J Antimicrob Chemother 2021; **76**: 1229–1233
doi:10.1093/jac/dkaa562 Advance Access publication 9 January 2021

Journal of Antimicrobial Chemotherapy

In vitro activity of the novel antifungal olorofim against dermatophytes and opportunistic moulds including *Penicillium* and *Talaromyces* species

Ashutosh Singh[1]†, Prerna Singh[1]†, Jacques F. Meis [2,3] and Anuradha Chowdhary [1]*

[1]*Department of Medical Mycology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India;* [2]*Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital (CWZ), Nijmegen, The Netherlands;* [3]*Centre of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands*

*Corresponding author. E-mail: dranuradha@hotmail.com
†These authors contributed equally.

Received 23 October 2020; accepted 22 December 2020

Objectives: Olorofim is a novel antifungal agent with *in vitro* activity against *Aspergillus* and other opportunistic moulds. We investigated the *in vitro* activity of olorofim against a range of filamentous fungi comprising isolates of *Aspergillus* species, *Scedosporium* species, *Alternaria alternata*, dermatophytes, including terbinafine- and multidrug-resistant *Trichophyton* species, and *Penicillium/Talaromyces* species originating from patients in North India.

Methods: Antifungal susceptibility of olorofim was tested against 241 mould isolates of *Penicillium/Talaromyces* species, *Trichophyton* species, *A. fumigatus* and cryptic *Aspergillus* species, *Scedosporium* species, and *Alternaria alternata* using CLSI broth microdilution. The comparators were five systemic azoles, amphotericin B, terbinafine, and luliconazole.

Results: Overall, olorofim showed highly potent *in vitro* activity against dermatophytes and opportunistic moulds (MIC range of 0.004–0.125 mg/L) except for *Alternaria alternata*. *Penicillium*, and *Talaromyces* species and *Trichophyton species* exhibited a low geometric mean (GM) MIC (GM 0.027 mg/L and 0.015 mg/L, respectively) of olorofim. Importantly, a 2–12 dilution step decrease in *in vitro* activity of olorofim as compared with azoles was observed against *Penicillium* and *Talaromyces*. Notably, olorofim displayed potent *in vitro* activity against *Trichophyton* isolates including terbinafine-resistant and azole-resistant *Trichophyton mentagrophytes/interdigitale* with a modal MIC value of 0.008 mg/L. Further, azole-resistant *A. fumigatus* isolates harbouring mutations in azole target *Cyp51A* genes and several cryptic aspergilli displayed low MICs (range 0.004–0.03 mg/L) of olorofim. However, no *in vitro* activity of olorofim against *Alternaria alternata* was observed.

Conclusions: The potent *in vitro* activity of olorofim against drug-resistant dermatophytes and opportunistic moulds is promising, warranting evaluation of the clinical utility of olorofim.

Introduction

Emerging opportunistic filamentous fungal pathogens, such as *Fusarium* species, *Scedosporium* species, *Penicillium* species, *Talaromyces* species, and *Lomentospora prolificans*, are becoming significantly more prevalent worldwide as agents of invasive fungal infections.[1] Other fungal pathogens that have gained global attention in the last few years are dermatophytes, specifically *Trichophyton* species exhibiting resistance to terbinafine, the first-line antifungal drug used for the treatment of dermatophytosis.[2,3] Superficial fungal infections caused by dermatophytes are the most common fungal diseases in humans, affecting one billion people with skin, hair, and nail infections.[4] Resistance in fungal pathogens to the currently available antifungals is presenting a major clinical challenge in human health care. In the given scenario of antifungal resistance, new antifungal therapies that act through novel mechanisms are needed to circumvent the emergence of resistance to existing therapies. Orotomides are a new class of antifungal drugs which act via the inhibition of fungal dihydroorotate dehydrogenase (DHODH), an important enzyme in pyrimidine biosynthesis that is essential for deoxyribonucleic acid synthesis. Olorofim (formerly F901318; F2G, Manchester, UK) is the most advanced representative of this novel class of antifungal compounds, and shows no significant activity against human

DHODH and therefore selectively inhibits fungal pyrimidine biosynthesis, with limited toxicity and a favourable safety profile.[5]

