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Article type : Original Article

Clinical Characteristics and Outcomes of invasive *Lomentospora prolificans* Infections: Analysis of Patients in the FungiScope® Registry

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Running title: *Lomentospora prolificans* Infection Outcomes

Keywords: *Lomentospora prolificans*, fungal infections, clinical presentation, treatment, outcomes

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Abstract

Objectives: Invasive fungal infections caused by Lomentospora prolificans are associated with very high mortality rates and can be challenging to treat given pan-drug resistance to available antifungal agents. The objective of this study was to describe the clinical presentation and outcomes in a cohort of patients with invasive L. prolificans infections.

Methods: We performed a retrospective review of medical records of patients with invasive L. prolificans infection in the FungiScope® registry of rare invasive fungal infections. Patients diagnosed between 01/01/2008 – 09/09/2019 were included in for analysis.

Results: The analysis included 41 patients with invasive L. prolificans infection from eight different countries. Haematological/oncological malignancies were the most frequent underlying disease (66%), disseminated infection was frequent (61%), and the lung was the most commonly involved organ (44%). Most infections (59%) were breakthrough infections. Progression/deterioration/treatment failure was observed in 23/40 (58%) of patients receiving

antifungal therapy. In total, 21/41 (51%) patients, and 77% of patients with underlying haematological/oncological malignancy, had a fatal outcome attributed to invasive fungal infection. Combination antifungal therapy was frequent (24/40) and associated with improved survival. In particular, treatment regimens including terbinafine were significantly associated with higher treatment success at final assessment (p=0.012), with a positive trend observed for treatment regimens that included voriconazole (p=0.054).

Conclusions: L. prolificans infections were associated with mortality rates of 77% and above in patients with underlying haematological/oncological malignancies and those with disseminated infections. While combination therapy is the preferred option for now, the hope lies with novel antifungals currently under development.

Introduction

Lomentospora prolificans are filamentous fungi commonly found in soil and polluted waters and are increasingly recognized as a cause of serious invasive fungal infections (IFIs) in Australia, California and the southern USA, and Europe [1-8]. *L. prolificans* is the causative agent in 1.6% and 0.9% of infections after haematopoetic stem cell transplant and solid organ transplantation (SOT) in the United States, respectively [9]. Risk factors for these infections vary but include underlying haematological malignancy, SOT, trauma including burns, poorly controlled diabetes mellitus, and other conditions leading to immunodeficiency [4,9]. Mortality rates of up to 90% are associated with these infections [10]. Treatment of invasive infections is challenging as *L. prolificans* isolates are often pan-drug resistant, with elevated minimum inhibitory concentrations (MICs) against all available antifungal agents [2,4,11-15]. More than 10 years ago, two relatively large studies reported that voriconazole was associated with survival rates between 44% and 66% [16-18] and voriconazole was deemed the treatment of choice for invasive *L. prolificans* infections [18-21]. This is supported by a recent review of patients published after 2000 in which overall mortality was lower in patients who received voriconazole compared to treatment with other antifungal agents [10]. Although voriconazole is considered the drug of choice, combination therapy, particularly with voriconazole plus terbinafine, is also frequently used to combat these infections [4,10,20]. The objective of this study was to describe the clinical presentation and outcomes in a cohort of 41 patients with invasive *L. prolificans* infections occurring between 2008 and 2019 that were documented in the FungiScope® Registry [22].

Methods

A retrospective review of medical records of all patients with IFIs caused by *L. prolificans* in FungiScope® diagnosed between 01/01/2008 – 09/09/2019 was performed. FungiScope® is a registry of rare IFIs and is currently active in 84 countries [22]. All proven and probable infections based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria were included in this analysis [23]. Of the 41 patients included, 20 originated from the Mycoses Study Group International Prospective Study of Phaeohyphomycosis [24], five had been published in a case-series in 2018 [4], and a total of six were included in a previous review of *Scedosporium* and *Lomentospora* infections [10]. Results of the superiority of antifungal combination therapy in this study cohort has been published elsewhere [25].

Breakthrough infections were classified according to recent MSG/European Confederation of Medical Mycology (ECMM) criteria [26]. Treatment success was defined as stable disease/partial response or complete response, while treatment failure was defined as deterioration/progression or failure of antifungal therapy at final assessment [27]. Infections were determined to be disseminated if *L. prolificans* was isolated from blood or two non-contiguous anatomic sites. IFI-related mortality was defined as death due to IFI as determined by the FungiScope® registry investigator(s).

