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Title: Squamous Cell Carcinoma of the Skin and Voriconazole Therapy in Lung Transplant Recipients: A Case Series

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Author contributions

All authors contributed to concept/design of the study, critical revision and approval of the article. C.F.N. also contributed in data collection, analysis/interpretation and writing the manuscript. G.I.S. and B.L. contributed by providing patients. G.I.S., B.L., O.M. and M.A.S. contributed to clinical case interpretation.

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Title: Squamous Cell Carcinoma of the Skin and Voriconazole Therapy in Lung Transplant Recipients: A Case Series

Abstract

Background: Prolonged voriconazole therapy may be associated with skin squamous cell carcinoma (SCC) in lung transplant (LTx) patients. This is of concern given the frequent use of voriconazole in the LTx setting. The impact of voriconazole therapy on the risk of developing skin SCC among an Australian LTx cohort who had an additional risk due to high-level of sun exposure remain unclear.

Aim: This study described the extent and outcomes of new or recurrent skin SCC among LTx patients receiving voriconazole.

Methods: This retrospective cohort study was undertaken at The Alfred Hospital, Australia. Adult LTx recipients with skin SCC who had received voriconazole between 1st July 2003 and 30th June 2010 were included. Medical records and histopathology reports were reviewed. Demographics, clinical characteristics, voriconazole exposure (dose and duration), potential risk factors for skin SCC and manifestations of the skin SCC were recorded. The Naranjo algorithm was used to determine the likelihood of skin SCC being due to voriconazole exposure.

Results: Of the 102 LTx patients receiving voriconazole, 14 (13.7%) had at least one episode of skin SCC: seven (group 1) had skin SCC during or after voriconazole exposure; three (group 2) had skin SCC before commencing voriconazole therapy, which recurred or worsened subsequently; three (group 3) had a history of skin SCC prior to voriconazole being prescribed but no skin SCC was noted during or after voriconazole exposure; and one (group 4) had multiple skin SCCs before LTx and voriconazole use, and developed further skin SCC

35 post-voriconazole. The median (interquartile range) of voriconazole exposure in group 1, 2
36 and 3 patients were 119 days (79.5, 693), 1,127 days (665.5, 1129) and 173 days (135.5,
37 341), respectively. The Naranjo score indicated a probable association between voriconazole
38 use and skin SCC in three patients and a possible relationship in eight.

39

40 Conclusions: Prolonged voriconazole exposure may contribute to the development,
41 recurrence and progression of skin SCC in LTx patients.

42

43 **Keyword:** voriconazole, lung transplant, skin squamous cell carcinoma

44 **Introduction**

45 In comparison to the general population, solid organ transplant (SOT) recipients have an
46 increased risk of developing squamous cell carcinoma (SCC), basal cell carcinoma (BCC)
47 and malignant melanoma.¹ The International Society for Heart and Lung Transplantation
48 reported that the incidence of skin malignancy among patients surviving 1, 5 and 10 years
49 post-LTx was 1.0%, 7.8% and 18.2%, respectively.²

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51 Several risk factors for developing skin carcinoma among SOT recipients have been
52 identified: high-level of immunosuppression, increased exposure to ultraviolet (UV)
53 radiation, Fitzpatrick skin type I, II, III, advanced age, history of non-melanoma skin cancer
54 or melanoma, and increased number of keratotic skin lesions.³ The emerging evidence for
55 causal associations between long-term voriconazole exposure and skin SCC⁴⁻¹¹ is of concern
56 given the frequent use of voriconazole prophylaxis, which is commonly administered for
57 months in LTx setting.¹² Also, residing in geographical locations with high-level sun
58 exposure has been identified as an independent risk factor for LTx patients developing skin
59 SCC.⁶ Thus, the aim of this case series was to describe the extent and outcomes of new or
60 recurrent skin SCC among LTx recipients who had been prescribed voriconazole, either for
61 prophylactic use or treatment, and to investigate the possible link between skin SCC and
62 voriconazole. This study provides new insights into the impact of voriconazole therapy on the
63 development of skin SCC among Australian LTx cohort, who had an additional risk due to
64 high-level of sun exposure, offering a different perspective from that published by other
65 international LTx centres.