This new antifungal is highly effective against a broad spectrum of filamentous moulds including *Aspergillus* species, and other difficult-to-treat moulds such as *Fusarium* species, *Madurella mycetomatis, Rasamsonia* species, *Scedosporium* species and *Lomentospora prolificans*, dimorphic fungi and limited number of *Trichophyton* species.[6–9] In the present study we investigated the *in vitro* activity of olorofim against dermatophytes with emphasis on terbinafine and multidrug-resistant *Trichophyton mentagrophytes/interdigitale* species complex isolates causing epidemics of difficult-to-treat dermatophytosis in India.[2,3] Terbinafine-resistant Indian *Trichophyton interdigitale/mentagrophytes* species complex isolates have recently been proposed as a new species, *T. indotineae* based on multigene phylogeny.[10]

Further, we also investigated the *in vitro* activity of olorofim against clinically significant species of *Penicillium* and *Talaromyces* (other than *marneffei*) isolated from patients with allergic, chronic and invasive respiratory disorders in India. Additionally, we report *in vitro* activity of olorofim against *Alternaria alternata, Scedosporium* species, azole-resistant *Aspergillus fumigatus*, and cryptic *Aspergillus* species.

Materials and methods

Fungal isolates and identification

A total of 241 mould isolates identified by sequencing the internal transcribed spacer region of the ribosomal DNA, calmodulin and β-tubulin genes were analysed. The isolates included *Penicillium* species ($n=47$), *Talaromyces* species ($n=10$), *Trichophyton* species ($n=56$), *Aspergillus* species ($n=80$), *A. alternata* ($n=35$) and *Scedosporium* species ($n=13$). The specimen distribution of these 185 filamentous moulds were sputum plugs and sputum ($n=109$), bronchoalveolar lavage/bronchial aspirates ($n=38$), endotracheal aspirates ($n=9$), skin biopsies ($n=9$), corneal scrapings ($n=6$), nasal aspirates/polyps ($n=11$), lung biopsy ($n=2$) and pleural fluid ($n=1$). A total of 56 *Trichophyton* isolates obtained from skin/scalp scrapings of patients with tinea corporis/cruris and tinea capitis were included.[9,10]

Antifungal susceptibility testing (AFST)

AFST was performed for olorofim (F2G Limited, Manchester, UK) and eight other drugs (itraconazole, voriconazole, isavuconazole, posaconazole, fluconazole, amphotericin B, terbinafine, and luliconazole) using the broth microdilution method according to CLSI M38-Ed3.[11] For non-dermatophyte moulds, MIC endpoints were defined as the lowest concentration that produced complete inhibition of growth by visual inspection at 48 h of incubation except for *Scedosporium* species, which were interpreted at 72 h of incubation. The epidemiological cut-off values (ECVs) of azoles (itraconazole, voriconazole and isavuconazole, 1 mg/L) for *Aspergillus fumigatus* were used for analysis of MICs of azoles against filamentous moulds.[12] Dermatophyte susceptibility testing was performed as described previously.[2,3] MIC endpoints for all the drugs were defined as the lowest concentration that inhibited ≥80% of the growth as read visually at 72 h incubation at 35°C for *T. indotineae* isolates as they grew luxuriantly in 3 days, whereas, for *Trichophyton rubrum* and *Trichophyton tonsurans*, MICs were interpreted after 5 days. Terbinafine MICs of >2 mg/L for *T. indotineae* isolates were considered high based on the previous correlation of *in vitro* terbinafine MIC data with treatment outcome of patients with dermatophytosis treated with terbinafine.[13]

Results

Antifungal susceptibility testing

The species distribution and antifungal susceptibility profiles of isolates are shown in Table 1. Overall, olorofim had potent *in vitro* activity (MIC range 0.004–0.125 mg/L) with a low median MIC value of 0.008 mg/L against all filamentous moulds and dermatophytes except for *A. alternata* (MIC 8 mg/L). A total of 12 species of *Penicillium* and *Talaromyces* including six each were identified including the most frequently isolated species, *Penicillium oxalicum* (37%; $n=21$) and *Penicillium citrinum* (31.5%; $n=18$). Notably, olorofim had potent *in vitro* activity (MIC range 0.004–0.03 mg/L) across all isolates of *Penicillium* and *Talaromyces* species, with modal MIC value of 0.016 mg/L. Interestingly, no species-specific MIC was noted among *Penicillium* and *Talaromyces*. Further, *in vitro* activity of olorofim against *Penicillium* species was unaffected by the concomitant high multi-azole MICs in 54% of *Penicillium* isolates including *P. citrinum, P. oxalicum,* and *P. chermesinum*. Interestingly, all species of *Talaromyces* except *T. atroroseus* had high MICs for voriconazole (range 2–16 mg/L) but highly potent *in vitro* activity of olorofim (range 0.004–0.03 mg/L). Olorofim demonstrated a 2–12 dilution step decrease in *in vitro* activity in comparison with azoles amongst all species of *Penicillium* and *Talaromyces*.

