Check for updates

Received: 7 February 2020 | Accepted: 11 April 2020

DOI: 10.1002/ppul.24789

ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

PEDIATRIC PULMONOLOGY WILEY

Combination antifungal therapy for *Scedosporium* species in cystic fibrosis

Siân Bentley BPharm[1] | Jane C. Davies MD, FRCPCH[2,3] | Siobhán B. Carr MSc, FRCPCH[2] | Ian M. Balfour-Lynn MD, FRCPCH[2]

[1]Department of Pharmacy, Royal Brompton Hospital, London, UK

[2]Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

[3]NHLI Imperial College, London, UK

Correspondence
Ian M. Balfour-Lynn, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.
Email: i.balfourlynn@ic.ac.uk

Abstract

Objective: To evaluate safety and efficacy of oral posaconazole and terbinafine for *Lomentospora prolificans* and *Scedosporium apiospermum* in children with cystic fibrosis.

Methods: Retrospective case review.

Results: There were five children (four girls), median age 15.0 years; three had *S. apiospermum* and two had *L. prolificans*. Treatment duration: median 5 months (range: 5-18 m). In no patient was eradication achieved, with the follow-up range being 6 months to 4 years. Effect on lung function was variable but encouraging. No adverse effects were reported, one child had transient elevation of liver enzymes.

Conclusions: While the combination therapy was well tolerated, it was unsuccessful at eradication.

KEYWORDS

antifungal, cystic fibrosis, *Lomentospora prolificans*, posaconazole, *Scedosporium apiospermum*, terbinafine

1 | INTRODUCTION

Scedosporium apiospermum and *Lomentospora prolificans* (previously called *Scedosporium prolificans)* are filamentous fungi found in respiratory cultures of people with cystic fibrosis (CF). Second only to *Aspergilllus fumigatus*, reported prevalence varies, with mean 3.1% in 12 German centers,[1] 4.5% in five Dutch centers,[2] and 3.2% from US Registry data on over 19 000 patients.[3] There is an impression of increasing prevalence,[2] which may largely relate to use of selective culture media, but is also associated with increased use of inhaled antibiotics.[3] Pathogenicity of *Scedosporium* species is not completely understood, however they are not respiratory tract commensals, and may cause allergic bronchopulmonary mycosis as well as infection and bronchitis.[4] These fungi may also cause significant problems after lung transplantation.[5]

Treatment can be difficult due to their innate resistance to therapy. Voriconazole is the drug of choice recommended in the European 2014 guidelines),[6] although posaconazole is being increasingly used mostly due to poor tolerance of voriconazole. Posaconazole has also been used via nebulizer and intrabronchial instillation in post-transplant patients.[5] However, while monotherapy may be sufficient for the more susceptible *S. apiospermum*, because *L. prolificans* is so resistant, the addition of terbinafine, an allylamine antifungal, has been "moderately recommended."[6] Indeed, a case series found the use of two or three drugs produced better outcomes than a single agent for scedosporiosis in adults and older children with CF.[4] There are no data published on the combination of oral posaconazole and terbinafine in children with CF, so we retrospectively evaluated their safety, tolerability, and efficacy in our clinic.

2 | METHODS

This is a retrospective case note review of all children with CF who started combination oral terbinafine and posaconazole for

 © 2020 Wiley Periodicals, Inc.

treatment of *Scedosporium* or *Lomentospora* species, grown on respiratory cultures (sputum or bronchoalveolar lavage). Setting was a tertiary pediatric CF center with a clinic population of 340 children; records covered 5 years (2015-2019). Children were identified from pharmacy records and clinical data were collected from computerized clinical notes. Children received oral terbinafine 250 mg orally once daily. Oral posaconazole was started at 300 mg orally once daily and adjusted to maintain therapeutic levels >1 mg/L and <5 mg/L. Terbinafine levels were not measured. Synergy testing was not carried out on any of the isolates. This was deemed a service evaluation/audit (registered 002012) and our R&D department said that formal ethics permission was not required. All parents/patients gave verbal consent for us to include them in the case series.