Statistical analyses used IBM SPSS Statistics v26 (IBM Corp., Armonk, NY). Age and treatment durations were presented as median and interquartile range (IQR) in days. 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 two-sided Fisher's exact test. The study protocol and all study-related procedures were approved by the University of California San Diego (UCSD), CA, USA Institutional Review Board (IRB) (Project #181119).

Results

Forty-one patients with invasive *L. prolificans* infection (36 proven, 5 probable) from 8 different countries were documented in FungiScope® registry, including patients from Australia (n=17), the United States (n=11, including 8 from the University of California San Diego), Germany (n=8), and five other countries with one case each. Description of each case including underlying risk factor(s), age, source of isolate, MIC's, antifungal treatment, adjunctive therapy (e.g. surgery), survival t 28 days, and outcomes are described (**Supplemental Table**). The majority of patients (66%; 27/41) were diagnosed in 2014 or later. Median age of patients was 65 years (IQR 48 – 69). Haematological/oncological malignancies were the most frequent

underlying diseases and observed in 27 (66%) of patients. Disseminated infection was detected in 25 (61%) of patients, 19 (46%) had growth of *L. prolificans* in blood culture, and the lung (18 patients; 44%) was the most frequently involved organ. Patient characteristics and outcomes are summarized in **Table 1.**

Most patients (24/41, 59%) were classified as breakthrough infections, of which nine (38%) occurred during posaconazole prophylaxis (8 suspension, 1 tablet formulation), six (25%) during voriconazole prophylaxis, five (21%) during fluconazole prophylaxis, and one each during prophylaxis with liposomal amphotericin B (LAmB), micafungin, and during empiric antifungal treatment with combination LAmB + posaconazole and LAmB + micafungin. While there was no significant association between breakthrough infection and antifungal treatment response, a trend was observed towards higher IFI-attributed mortality in those with breakthrough infection (p=0.061).

Overall, treatment failure occurred in 23/40 infections receiving antifungal therapy (58%), and both 28-day overall mortality and overall death attributable to *L. prolificans* infection were observed in 51% of patients (21/41) each. Treatment failure (84% and 81%) and IFI-attributed mortality (80% and 77%, respectively) were highest among patients with disseminated infection and those with underlying haematological/oncological malignancy.

Nineteen patients were treated with a terbinafine containing regimen (Table 1); Most patients (18 /19) received terbinafine in combination with other antifungals, the most frequent combination with voriconazole + terbinafine (16 of 18). Compared to other antifungal regimens, treatment with terbinafine (vast majority used dosages of 250 mg daily or 250 mg twice daily) was significantly associated with higher treatment success overall at final assessment (p=0.012), with a positive trend also observed for treatment regimens that included voriconazole (n=31; including 16 who received voriconazole + terbinafine combination; p=0.054). Treatment containing LAmB (n=15; 11/15 combination therapy) was associated with both treatment failure (4/4 with monotherapy and 8/11 with combination therapy failed treatment; p=0.046) and higher IFI-attributed mortality (p=0.043). Among those who received treatment with voriconazole but without terbinafine, 6/15 (40%) responded to treatment, which was slightly lower than the 44% (11/25) treatment response observed for other treatments. Only seven patients received voriconazole monotherapy (median 22 days, IQR 3-47 days); of those, 4/7 (57%) had treatment failure with IFI-attributed mortality within 28 days of diagnosis, while 3/7 (43%) survived. Better outcomes was observed in those with combination antifungal therapy, and specifically those receiving voriconazole + terbinafine combination therapy are described in detail elsewhere [28].

Seven patients underwent surgical treatment (Table 1), which was significantly associated with higher 28-day survival rates (p=0.045; 3/4 of those receiving surgery for eye infections and 2/3 receiving other surgery survived).