Olorofim also displayed potent *in vitro* activity (modal MIC of 0.008 mg/L) for all *Trichophyton* isolates including terbinafine-resistant isolates. Notably, a low MIC range (0.004–0.06 mg/L) of olorofim against *T. indotineae* was observed including 67% of isolates that harboured known *SQLE* mutations (F397L, $n=19$; and L393L, $n=3$) conferring high terbinafine MICs (4–32 mg/L). Also, concomitant azole-resistant isolates of *T. indotineae* had low olorofim MICs (range 0.004–0.06 mg/L). Furthermore, among *T. tonsurans* and *T. rubrum* isolates, a 6 dilution step (12-fold) and a 3 dilution step (6-fold) decrease, respectively in MIC value of olorofim as compared with terbinafine was observed.

Olorofim showed potent *in vitro* activity against all *Aspergillus* species with a modal and geometric mean (GM) MIC of 0.004 mg/L including azole-resistant *A. fumigatus* isolates harbouring *Cyp51A* mutations. Interestingly, 35% of cryptic *Aspergillus* species that had elevated MICs of azoles (*A. clavatus, A. nidulans,* and *A. sydowii)* and a single multi-azole resistant *A. flavus* (itraconazole MIC >16 mg/L; voriconazole MIC 2 mg/L; isavuconazole MIC 4 mg/L) also showed a low MIC (0.004 mg/L) of olorofim. In an overall comparison of all *Aspergillus* species, olorofim exhibited a 5 dilution step (10-fold) decrease in modal MIC compared with voriconazole, a widely used first-line treatment drug. Further, olorofim demonstrated a low MIC range (0.004–0.06 mg/L) for *Scedosporium apiospermum, Scedosporium aurantiacum,* and *Scedosporium dehoogii* whereas *A. alternata* isolates showed no *in vitro* activity.

Discussion

In this study, olorofim displayed potent *in vitro* activity against clinical isolates of *Penicillium* species, *Talaromyces* species, and *Trichophyton* species. Notably, the potent *in vitro* activity of olorofim against *Trichophyton* included isolates of *T. indotineae* that

Table 1. The MIC distribution of tested species against olorofim and comparator antifungals using CLSI-BMD method