66

67 **Methods**

68 This retrospective cohort study was undertaken at The Alfred Hospital, Melbourne, Australia.
69 Adult (i.e. ≥ 18 years old) LTx patients who had received voriconazole between 1st July 2003
70 and 30th June 2010 were identified using LTx unit's database and pharmacy dispensing data.
71 Patients' medical records and histopathology reports of biopsy specimens were reviewed. All
72 patient's demographics and clinical characteristics, details of voriconazole exposure (dose
73 and duration), potential risk factors for skin SCC and manifestations of skin SCC were
74 collected by one researcher (CFN) to ensure the consistency of data collection. The Naranjo
75 algorithm (comprising 10 validated questions) was used to determine the association between
76 skin SCC and voriconazole exposure.¹³ Each question was assigned a score of +1, +2, 0 or -1
77 based on the answers (yes, no, unknown or not applicable); the probability of SCC being
78 associated with voriconazole was then determined by the total cumulative score, defined as
79 definite (9-10), probable (5-8), possible (1-4) or doubtful (0).¹³ Each patient was followed up
80 from the first onset of skin SCC until 30th June 2011.

81

82 The incidence of SCC was self-reported or noted by LTx physicians during review in clinic,
83 and all patients were then referred to dermatology clinic for further follow-up. The study was
84 approved by the Human Research Ethics Committees of The Alfred Hospital and Monash
85 University.

86

87 **Immunosuppression protocol and antimicrobial prophylaxis**

88 Between July 2003 and July 2008, most LTx patients received a cyclosporin-based
89 immunosuppressive regimen post-LTx. From August 2008, tacrolimus replaced cyclosporin.
90 Induction therapy (i.e. immunosuppressant therapy administered usually peri-operatively to
91 reduce the risk of acute rejection and to also delay initiation of maintenance
92 immunosuppression), was not routinely given except in patients with a positive B-cell cross-
93 match or limited renal function. All patients received trimethoprim/sulfamethoxazole
94 (TMP/SMX) for *Pneumocystis jirovecii* prophylaxis. For cytomegalovirus (CMV)
95 prophylaxis, all at-risk patients received intravenous (IV) ganciclovir, followed by oral
96 valganciclovir \pm IV CMV hyperimmunoglobulin, or oral valaciclovir. Administration of
97 voriconazole prophylaxis and treatment were guided by microbiological findings from
98 respiratory specimens, and clinical signs and symptoms.¹⁴

99

100 **Results**

101 Of the 102 LTx patients receiving voriconazole, 14 (13.7%) had at least one episode of skin
102 SCC: seven had skin SCC during or after voriconazole exposure (group 1); three (2.9%) had
103 skin SCC before commencing voriconazole therapy, which recurred or progressed subsequent
104 to voriconazole administration (group 2); three (2.9%) had a history of skin SCC prior to
105 voriconazole being prescribed but no skin SCC was noted during or after voriconazole
106 exposure (group 3); and one had multiple skin SCC before lung transplantation and
107 voriconazole use, and developed further skin SCC post-voriconazole exposure (group 4).

108

109 **Demographics, clinical characteristics and potential risk factors**

110 Details of the 14 patients are shown in Table 1. All patients were Caucasian, with a median
111 age of 56.5 years at the first skin SCC diagnosis. The majority of the patients were male
112 (10/14, 71.4%). The median (interquartile range) time to first onset of skin SCC was 1,445
113 (519.5, 2607.5) days post-LTx. All except four patients received standard triple
114 immunosuppressive regimen (i.e. prednisolone, calcineurin inhibitor and anti-metabolite)
115 whilst being prescribed voriconazole (Table 1). During voriconazole therapy, all patients
116 received, concomitantly, a number of photosensitising agents with TMP/SMX being the most
117 common (13/14, 92.8%), followed by statins (6/14, 42.9%). Other potential risk factors for
118 skin SCC are given in Table 1.

119

120 **Voriconazole exposure**

121 Fifteen courses of voriconazole [median (interquartile range) = 2 (1, 3)] were prescribed for
122 group 1 patients, with more than half (8/15) for prophylaxis. The median (interquartile range)
123 cumulative voriconazole dose was 32.1 g (29.8, 199.5) and the median (interquartile range)
124 duration of voriconazole exposure was 119 days (79.5, 693). The median (interquartile range)
125 time to first onset of skin SCC after the first course of voriconazole was 533 days (436, 591).
126 Group 2 patients received a total of five courses of voriconazole, three of which were for
127 prophylaxis. The median (interquartile range) of cumulative dose of voriconazole was 327.8
128 g (196.3, 389.3) and the median (interquartile range) duration of exposure to voriconazole
129 was 1,127 days (665.5, 1129). Patients in group 3 had a total of six courses of voriconazole,
130 all as prophylaxis. They had lower median (interquartile range) cumulative dose of
131 voriconazole of 39.2 g (36.4, 118.7) and shorter median (interquartile range) duration of
132 voriconazole therapy, 173 days (135.5, 341), compared to group 2 patients. The only patient
133 in group 4 received a cumulative voriconazole dose of 10.0 g over 27 days for prophylaxis.