Discussion

We analysed clinical characteristics, antifungal treatment and outcome of 41 patients with invasive *L. prolificans* infections in the United States, Australia and Europe. Haematological/oncological malignancies were the most frequently observed underlying disease (66%), disseminated infection was frequent (61%), the lung was the most frequently involved organ (44%), and most patients (59%) were classified as breakthrough infections. These findings further confirm another recent large survey of *L. prolificans* infections, in which 63% had underlying haematological/oncological malignancy, 59% disseminated infection, and lung was the most frequently involved organ (39%) as well [10]. Overall, 28-day mortality rates were high with more than 50% failing antifungal treatment, similar to previous studies [1,3,10,17]. Mortality rates were highest in patients with underlying hematologic/oncologic malignancies, with more than 80% failing antifungal treatment, and in those with disseminated infection, with 84% failing treatment.

In vitro synergism has been demonstrated for combination antifungal therapy with terbinafine + itraconazole against Mucorales [29], terbinafine + voriconazole against *Fusarium* spp [30], and terbinafine + voriconazole against *L. prolificans* [31-33], and it was suggested almost twenty years ago that combination therapy with an azole plus terbinafine may be a treatment option for these infections [34]. However, the benefit of terbinafine-based regimens was not significant in the recent review of 56 published cases of invasive lomentosporiosis (including 5 more recent cases that were also included in this study), where voriconazole-based regimens were superior but significance was not reached in the subgroups of combination treatment [10]. Previous *in vitro* studies have shown that while some *L. prolificans* isolates are susceptible to voriconazole [35], the majority have high MICs to all antifungal agents, including voriconazole, which may correlate with treatment failure with voriconazole monotherapy [36]. Clinical studies have demonstrated the

superiority of voriconazole-based treatment regimens for *L. prolificans* infections compared to LAmB-based regimens [1,16], a finding that was confirmed in our study. Furthermore, recently published data from our cohort [28] showed the highest treatment success with voriconazole when used in combination with another antifungal agent. Importantly, 39% of patients in our cohort had *L. prolificans* breakthrough infections occurring under triazole prophylaxis/empirical therapy, with more than a third occurring during voriconazole prophylaxis, further evidence that voriconazole alone may be insufficient to prevent or treat infections caused by *L. prolificans*. This study shows for the first time that terbinafine-based regimens were significantly associated with treatment success and survival, and that the treatment response rate using voriconazole in combination with terbinafine was twice that of other antifungal regimens. Our study also showed a significant survival benefit in those receiving surgery, which was also recently shown in children with invasive Scedosporium and Lomentospora infections who underwent surgery and received voriconazole [8]. Importantly, the majority of infections in this analysis occurred in 2014 and later, with outcomes likely influenced by potential changes in the epidemiology of lomentosporiosis associated with the rise of mould active antifungal prophylaxis and advances in treatment of haematological/oncological malignancies. As a result, patients who develop lomentosporiosis today may be more immunosuppressed than those who developed the infection 20 years ago, a theory that is supported by the fact that high mortality rates remained mostly unchanged despite the introduction of newer and better tolerated antifungals [4,16].

In conclusion, *L. prolificans* infections are associated with high mortality, particularly in patients with underlying haematological/oncological malignancies and those with disseminated infection. While combination therapy shows some success in lowering persistently high mortality rates, hope lies on novel antifungals that are currently being developed, specifically F901318 (Olorofim; F2G, Manchester, U.K.), which shows excellent activity against *L. prolificans* [37] and which is currently being evaluated in a Phase 2b open-label study (NCT03583164). Until novel drugs are available, our findings suggest that voriconazole or terbinafine-based regimens, particularly voriconazole + terbinafine combination therapy, could be the preferred choice for the treatment of invasive *L. prolificans* infections.

Funding:

FungiScope® is supported by unrestricted grants of Amplyx Pharmaceuticals, Basilea Pharmaceutica, Cidara Therapeutics, F2G Ltd., Matinas BioPharma, and Pfizer Inc. FungiScope® has been supported by unrestricted grants of Astellas Pharma GmbH, Gilead

Sciences GmbH, MSD Sharp & Dohme GmbH, and SCYNEXIS Inc. The MSG 06 study was supported by Astellas, Gilead, and Merck.

Author Contributions:

Jenks JD, Hoenigl M, Seidel D, and Cornely O conceived the idea for this study. Seidel D compiled the data for analysis. Hoenigl M and Jenks JD analyzed the data. Cornely O, Chen S, Hoenigl M, Jenks JD, Kauffman C, Miceli M, Heinemann M, Christner M, Sáenz A, Burchardt A, Kemmerling B, Herbrecht R, Steinmann J, Shoham S, Gräber S, Pagano L, Van Hal S, Deeren D, and Slavin M contributed cases to the Fungiscope® registry that were analyzed for this manuscript. All authors contributed to the writing, revision, and finalization of this manuscript.

