Pompidou, Paris, France, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Paolo A. Grossi is an employee of the University of Insubria, Varese, Italy, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Oriol Manuel is an employee of the University Hospital of Lausanne, Lausanne, Switzerland, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Deborah J. Levine is an employee of the University of Texas Health Science Center San Antonio, San Antonio, TX, USA, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Dr Richard G. Barbers is an employee of the KECK Medical Center of the University of Southern California, Los Angeles, CA, USA, which received financial support for the conduct of this study from the University Health Network/University of Toronto. University Health Network received financial support from Pfizer in connection with the study and development of the manuscript. Drs Jalal Aram, Jean Yan, Jingping Mo, and Muhammad Younus are employees of Pfizer and own stock in Pfizer.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Hamandi B, Fegbeutel C, Silveira FP, et al. Voriconazole and squamous cell carcinoma after lung transplantation: A multicenter study. *Am J Transplant*. 2018;18:113–124. https://doi.org/10.1111/ajt.14500