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Research note

Voriconazole plus terbinafine combination antifungal therapy for invasive *Lomentospora prolificans* infections: analysis of 41 patients from the FungiScope® registry 2008–2019

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ABSTRACT

Objectives: *Lomentospora prolificans* is an emerging cause of serious invasive fungal infections. Optimal treatment of these infections is unknown, although voriconazole-containing treatment regimens are considered the treatment of choice. The objective of this study was to evaluate the role of combination antifungal therapy for *L. prolificans* infections.
Methods: We performed a retrospective review of medical records of patients with invasive *L. prolificans* infection diagnosed between 1 January 2008 and 9 September 2019 that were documented in the FungiScope® registry of rare invasive fungal infections. We compared clinical outcomes between antifungal treatment strategies.
Results: Over the study period, 41 individuals with invasive *L. prolificans* infection from eight different countries were documented in the FungiScope® registry. Overall, 17/40 (43%) had treatment response/stable disease and 21/40 (53%) had a fatal outcome attributed to invasive fungal infection. Combination

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Olorofim
Outcomes
Treatment
Terbinafine
Scedosporium
Voriconazole

antifungal therapy was associated with increased 28-day survival (15/24 survived versus 4/16 receiving monotherapy; p 0.027) and the combination voriconazole plus terbinafine trended to be associated with higher rates of treatment success (10/16, 63%, 95% CI 35%–85%) compared with other antifungal treatment regimens (7/24, 29%, 95% CI 13%–51%, p 0.053). In Kaplan–Meier survival analysis there was a higher survival probability in individuals receiving the voriconazole/terbinafine combination compared with other antifungal regimens (median survival 150 days versus 17 days).

Conclusions: While overall mortality was high, combination antifungal treatment, and in particular combination therapy with voriconazole plus terbinafine may be associated with improved treatment outcomes compared with other antifungal regimens for the treatment of invasive *L. prolificans* infections.

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Introduction

Invasive infection from multidrug-resistant *Lomentospora prolificans* (formerly *Scedosporium prolificans*) is associated with devastating mortality rates, particularly among immunocompromised hosts. Although voriconazole is considered the drug of choice [1–3], the MICs observed against voriconazole are high, and there has been an increasing number of case reports and case series describing the successful use of combination antifungal treatment, particularly with voriconazole plus terbinafine [2,4,5]. Still, the exact role of antifungal combination treatment for invasive *L. prolificans* infections and the impact on patient outcomes is uncertain. The objective of this study was to evaluate the role of combination antifungal therapy in individuals with invasive *L. prolificans* infections occurring between 2008 and 2019 that were documented in the FungiScope® Registry [6].

Materials and methods

We performed a retrospective review of medical records of all FungiScope® patients with probable or proven invasive fungal infections (IFIs) caused by *L. prolificans* that were diagnosed between 1 January 2008 and 9 September 2019 [6]. Clinical characteristics of a subset of the cohort have been published previously [4,5,7]. Treatment response and breakthrough infections were classified following consensus statements [8,9]. Infections were determined to be disseminated if *L. prolificans* was isolated from blood or two non-contiguous anatomical sites. IFI-related mortality was defined as death due to IFI as determined by the investigator(s) who documented the case into the FungiScope® registry. Antifungal treatment was defined as receiving an antifungal drug for treatment of (suspected) fungal infection for ≥2 consecutive days; individuals who were receiving two or more antifungal drugs combined for ≥2 consecutive days were classified as receiving combination treatment, whereas others who received antifungal treatment were classified as receiving monotherapy.

Statistical analyses were performed using IBM SPSS STATISTICS v26 (IBM Corp., Armonk, NY, USA). Age and treatment durations were presented as median and interquartile range (IQR). Underlying conditions, clinical manifestations and treatment regimens were compared between those with treatment success versus treatment failure, 28-day overall survival versus mortality, and those with versus without IFI-attributed mortality using Wilcoxon Rank Sum test, or two-tailed Fisher's exact test, as appropriate. Long-term survival probability was tested using Kaplan–Meier survival plots for days 84 and 360 after treatment initiation, with log-rank tests to determine significant differences between groups' survival lines. The study protocol and all study-related procedures were approved by the University of California San Diego, CA, USA Institutional Review Board (IRB) (Project #181119).