3 | RESULTS

3.1 | Subjects

There were five children (four girls) with a median age of 15.0 years (range: 9-16 years) at the time of starting combination therapy with oral posaconazole and terbinafine for *L. prolificans* (n = 2) and *S. apiospermum* (n = 3) (Table 1). Their median forced expiratory volume in 1 second (FEV_1) % predicted was 85% (range: 51%-102%), and FVC 97% (range: 54%-106%). Length of treatment was median 5 months (range: 5-18 months) and was guided by clinical improvement or lack of response. All but one patient was receiving antifungal therapy before commencing this combination therapy (Table 1).

3.2 | Outcomes

In no patient was *Lomentospora/Scedosporium* eradicated, at a follow-up ranging from 6 months to 4 years (median 3.8 years) after completion of dual therapy. Two children had a further three courses. After their first course, in two children lung function improved, in two it did not change, and in one it fell (Table 2). No adverse effects from the combination were reported in any of the patients. One patient had raised liver enzymes that later normalized. Posaconazole levels were therapeutic (>1 mg/L) in all children (range: 1.22-3.85 mg/L).

4 | DISCUSSION

We used a combination of oral posaconazole and terbinafine in five older children with *Scedosporium/Lomentospora*, a clinical decision made with our hospital mycologist. It was well tolerated, with just one patient having a short-lived rise in liver enzymes, and no one having to stop the therapy for adverse effects. However, treatment was unsuccessful, at eradication, as despite courses lasting 2 to 18 months, and some being repeated, we were unable to eradicate the fungi in any patient, even 4 years later.

The patients received posaconazole, despite in vitro studies demonstrating that voriconazole displays the lowest minimum inhibitory concentration in CF respiratory isolates, followed by posaconazole then itraconazole.[1] Posaconazole is unlicensed in children, and there are no large trials in CF, however our experience with *Aspergillus* has shown that posaconazole is better tolerated than

TABLE 1 Patient characteristics

Patient	Age, y	Sex	CFTR genotype	Scedosporium spp.	Concurrent pathology	Total IgE, IU/mL	Nebulized antibiotics	Recent antifungal therapy	Sensitivity
1	15.5	F	Phe508del/ Ile947Pefs*21	*L. prolificans*	Chronic PsA CFRD	19	COL TOB	Oral ICZ IV AmpB Neb AmpB	POS - R TBF - R
2	10.3	F	Phe508del/ W1282X	*L. prolificans*	Chronic PsA	165	TOB	Nil	POS - R TBF - R
3	16.2	F	Phe508del/ Phe508del	*S. apiospermum*	Chronic PsA *Exophiala dermatididis* CFRD	326	COL TOB	Oral ICZ	POS - S TBF - R
4	15.0	F	Phe508del/ Phe508del	*S. apiospermum*	Chronic PsA CFRD MRSA	10	AZT TOB	Oral POS	POS - I TBF - R
5	9.8	M	Phe508del/ Phe508del	*S. apiospermum*	None No PsA 4 y	93	COL	Oral POS	POS - I

Note: Patient 4 was suffering from significant nutritional complications both before and during the study period.
Abbreviations: AmpB, amphotericin B; AZT, aztreonam; CFRD, CF-related diabetes; CFTR, CF transmembrane conductance regulator; COL, colistin; I, intermediate sensitivity; ICZ, itraconazole; MRSA, methicillin-resistant *Staphylococcus aureus*; POS, posaconazole; PsA, *Pseudomonas aeruginosa*; R, resistant; S, sensitive; TBF, terbinafine; TOB, tobramycin.

TABLE 2 Outcomes of dual antifungal therapy

Patient	Duration of treatment, mo	Eradicated? Length follow-up	Weight centile at start	Body mass index centile at start	FEV_1 & FVC % predicted start	FEV_1 & FVC % predicted end 1st course
1	2	No @4.1 y	5%	30%	55/72	69/87
2	2	No @4.1 y	25%	25%	88/97	102/103
3	18	No @3.6 y	25%-50%	9%	85/99	86/103
4	18	No @3.8 y	9%-25%	9%	51/54	36/54
5	5	No @0.5 y	75%	91%	102/106	107/108

Note: FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity, % predicted for sex, height, and ethnicity.

voriconazole. In our series, three of the patients had previously experienced an adverse drug reaction to voriconazole. Additionally, therapeutic posaconazole levels can be readily obtained, contrary to voriconazole and itraconazole.