Conflicts of Interest:

OAC has received research grants from Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Janssen Pharmaceuticals, Medicines Company, MedPace, Melinta Therapeutics, Merck/MSD, Pfizer, Scynexis, is a consultant to Actelion, Allecra Therapeutics, Amplyx, Astellas, Basilea, Biosys UK Limited, Cidara, Da Volterra, Entasis, F2G, Gilead, Matinas, MedPace, Menarini Ricerche, Roche Diagnostics, Merck/MSD, Nabriva Therapeutics, Octapharma, Paratek Pharmaceuticals, Pfizer, PSI, Rempex, Scynexis, Seres Therapeutics, Tetraphase, Vical, and received lecture honoraria from Astellas, Basilea, Gilead, Grupo Biotoscana, Merck/MSD and Pfizer.

SC has received grant funding from Merck, Astellas, and Gilead and serves or has served on advisory boards for Merck, Gilead, Pfizer and F2G

SVH has received grant funding from Merck, Astellas, and Gilead.

CK serves on a Data Safety Monitoring Board for Cidara Therapeutics.

MHM received grant funding from Astellas, Scynexis and Mayne Pharmaceutical as well as consulting fees from Astellas and Scynexis.

MHe received grant funding from Bayer

RH reports grants and personal fees from Gilead and Pfizer personal fees from Astellas, Basilea, MSD, and Novartis.

JS received lecture honoraria from Gilead and Pfizer.

SS receive research funding from Merck, Astellas, F2G, Scynexis, Cidara.

LP has received grant funding from Merck, Pfizer and Gilead, and served on advisory boards for Merck, Gilead, Pfizer, Jazz, Cidara

DD has received advisory board honoraria from Alexion, Amgen, Janssen, Roche, Sunesis, and Takeda, and research support from Sanofi.

MS has received grant funding from Merck, Astellas, and Gilead, and educational grants from Merck and Gilead Sciences and served on advisory boards for Merck, Gilead, Pfizer and F2G.

MH received grant funding from Gilead and Scynexis

Other authors: no conflicts

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412 **Table 1.** Demographic and clinical characteristics of the study cohort.

	Study Cohort (n=41)
Female Sex	16 (39%)
Age (median, interquartile range)	65 (48 – 69)
Country Case Occurred	
Australia	17 (41%)
United States	11 (27%)
Germany	8 (20%)
Other[#]	5 (12%)
Underlying Diseases/Main Risk Factors	
Hematological/Oncological Malignancies	27 (66%)
Trauma/Surgery	6 (15%)
Solid Organ Transplantation	3 (7%)
Other[$]	5 (12%)
Intensive Care Unit	6 (15%)
Site(s) of Infection	
Disseminated infection	25 (61%)
Growth in Blood Culture	19 (46%)
Lung	18 (44%)
Eye	9 (22%)
Skin / Deep Soft Tissue	5 (12%)
Bone	4 (10%)
Brain / Central Nervous System	5 (12%)
Breakthrough Infection	24 (59%)
Antifungal Treatment*	
Voriconazole +/- other antifungals	31/40 (78%)
Terbinafine +/- other antifungals	19/40 (48%)
LAmB +/- other antifungals	15/40 (38%)
Antifungal Combination Therapy (versus Monotherapy)	24/40 (60%)
Combination Voriconazole + Terbinafine +/- other antifungals	16/40 (40%)
Surgery	7 (18%)
Outcomes¥	
Progression, Deterioration, or Failure of	23/40 (58%)

Antifungal Treatment	
28-day Overall Mortality	21 (51%)
Death attributable to L. prolificans infection	21 (51%)

* Those who survived received antifungal treatment for a median of 181 days (IQR 47-332 days).

Countries include: Belgium, France, Italy, The Netherlands and Spain (each one case)

$ Other includes Burn, chronic granulomatous disease, chronic pulmonary disease, chronic cardiovascular disease/obesity and contact lenses.

¥ Final response assessment was conducted at a median of 241 days (IQR 84-335) after diagnosis in those who survived and median 13 days (IQR 4-35 days) after IFI diagnosis in the deceased (i.e. final assessment on the day of death).