Genus/species (no. of isolates)		MIC (mg/L)					
		OLO	ITC	VRC	ISA	POS	AMB
Penicillium							
P. oxalicum (21)	Range	0.008–0.03	0.5–2	0.25–8	0.5–8	0.25–1	0.06–1
	GM MIC[a]	0.013	1.26	1.26	2.69	0.42	0.12
	MIC_{50}[b]	0.016	1	1	2	0.5	0.125
	MIC_{90}[c]	0.016	2	2	8	1	0.25
P. citrinum (18)	Range	0.004–0.016	1–4	1–16	2	0.25–2	0.25–1
	GM MIC	0.12	2.33	13.72	2	0.79	0.63
	MIC_{50}	0.25	2	16	2	1	0.5
	MIC_{90}	0.25	4	16	2	1.3	1
P. chrysogenum (4)	Range	0.008–0.016	0.125–0.5	0.5–1	0.5–1	0.06–0.25	1–2
P. lanosocoeruleum (2)	Range	0.016	0.25- 0.5	0.25	0.5	0.25	1
P. griseofulvum (1)	MIC	0.008	2	1	1	0.5	2
P. chermesinum (1)	MIC	0.004	4	4	2	1	0.5
Talaromyces							
T. islandicus (3)	Range	0.016	0.5–4	2–4	0.5–2	0.5–1	0.5–2
T. beijingensis (2)	Range	0.008–0.03	16	4–8	4–8	0.125–16	0.06–0.125
T. atroroseus (2)	Range	0.004–0.016	1	0.25	0.25	0.125	0.06
T. stollii (1)	MIC	0.008	2	2	2	1	1
T. cnidii (1)	MIC	0.008	16	16	16	16	0.125
T. fusiformis (1)	MIC	0.016	2	4	1	1	1
Trichophyton							
T. indotineae[d] (46)	Range	0.004–0.06	0.03–8	0.03–16	0.25–8	0.03–8	0.125–0.5
	GM MIC	0.01	1.82	0.51	1.50	0.36	0.32
	MIC_{50}	0.008	4	0.5	2	0.25	0.5
	MIC_{90}	0.03	8	2	8	1	0.5
T. tonsurans[e] (7)	Range	0.03–0.125	0.25–1	0.06–1	0.5–4	0.25–1	0.25
T. rubrum[f] (3)	Range	0.06	1	0.06–1	0.125–0.5	1–2	0.5
Aspergillus							
A. fumigatus	Range	0.004	4–16	2–4	2–4	1–2	0.03–1
TR34/L98H (13)	GM MIC	0.004	4.95	1.45	1.70	0.47	8.44
	MIC_{50}	0.004	4	2	2	0.5	8
	MIC_{90}	0.004	16	2	4	0.9	8
A. fumigatus	Range	0.004	0.25–1	4–16	2–8	0.25–0.5	0.125–1
TR46/Y121F/T289A (10)	GM MIC	0.004	0.41	12.13	6.50	0.33	8
	MIC_{50}	0.004	0.5	16	8	0.25	8
	MIC_{90}	0.004	0.55	16	8	0.5	8
*A. fumigatus*_G54W (6)	Range	0.004	2–16	2–4	0.016–0.125	0.5–2	0.03–0.5
*A. fumigatus*_M220I (3)	Range	0.004	2–4	4	1–4	0.25–2	0.03–1
*A. fumigatus*_F46Y (1)	MIC	0.004	1	4	2	0.125	0.5
*A. fumigatus*_ TR92/Y121F/T289A (1)	MIC	0.004	0.5	16	8	0.5	80.5
A. flavus (8)	Range	0.004	0.25–16	0.125–2	0.125–4	0.125–0.5	0.5–2
A. terreus (7)	Range	0.004–0.016	0.03–0.25	0.03–0.125	0.03–0.125	0.03–0.125	0.5–2
A. clavatus (7)	Range	0.004	2	0.25–0.5	0.125–0.25	1	0.125–0.5
A. nidulans (7)	Range	0.004–0.016	0.06–2	0.03–16	0.016–8	0.03–1	0.03–8
A. niger (5)	Range	0.008–0.03	0.125–0.25	0.03–0.125	0.06–0.125	0.03–0.06	0.06–0.25
A. tamarii (3)	Range	0.004	0.06–0.125	0.125	0.125	0.125–0.25	0.03–1
A. hortai (2)	Range	0.004	0.125	0.06–0.125	0.03–0.125	0.125	4–16
A. sydowii (2)	Range	0.004	0.5–2	0.125–4	0.125–2	0.125–1	1–2
A. flavipes (1)	MIC	0.004	0.125	0.06–0.125	0.03–0.125	0.125	0.125
A. fijiensis (1)	MIC	0.004	0.125	0.03	0.06	0.125	0.06

Continued

Table 1. *Continued*

Genus/species (no. of isolates)		MIC (mg/L)					
		OLO	ITC	VRC	ISA	POS	AMB
A. tritici (1)	MIC	0.004	0.03	0.03	0.016	0.06	0.125
A. aculeatus (1)	MIC	0.004	0.03	0.06	0.125	0.125	0.03
A. oryzae (1)	MIC	0.004	0.5	0.125	0.125	0.125	0.25
Alternaria							
A. alternata (32)	Range	8	0.03–16	0.03–1	0.25–2	0.125–0.5	1–8
	GM MIC	2	0.94	0.38	0.91	0.36	2.16
	MIC_{50}	2	0.5	0.5	1	0.5	2
	MIC_{90}	2	16	0.8	2	0.5	4
Scedosporium							
S. apiospermum (11)	Range	0.004–0.06	0.06–2	0.03–0.5	0.016–4	0.25–8	0.25–16
	GM MIC	0.009	0.34	0.11	0.44	1.13	7.05
	MIC_{50}	0.004	0.25	0.125	0.5	1	16
	MIC_{90}	0.03	1	0.25	2	4	16
S. aurantiacum (1)	MIC	0.03	0.5	0.06	1	0.5	16
S. dehoogii (1)	MIC	0.06	0.25	0.25	0.5	0.5	8