Results

Over the study period, 41 individuals with invasive *L. prolificans* infection (36 proven, 5 probable; 24 classified as breakthrough infections) from eight different countries were documented in FungiScope® registry. Patients were diagnosed between 2008 and 2019, with 66% (27/41) of them diagnosed in 2014 or later. Median age was 65 years (IQR 48–69 years).

Table 1 displays differences in demographic and clinical characteristics, as well as treatment, between: (a) those with treatment response/stable disease (n = 17/40, 43% of those with evaluable outcome) versus those with deterioration/progression/failure (n = 23/40; 58%) at final assessment, (b) those who survived day 28 after diagnosis of IFI (n = 20/41; 49%) versus those who died before day 28 (n = 21/41; 51%), and (c) those with IFI-attributed mortality (21/40; 53%). Final response assessment was conducted at a median of 241 days (IQR 84–335 days) after diagnosis in those who survived and a median of 13 days (IQR 4–35 days) after IFI diagnosis in the deceased (i.e. final assessment on the day of death).

Those who survived received antifungal treatment for a median of 181 days (IQR 47–332 days). Overall, combination antifungal therapy was associated with increased 28-day survival (15/24 survived versus 4/16 receiving monotherapy; p 0.027) and there was a trend towards higher rates of treatment response, particularly driven by voriconazole/terbinafine combination therapy response rates (10/16, 63%; 95% CI 35%–85%) when compared with other antifungal treatment regimens (7/24, 29%; 95% CI 13%–51%; p 0.053). Median duration of voriconazole/terbinafine combination was 69 days (IQR 9–204 days), median duration in survivors 181 days (IQR 69–332 days). Half of the individuals receiving the voriconazole/terbinafine combination received a third antifungal agent (five received echinocandin and three received liposomal amphotericin B) and similar treatment response rates were observed in those with triple therapy compared with the two-drug therapies. Patients successfully treated with a voriconazole/terbinafine combination therapy included three with haematological malignancies (1/3 with disseminated infection) and three with trauma/surgery (1/3 with disseminated infection). Three of the five (60%) individuals with underlying haematological or oncological malignancies who responded to treatment received voriconazole/terbinafine whereas the other two received voriconazole monotherapy (both localized infections). Two of the four (50%)

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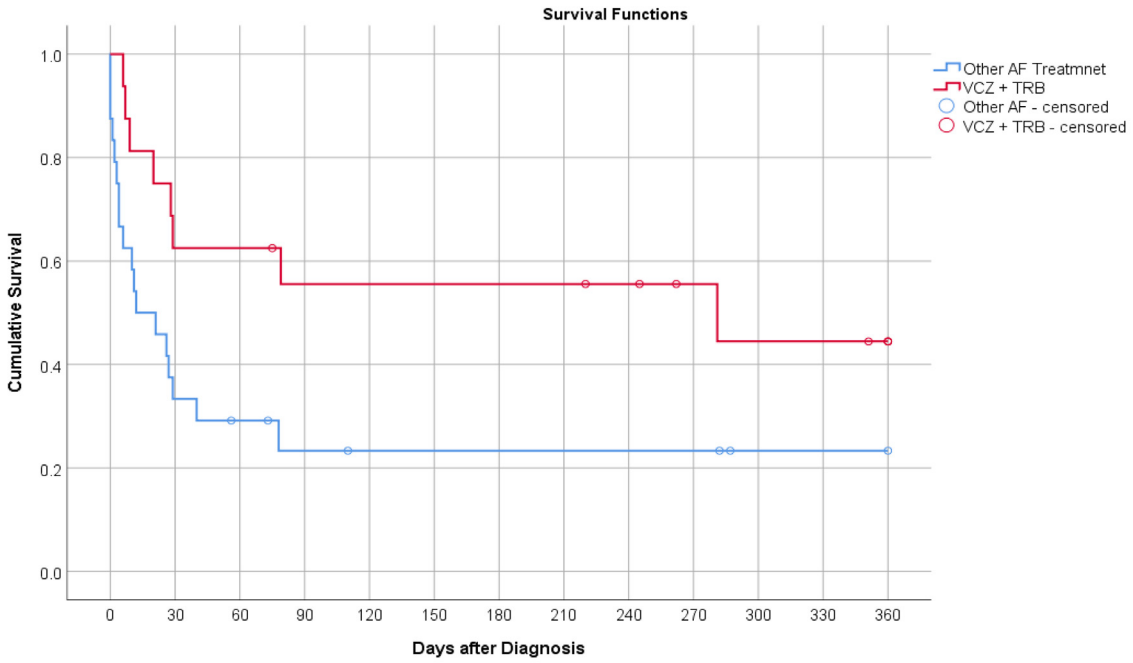
Table 1
Differences in demographic and clinical characteristics as well as treatment between (a) those with treatment response/stable disease versus those with deterioration/progression/failure at final assessment, (b) those who survived day 28 after diagnosis of the infection versus those who died before day 28, and (c) those with fungal-infection-attributable mortality