134 Serum voriconazole concentrations were monitored in only three patients; median
135 (interquartile range) of 1.35 mg/L (0.8, 1.9) was reported.

136

137 **Clinical details of skin SCC, treatments and outcomes**

138 All patients (n = 14) had their skin SCC lesions surgically excised. Clinical details of skin
139 SCC for the patients in group 1 and group 2 are shown in Table 2. Two patients in group 2
140 who had invasive skin SCC received radiotherapy. One in group 1 had parotid gland
141 metastasis that required parotidectomy, followed by radiotherapy and chemotherapy with
142 capecitabine. Half of the patients (7/14) died, within a median (range) of 11.6 years (5.8-
143 15.8) post-LTx and 4.2 years (1.8-8.9) post-SCC diagnosis.

144

145 **Naranjo algorithm**

146 According to the Naranjo probability scale, two patients in group 1 and one in group 2 had a
147 score of 5 (probable reaction). The remainder scored in the possible range (a score of 2-4).
148 All group 3 patients had score of 0 (doubtful reaction); while the patient in group 4 had a
149 score of 1 (possible reaction).

150

151 **Discussion**

152 This case series describes a LTx cohort who developed skin SCC lesions after prolonged
153 voriconazole use in an Australian setting. The association between voriconazole therapy and
154 skin SCC has recently been recognised in various immunosuppressed hosts.^{4,5,7} A strength of
155 the present case series is that it included those who had recurrent or multiple aggressive skin
156 SCC following long-term voriconazole exposure, providing new insights to the current
157 evidence gap.

158

159 The most common skin reaction that has been previously reported with the use of
160 voriconazole is drug-related photosensitivity,¹⁵⁻¹⁸ followed by pseudophorphyria,^{19, 20}
161 erythematous eruptions,²¹ photoaging,¹⁶ Stevens-Johnson syndrome and toxic epidermal
162 necrolysis.²² The etiology for voriconazole-induced photosensitivity remains unknown. Two
163 mechanisms have been postulated. The photosensitivity reactions could be a direct effect of
164 voriconazole therapy, involving the inhibition of metabolic breakdown of vitamin A (all-
165 trans retinol), leading to an accumulation of phototoxic retinoid compound in the plasma.²³
166 On the other hand, the phototoxic complications could be an indirect effect of a major

167 metabolite, voriconazole N-oxide that absorbs the UV A and B spectrum and acts as a vital
168 chromophore.²³

169

170 Patients in earlier publications were reported to have concurrent manifestations of
171 photosensitivity eruptions, followed by multiple **actinic keratosis** (AK) and skin SCC lesions
172 occurring a few months after the introduction of voriconazole.^{4, 5, 7} Thus, it has been
173 speculated that prolonged voriconazole therapy resulted in chronic phototoxicity, which then
174 contributed to the development of skin SCC in transplant patients.⁴ Erythema of photo-
175 exposed surfaces, however, was observed in only one patient in our cohort, which preceded
176 the first skin SCC diagnosis by two months.¹⁰ Given the retrospective nature of this study, it
177 is possible that the incidence of voriconazole-induced photosensitivity prior to SCC was not
178 reported in the medical history or by the patients during routine review.

179

180 While Singer et al.⁸ reported high cumulative voriconazole dose was an independent risk
181 factor for skin SCC in LTx patients, Vadnerker et al.⁶ revealed that the occurrence of skin
182 SCC among LTx patients was related to the duration of voriconazole therapy,⁶ consistent
183 with Feist et al.⁹ and Zwald et al.¹¹ A recent study revealed that LTx recipients had a 73%
184 increased risk of developing skin SCC post voriconazole exposure; the risk was increased by
185 3% for each additional 30-day exposure at standard voriconazole dose.²⁴ In the current case
186 series, the median duration of voriconazole exposure among group 1 patients was
187 approximately 1.5 months longer than the patients in the study by Vadnerker et al., and the
188 median cumulative dose of voriconazole was 46.1 g higher.⁶ Similar to Vadnerker et al., the
189 majority of group 1 patients in our cohort had skin SCC lesions located on the head and neck,
190 and were not taking voriconazole at the time of skin SCC diagnosis.⁶