OLO, olorofim; ITC, itraconazole; VRC, voriconazole; ISA, isavuconazole; POS, posaconazole; AMB, amphotericin B; FLC, fluconazole; TRB, terbinafine; LUZ, luliconazole. Drug concentration (10 dilutions) ranges were: ITC and VRC, 0.03–16 mg/L; ISA, POS, AMB, 0.016–8 mg/L; TRB, 0.06–32 mg/L; FLC, 0.25–128 mg/L; OLO and LUZ, 0.004–2 mg/L. For *A. alternata* a range of 0.016–8 mg/L were tested for OLO.
[a]Geometric mean MICs.
[b]MIC_{50}, MIC at which 50% of test isolates were inhibited.
[c]MIC_{90}, MIC at which 90% of test isolates were inhibited.
[d]For *T. indotineae* (mg/L): FLC, range, 4–128; GM MIC, 39.52; MIC_{50}, 32; MIC_{90}, 128. TRB, range, 0.5–32; GM MIC, 4.79; MIC_{50}, 2; MIC_{90}, 32. LUZ, range, 0.004–0.25; GM MIC, 0.004; MIC_{50}, 0.004; MIC_{90}, 0.004.
[e]For *T. tonsurans* (mg/L): range for FLC, TRB and LUZ were 4–128, 0.25–2, 0.004–0.03, respectively.
[f]For *T. rubrum* (mg/L): range for FLC, TRB and LUZ were 4–8, 0.25–0.5, 0.004, respectively.

exhibited multidrug and or terbinafine resistance. Similarly, potent *in vitro* activity was observed for multi-azole-resistant *Talaromyces* and *Penicillium* species. Further, a three dilution step difference (6-fold) among the modal MICs of *T. indotineae* (modal MIC 0.008 mg/L) as compared with *T. tonsurans* and *T. rubrum* isolates was observed, suggesting species-specific MIC differences among *Trichophyton* species. Recently, potent olorofim *in vitro* activity (MIC range 0.008–0.25 mg/L) against 30 Danish dermatophyte isolates has been reported using the EUCAST method.[9] In recent years, *T. indotineae* isolates, predominantly comprising highly terbinafine-resistant Indian strains, seem to be driving an ongoing outbreak of dermatophytosis in countries other than India.[10] The emergence of terbinafine resistance in dermatophytes has been observed in Iran, Japan, and Europe which can lead to epidemics or extensive infections.[10,14,15] The present study also focused on the susceptibility profile of olorofim on the varied spectrum of non-*marneffei* species of *Penicillium* and *Talaromyces*, causative agents of rare invasive fungal diseases. Notably, species of *Penicillium* and *Talaromyces* are known for their inherent resistance to azoles and amphotericin B. A multi-centre epidemiological study conducted in Spain, FILPOP 2 (2016–17), showed a high voriconazole modal MIC of 16 mg/L against *P. citrinum*, which is in concordance with this study.[16] Both *P. citrinum* and *P. oxalicum* have been previously reported as agents of invasive mycoses causing breakthrough infections in patients on voriconazole therapy.[17,18] In the present study, a 1–9 dilution step (2–18-fold) and a 2–12 dilution step (4–24-fold) decrease in *in vitro* activity of olorofim as compared with amphotericin B and systemic azoles, respectively, were observed, suggesting the novel antifungal to be a promising candidate in treatment of infections with *Penicillium* and *Talaromyces* species.

In concordance with previous reports the Indian azole-resistant *A. fumigatus* isolates harbouring TR34/L98H, TR46/Y121F/T289A, and TR92/Y121F/T289A, and *Scedosporium* species showed high susceptibility to olorofim.[19,20] The favourable *in vitro* activity of olorofim against multidrug- and terbinafine-resistant dermatophytes could indicate the drug as a potential antifungal agent against dermatophyte infections. Further studies on *in vitro* susceptibility data of olorofim encompassing geographically distinct dermatophytes and its evaluation in patients with superficial dermatophyte infections are warranted. In conclusion, olorofim *in vitro* activity against pathogenic moulds such as *Penicillium* species, *Talaromyces* species, *Trichophyton* species, *Aspergillus* species, and *Scedosporium* species shows a promising aid in treatment, as these pathogens are gaining global recognition in healthcare settings due to increasing antifungal resistance.

Funding

This work was supported by a grant from F2G to J.F.M. and in part by a research grant from the Council of Scientific & Industrial Research, India [F. No. 09/174(0068)/2014-EMR-I] to A.S.

Transparency declarations

J.F.M. received grants from F2G and Pulmozyme. He has been a consultant to Scynexis and has received speaker's fees from United Medical, TEVA and Gilead. All other authors have none to declare. The authors alone are responsible for the content and writing of the paper.

References

1 Lass-Flörl C, Cuenca-Estrella M. Changes in the epidemiological landscape of invasive mould infections and disease. *J Antimicrob Chemother* 2017; **72** Suppl 1: i5–11.