	Progression, deterioration, or failure of antifungal treatment (n = 23)	Complete or partial response or stable disease under antifungal treatment (n = 17)	p-value[a]	28-day overall mortality (n = 21)	28-day survival (n = 20)	p-value[a]	Death attributable to L. prolificans infection (n = 21)
Female sex	7 (30%)	9 (53%)	0.151	6 (29%)	10 (50%)	0.160	6 (29%)
Age (median, IQR)	67 (58–70)	58 (29–69)	0.141	63 (56–69)	66 (32–72; *n* = 18)	0.938	67 (59–70)
Year infection diagnosed (median, IQR)	2015 (2012–2016)	2014 (2012–2017)	0.725	2015 (2012–2017)	2014 (2012–2015)	0.344	2015 (2011–2017)
Country in which case occurred	0.065			0.211			
Australia	9 (39%)	8 (47%)		9 (43%)	8 (40%)		9 (43%)
USA	3 (13%)	7 (41%)		3 (14%)	8 (40%)		2 (10%)
Germany	7 (30%)	1 (6%)		6 (29%)	2 (10%)		7 (33%)
Other[b]	4 (17%)	1 (6%)		3 (14%)	2 (10%)		3 (14%)
Underlying diseases/main risk factors	<0.001			0.008			
Haematological/oncological malignancies	21 (91%)	5 (29%)		19 (90%)	8 (40%)		20 (95%)
Trauma/surgery	2 (9%)	4 (24%)		1 (5%)	5 (25%)		1 (5%)
Solid organ transplantation	0	3 (18%)		0	3 (15%)		0
Other[c]	0	5 (29%)		1 (5%)	4 (20%)		0
Intensive care unit	6 (26%)	0	0.030	5 (24%)	1 (5%)	0.184	6 (29%)
Site(s) of Infection							
Disseminated infection	21 (91%)	4 (24%)	<0.001	19 (90%)	6 (30%)	<0.001	20 (95%)
Growth in blood culture	17 (74%)	2 (12%)	<0.001	17 (81%)	2 (10%)	<0.001	16 (76%)
Lung	11 (48%)	7 (41%)	0.676	10 (48%)	8 (40%)	0.623	11 (52%)
Eye	3 (13%)	5 (29%)	0.250	3 (14%)	6 (30%)	0.277	2 (10%)
Skin/deep soft tissue	2 (9%)	3 (18%)	0.634	2 (10%)	3 (15%)	0.663	2 (10%)
Bone	1 (4%)	3 (18%)	0.294	1 (5%)	3 (15%)	0.343	1 (5%)
Brain/central nervous system	4 (17%)	1 (6%)	0.373	4 (19%)	1 (5%)	0.345	4 (19%)
Breakthrough Infection[d]	15 (65%)	9 (53%)	0.433	15 (71%)	9 (45%)	0.086	15 (71%)
Antifungal treatment							
Voriconazole ± other antifungals	15 (65%)	16 (94%)	0.054	13 (62%)	18/19 (95%)	0.021	14 (67%)
Terbinafine ± other antifungals	7 (30%)	12 (71%)	0.012	7 (33%)	12/19 (63%)	0.112	7 (33%)
LAmB ± other antifungals	12 (52%)	3 (18%)	0.046	10 (48%)	5/19 (26%)	0.204	11 (52%)
Antifungal combination therapy (versus monotherapy)	11 (48%)	13 (76%)	0.104	9 (43%)	15/19 (79%)	0.027	10 (48%)
Combination voriconazole + terbinafine ± other antifungals	6 (26%)	10 (59%)	0.053	6 (29%)	10/19 (53%)	0.197	6 (29%)
Surgery	1 (4%)	5 (29%)	0.067	1 (5%)	6 (30%)	0.045	1 (5%)

LAmB, liposomal amphotericin B.
[a] Calculated by Fisher's exact test or Wilcoxon's rank sum test, as appropriate.
[b] Countries include: Belgium, France, Italy, the Netherlands and Spain (each one case).
[c] Other includes burn, chronic granulomatous disease, chronic pulmonary disease, chronic cardiovascular disease/obesity and contact lenses.
[d] Of 21 breakthrough infections, nine (38%) occurred during posaconazole prophylaxis (eight suspension, one tablet formulation), six (25%) during voriconazole prophylaxis, and five (21%) during fluconazole prophylaxis.