There is conflicting in vitro data regarding synergy of terbinafine with triazoles for the treatment of *Scedosporium* species, with susceptibility data suggesting that there is no synergy between posaconazole and terbinafine, for either of the *Scedosporium* species we were treating.[7] This is in contrast to in vitro synergy shown between voriconazole & terbinafine for *L. prolificans*, and itraconazole and terbinafine for *S. apiospermum*.[7] In vivo efficacy data of combination treatment with triazoles and terbinafine are limited; one case series suggested two or three drugs should be combined (including voriconazole, itraconazole, caspofungin, micafungin, amphotericin B) but in only one of the 31 cases was terbinafine used (with voriconazole) for *L. prolificans*.[4]

Despite lack of microbiological eradication, lung function did improve significantly in two patients, and was stable in two others. This raises the possibility that the drugs were suppressing infection similarly to chronically administered inhaled anti-pseudomonal antibiotics. Of course, co-morbidities and bacterial co-infection play a large part in determining outcomes. It is not always clear when *Scedosporium* species is causing the clinical deterioration and when to treat it. Certainly though, if it is to be treated then this is difficult. Aggressive combination therapy is likely to be needed, perhaps including intravenous medication, and a long treatment course is necessary. Other treatments that may be of use are nebulized colistin and intravenous caspofungin. We can be confident though that the combination of posaconazole and terbinafine is not the answer.

ACKNOWLEDGMENTS

The authors thank the children and young people who allowed them to present their cases. The authors also thank Dr. Darius Armstrong-James for his advice over antifungal therapies.

ORCID

Siân Bentley http://orcid.org/0000-0001-7743-3283
Jane C. Davies http://orcid.org/0000-0003-3506-1199
Siobhán B. Carr http://orcid.org/0000-0003-0580-2478
Ian M. Balfour-Lynn http://orcid.org/0000-0002-0754-3863

REFERENCES

1. Sedlacek L, Graf B, Schwarz C, et al. Prevalence of *Scedosporium* species and *Lomentospora prolificans* in patients with cystic fibrosis in a multicenter trial by use of a selective medium. *J Cyst Fibros*. 2015;14:237-241.
2. Engel TGP, Slabbers L, de Jong C, et al. Dutch Cystic fibrosis Fungal Collection Consortium. Prevalence and diversity of filamentous fungi in the airways of cystic fibrosis patients—A Dutch, multicentre study. *J Cyst Fibros*. 2019;18:221-226.
3. Hong G, Lechtzin N, Hadjiliadis D, Kawut SM. Inhaled antibiotic use is associated with *Scedosporium/Lomentospora* species isolation in cystic fibrosis. *Pediatr Pulmonol*. 2019;54:133-140.
4. Schwarz C, Brandt C, Melichar V, et al. Combined antifungal therapy is superior to monotherapy in pulmonary scedosporiosis in cystic fibrosis. *J Cyst Fibros*. 2019;18:227-232.
5. Solé A, García-Robles AA, Jordá C, et al. Salvage therapy with topical posaconazole in lung transplant recipients with invasive *Scedosporium* infection. *Am J Transplant*. 2018;18:504-509.
6. Tortorano AM, Richardson M, Roilides E, et al. European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. *Clin Microbiol Infect*. 2014;20(Suppl 3):27-46.
7. Cuenca-Estrella M, Alastruey-Izquierdo A, Alcazar-Fuoli L, et al. In vitro activities of 35 double combinations of antifungal agents against *Scedosporium apiospermum* and *Scedosporium prolificans*. *Antimicrob Agents Chemother*. 2008;52:1136-1139.

How to cite this article: Bentley S, Davies JC, Carr SB, Balfour-Lynn IM. Combination antifungal therapy for *Scedosporium* species in cystic fibrosis. *Pediatric Pulmonology*. 2020;55:1993–1995. https://doi.org/10.1002/ppul.24789