191

192 **In our cohort, therapeutic drug monitoring (TDM) for voriconazole was conducted in only
193 three patients; none had reported levels above 6 mg/L, the level associated with toxicity.²⁵**

194 **The low uptake of voriconazole TDM is probably due to limited access to timely results (off-
195 site testing), and the lack of clarity related to the role of TDM for voriconazole in LTx
196 recipients during the study period. In recent years, there has been increasing trend towards
197 routine monitoring of serum voriconazole levels among LTx centres.¹² The relationships
198 between voriconazole plasma concentration and skin SCC should be explored in future
199 studies.**

200

201 Unlike group 1 patients, it appears that group 2 patients had a higher incidence of invasive
202 SCC, with recurrent or progressive skin SCC lesions predominately noted when patients were
203 taking voriconazole. Invasive skin SCC lesions on the scalp with perineural invasion were
204 noted only in case 10 (group 2) following voriconazole prophylaxis. The reason for the
205 differences in skin SCC during or after voriconazole exposure between the two groups cannot
206 be determined. Contributing factors may include the 9-fold increased duration of
207 voriconazole exposure, the 10-fold increased total cumulative dose of voriconazole or the 2-
208 fold longer duration of immunosuppressive therapy among the group 2 patients. More
209 importantly, prolonged use of voriconazole prophylaxis may indicate a more compromised
210 immune system which could have impacted on the risk of developing skin SCC in LTx
211 patients.¹⁰ As such, clinicians should consider discontinuing voriconazole and switching to
212 alternatives such as posaconazole or itraconazole, if prolonged antifungal prophylaxis is
213 required, given the low incidence of skin adverse events associated with these two azoles.²³

214
215 Apart from long-term voriconazole use, high level of sun exposure has been associated with
216 the development of skin SCC in LTx patients.⁶ Higher incidence of skin SCC has been noted
217 in areas of significant exposure to UV radiation, a known distinct mutagen of keratinocytes.⁶
218 ²³ Australia is one of the countries that has year-round high-level UV radiation,⁵ and in our
219 study, all patients had multiple skin SCC lesions located on photo-exposed areas (i.e. scalp,
220 forehead, cheek, lower legs, extensor forearms and dorsum of the hands), in line with other
221 studies.^{4,5} In addition, five patients in this study had extensive sun exposure with a history of
222 sun-burn. The current cohort had a median age of 56.5 years at the first skin SCC diagnosis.
223 Higher rate of skin SCC was noted in older populations;⁹ accumulation of high-dose UV
224 radiation over a prolonged period of time could have been the reason behind this observation.
225 In light of this, it would be prudent to give appropriate advice on sun protection (e.g. wear
226 sunscreen and protective clothing) and to undertake prospective skin monitoring in LTx
227 recipients who receive voriconazole therapy for 3 months and above.

228
229 Another prominent risk factor for the development of skin SCC among transplant recipients
230 is the level of immunosuppression. Studies have shown that longer duration and more
231 intensive immunosuppressive regimens contribute to a higher risk of developing skin
232 cancer.^{1,3,26} In our series, all LTx patients had two or more immunosuppressive agents, with
233 a median duration of immunosuppression of nearly 4.0 years prior to the first skin SCC being
234 diagnosed. Unlike the study by Vadnerker et al.,⁶ our LTx centre did not routinely use

235 alemtuzumab induction therapy, which would have further compromised patients' immune
236 systems.

237

238 It is possible that the skin SCCs observed in our study were due to patients receiving
239 concomitant photosensitising agents (i.e. TMP/SMX, statins), given the reported association
240 between photosensitising drug exposure and non-melanoma skin carcinoma.²⁷ However, the
241 types of SCC lesions found in the current cohort are not usually seen with these agents.^{4, 28}
242 Additionally, skin carcinoma pre-transplant⁹ could be important, such as in case 14, given
243 that this patient had multiple skin SCC lesions before LTx and voriconazole therapy.