Patients available for Follow Up	Day 0	Day 14	Day 28	Day 56	Day 84	Day 360
VCZ+TRB	16	13	12	10	8	3
Other AF	24	12	9	7	4	1

Fig. 1. Kaplan–Meier analysis of individuals receiving voriconazole plus terbinafine (±other antifungals) combination therapy versus other antifungal therapy at day 360 after diagnosis (log rank p 0.039).

individuals with disseminated infection who responded to therapy received a voriconazole/terbinafine combination (conservative therapy only), whereas the other two who survived received extensive surgery.

On both days 84 and 360 after diagnosis, individuals with voriconazole/terbinafine combination therapy had a higher survival probability compared with those receiving other antifungal regimens (Kaplan–Meier survival analysis; log rank p 0.024 and p 0.039, respectively; Fig. 1).

Discussion

We analysed the role of antifungal combination therapy in 41 individuals with invasive *L. prolificans* infections in the USA, Australia and Europe, of which the majority occurred within the past 5 years. In line with previous studies [5,10], overall 28-day mortality rates were high with more than 50% failing antifungal treatment.

Importantly, this study shows for the first time the potential benefit of combination antifungal treatment. Although combination therapy in general was associated with increased 28-day survival, combination treatment with voriconazole/terbinafine resulted in treatment response rates twice those of other antifungal regimens (63% treatment response with voriconazole/terbinafine ± other antifungals versus 29% with other antifungal regimens) and increased overall survival in Kaplan–Meier analyses. These findings confirmed the trends observed in a recent review of 56 published patients with invasive lomentosporosis infection, where voriconazole-based regimens in general were superior [5]. Also in that review, the highest survival probability tended to be observed in those receiving combination therapy of voriconazole/terbinafine ± other antifungals (1.5 times higher overall survival versus those with voriconazole but without terbinafine starting on day 30 and throughout the observation period), although this did not reach statistical significance because of the comparably smaller survival difference and low number of individuals receiving voriconazole/terbinafine combination in that review [5]. Of note, terbinafine is associated with strong lipophilicity and serum protein binding that reduces bioavailability and hinders the drug from reaching its target in the internal organ systems [11], but may still be effective in preventing dissemination. Voriconazole/terbinafine combination therapy is also supported by *in vitro* studies suggesting a synergistic effect when using this combination [12–15] and this combination regimen is supported by Australian guidelines for the treatment of IFIs in immunocompromised individuals [2]. Therefore, this focused analysis further supports *in vitro* studies and demonstrates the survival benefit of voriconazole (intravenous 6 mg loading dose followed by 4 mg twice daily, with therapeutic drug monitoring)/terbinafine (250 mg daily or twice daily) combination therapy for invasive *Lomentospora* infections.

There are several limitations to this study. As with all retrospective multicentre studies, our findings are naturally limited by the data available to us across centres for analysis. In addition, this patient cohort was heterogeneous and the size of our cohort did not allow for any subgroup analysis, a limitation common to any retrospective study of a very rare disease such as this. Other limitations include that our analysis did not adjust for other risk factors for a fatal outcome, a possible bias related to the choice of regimen by the clinician, and a possible immortal time bias with combination.

In conclusion, our study suggests that although overall mortality remains high, combination antifungal treatment, and in particular combination therapy with voriconazole plus terbinafine, may be

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associated with improved treatment outcomes compared with other antifungal regimens for the treatment of invasive L. prolificans infections.

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Transparency declaration

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Author contributions

JJ, MH, DS and OC conceived the idea for this study. DS compiled the data for analysis. MH and JJ analysed the data; OC, SC, MH, JJ, CK, MM, MHe, MC, AS, AB, BK, RH, JS, SS, SG, LP, SVH, DD, SRev, JB, SRM, SRe, RT, SA and MS contributed cases to the Fungiscope® registry that were analysed for this manuscript. All authors contributed to the writing, revision and finalization of this manuscript.

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