244

245 In the current study, there were only three patients with a Naranjo score indicating a probable
246 causal relationship between SCC and voriconazole therapy. As this retrospective study has no
247 control arm, the direct causal relationship between drug exposure and skin carcinoma cannot
248 be fully elucidated, but given the clinical implications, further investigation involving large
249 prospective studies is warranted. In summary, prolonged voriconazole exposure may have
250 contributed to the development, recurrence or progression of SCC in LTx patients. The
251 patient who has already had skin SCC should be cause for concern when starting
252 voriconazole as at least 50% of them in this series had recurrence/worsening. The long-term
253 use of voriconazole should be administered with care and routine monitoring for skin SCC
254 should be performed, particularly in those at high risk of skin carcinoma.

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Table 1 Demographics and clinical characteristics of the LTx patients with skin SCC (n = 14)

Patient	Age/ gender	Indication for lung transplantation	Voriconazole dose and duration	Immunosuppressant agents during voriconazole use	Other photosensitising agents during voriconazole use	Photosensitivity during voriconazole use	Types of skin cancer lesions*	Survived/ dead at end of follow-up
(a) Group 1: Had skin SCC during or after voriconazole exposure (n = 7)								
1†	45/F	1) PPH 2) BOS 3) BOS	1) 200 mg BD for 397 days 2) 200 mg BD for 322 days 3) 200 mg BD, then 100 mg BD for 219 days	1) Pred/Tacro/MMF 2) Pred/Tacro/MMF 3) Pred/Tacro/Aza	TMP/SMX, Simvastatin	Erythema of photoexposed areas	AK SCC BCC	Dead
2‡	66/M	IPF	1) 200 mg BD for 77 days	1) Pred/Tacro/MMF	TMP/SMX, atorvastatin	Not documented	AK SCC Bowen's disease BCC	Dead

Table 1 Continued

Patient	Age/ gender	Indication for lung transplantation	Voriconazole dose and duration	Immunosuppressant agents during voriconazole use	Other photosensitising agents during voriconazole use	Photosensitivity during voriconazole use	Types of skin cancer lesions*	Survived/ dead at end of follow-up
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3† §	59/F	Alpha antitrypsin deficiency	1-	1) 200 mg BD for 7 days 2) 100 mg BD , then 200 mg BD for 76 days	1) Pred/Cyclo 2) Pred/Cyclo	TMP/SMX	Not documented	SCC Bowen's disease BCC	Dead
4†	51/M	COPD		1) 200 mg BD for 39 days 2) 200 mg BD for 93 days 3) 200 mg BD for 317 days	1) Pred/Cyclo/Aza 2) Pred/Tacro/Aza 3) Pred/Tacro/Aza/Evero	TMP/SMX, Atorvastatin	Not documented	AK SCC Bowen's disease BCC	Survived
5	51/F	Asthma		1) 200 mg OD for 126 days 2) 200 mg OD for 681 days 3) 200 mg BD for 145 days	1) Pred/Tacro 2) Pred/Tacro 3) Pred/Tacro/MMF	TMP/SMX	Not documented	AK SCC Bowen's disease BCC	Dead

Table 1 Continued

Patient	Age/ gender	Indication for lung transplantation	for	Voriconazole dose and duration	Immunosuppressant agents during voriconazole use	Other photosensitising agents during voriconazole use	Photosensitivity during voriconazole use	Types of skin cancer lesions*	Survived/ dead at end of follow-up
6	66/M	COPD		1) 200 mg BD for 21 days	1) Pred/Tacro/Aza	TMP/SMX, Atorvastatin	Not documented	AK Bowen's disease	Survived
7†	53/M	Alpha antitrypsin	1-	1) 200 mg BD for 45 days 2) 100 mg BD, then 50 mg BD	1) Pred/Cyclo/Aza 2) Pred/Tacro	TMP/SMX	Not documented	AK SCC	Survived

deficiency for 74 days

Bowen's disease
BCC
Lentigo maligna

Table 1 Continued

Patient	Age/ gender	Indication for lung transplantation	Voriconazole dose and duration	Immunosuppressant agents during voriconazole use	Other photosensitising agents during voriconazole use	Photosensitivity during voriconazole use	Types of skin cancer lesions*	Survived/ dead at end of follow-up
(b) Group 2: Had skin SCC prior to voriconazole exposure with recurrence or worsened skin SCC when voriconazole was administered (n = 3)								
8	41/M	Secondary pulmonary hypertension	1) 200 mg BD for 1,127 days	1) Pred/Tacro/MMF/ Evero	Pravastatin	Not documented	AK SCC Bowen's disease	Survived
9	61/M	Emphysema	1) 200 mg BD, then 100 mg BD for 145 days 2) 100 mg BD, then 50 mg BD for 59 days	1) Pred/Siro 2) Pred/Evero	TMP/SMX, Atorvastatin	Not documented	SCC Bowen's disease BCC	Dead
10	56/F	Bronchiectasis	1) 200 mg BD for 217 days 2) 100 mg BD, then 150 mg BD	1) Pred/Tacro/MMF	TMP/SMX	Not documented	SCC Bowen's disease	Survived

for 914 days

Table 1 Continued

Patient	Age/ gender	Indication for lung transplantation	Voriconazole dose and duration	Immunosuppressant agents during voriconazole use	Other photosensitising agents during voriconazole use	Photosensitivity during voriconazole use	Types of skin cancer lesions*	Survived/ dead at end of follow-up
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(c) Group 3: Had skin SCC prior to voriconazole exposure but no recurrence skin SCC after commencing voriconazole (n = 3)

11† §	69/M	Bronchiectasis	1) 100 mg BD for 27 days 2) 200 mg BD for 482 days	1) Pred/Tacro 2) Pred/Tacro	TMP/SMX	Not documented	Not Documented	Survived
12	57/M	Emphysema	1) 200 mg BD for 70 days 2) 200 mg BD for 28 days	1) Pred/Cyclo/MMF 2) Pred/Cyclo/MMF	TMP/SMX	Not documented	Not Documented	Dead
13	60/M	Emphysema	1) 200 mg BD for 72 days 2) 200 mg OD for 101 days	1) Pred/Cyclo 2) Pred/Cyclo	TMP/SMX	Not documented	Not documented	Dead

Table 1 Continued

Patient	Age/ gender	Indication for lung transplantation	Voriconazole dose and duration	Immunosuppressant agents during voriconazole use	Other photosensitising agents during voriconazole use	Photosensitivity during voriconazole use	Types of skin cancer lesions*	Survived/ dead at end of follow-up
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				voriconazole use	use	follow-up		
(d) Group 4: Had skin SCC prior to LTx and voriconazole exposure, and with recurrence skin SCC after voriconazole exposure (n = 1)								
14	52/M	COPD	1) 100 mg BD for 4 days 2) 200 mg BD for 23 days	1) Pred/Cyclo/MMF 2) Pred/Cyclo/MMF	TMP/SMX	Not documented	Bowen's disease BCC	Survived

* Appeared during or after voriconazole exposure

† Had extensive sun exposure or sun-burn prior or during voriconazole therapy

‡ Had an episode of chronic rejection requiring lymphocyte immune globulin

§ Had Fitzpatrick skin type II

|| Had family or personal history of skin carcinoma

AK = Actinic keratosis; BCC = Basal cell carcinoma; SCC = Squamous cell carcinoma; COPD = Chronic obstructive pulmonary disease; BOS = Bronchiolitis obliterans syndromes; IPF = Idiopathic pulmonary fibrosis; PPH = Primary pulmonary hypertension; Aza = Azathioprine; Cyclo = Cyclosporine; Evero = Everolimus; MMF = Mycophenolate mofetil; Pred = Prednisolone; Siro = Sirolimus; Tacro = Tacrolimus; BD = Twice daily

Table 2 Details of skin SCC episodes* †

	Group 1 patients (n = 7)	Group 2 patients (n = 3)
Total episodes of skin SCC (median, range)	37 (5, 1–11)	16 (5, 4–7)
Types of skin SCC lesions while taking voriconazole		
SCC	1	2
SCC in situ (Bowen's disease)	0	3
Types of skin SCC lesions post- voriconazole exposure		
SCC	6	2
SCC in situ (Bowen's disease)	6	2
Location of skin SCC lesions		
Head (e.g. scalp, forehead, ear, lips, nose, eye brow) and neck	5	3
Upper limb (e.g. forearm, hand)	4	1
Trunk (e.g. abdomen, back)	1	0
Lower limb (e.g. leg, foot)	2	0
Invasive or aggressive SCC	0	2
Distant metastasis SCC	1	0

* All data are shown as number of patients unless otherwise indicated.

† Details of skin SCC for group 3 patients were not included as no skin SCC was noted during and after voriconazole exposure; while the only one patient in group 4 developed one episode of Bowen's disease post-voriconazole.