2 Singh A, Masih A, Khurana A *et al.* High terbinafine resistance in *Trichophyton interdigitale* isolates in Delhi, India harbouring mutations in the squalene epoxidase gene. *Mycoses* 2018; **61**: 477–84.

3 Singh A, Masih A, Monroy-Nieto J *et al.* A unique multidrug-resistant clonal *Trichophyton* population distinct from *Trichophyton mentagrophytes/Trichophyton interdigitale* complex causing an ongoing alarming dermatophytosis outbreak in India: genomic insights and resistance profile. *Fungal Genet Biol* 2019; **133**: 103266.

4 Brown GD, Denning DW, Gow NA *et al.* Hidden killers: human fungal infections. *Sci Transl Med* 2012; **4**: 165rv13.

5 Oliver JD, Sibley GEM, Beckmann N *et al.* F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase. *Proc Natl Acad Sci USA* 2016; **113**: 12809–14.

6 Kirchhoff L, Dittmer S, Buer J *et al. In-vitro* activity of olorofim (F901318) against fungi of the genus, *Scedosporium* and *Rasamsonia* as well as against *Lomentospora prolificans, Exophiala dermatitidis* and azole-resistant *Aspergillus fumigatus*. *Int J Antimicrob Agents* 2020; **56**: 106105.

7 Wiederhold NP. Review of the novel investigational antifungal olorofim. *J Fungi (Basel)* 2020; **6**: 122.

8 Jørgensen KM, Astvad KMT, Hare RK *et al.* EUCAST determination of olorofim (F901318) susceptibility of mold species, method validation, and MICs. *Antimicrob Agents Chemother* 2018; **62**: e00487–18.

9 Astvad KMT, Jørgensen KM, Hare RK *et al.* Olorofim susceptibility testing of 1423 Danish mould isolates 2018-2019 confirms uniform and broad-spectrum activity. *Antimicrob Agents Chemother* 2020; **65**: e01527–20.

10 Kano R, Kimura U, Kakurai M *et al. Trichophyton indotineae* sp. nov.: a new highly terbinafine-resistant anthropophilic dermatophyte species. *Mycopathologia* 2020; doi:10.1007/s11046-020-00455-8.

11 CLSI. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi—Third Edition: M38*. 2017.

12 CLSI. *Epidemiological Cut-off Values for Antifungal Susceptibility Testing—Second Edition: M59*. 2018.

13 Khurana A, Masih A, Chowdhary A *et al.* Correlation of *in-vitro* susceptibility based on MICs and squalene epoxidase mutations with clinical response to terbinafine in patients with tinea corporis/cruris. *Antimicrob Agents Chemother* 2018; **62**: e01038-18.

14 Taghipour S, Shamsizadeh F, Pchelin IM *et al*. Emergence of terbinafine resistant *Trichophyton mentagrophytes* in Iran, harboring mutations in the squalene epoxidase (SQLE) gene. *Infect Drug Resist* 2020; **13**: 845–50.

15 Nenoff P, Verma SB, Ebert A *et al.* Spread of terbinafine-resistant *Trichophyton mentagrophytes* Type VIII (India) in Germany-"The Tip of the Iceberg?". *J Fungi (Basel)* 2020; **6**: 207.

16 Alastruey-Izquierdo A, Alcazar-Fuoli L, Rivero-Menéndez O *et al.* The FILPOP2 Project from GEMICOMED (SEIMC) and REIPI. Molecular identification and susceptibility testing of molds isolated in a prospective surveillance of triazole resistance in Spain (FILPOP2 Study). *Antimicrob Agents Chemother* 2018; **62**: e00358–18.

17 Chowdhary A, Kathuria S, Agarwal K *et al.* Voriconazole-resistant *Penicillium oxalicum*: an emerging pathogen in immunocompromised hosts. *Open Forum Infect Dis* 2014; **1**: ofu029.

18 Ramírez I, Hidrón A, Cardona R. Successful treatment of pulmonary invasive fungal infection by *Penicillium* non-*marneffei* in lymphoblastic lymphoma: case report and literature review. *Clin Case Rep* 2018; **6**: 1153–7.

19 Buil JB, Rijs AJMM, Meis JF *et al*. In vitro activity of the novel antifungal compound F901318 against difficult-to-treat *Aspergillus* isolates. *J Antimicrob Chemother* 2017; **72**: 2548–52.

20 Rivero-Menendez O, Cuenca-Estrella M, Alastruey-Izquierdo A. In vitro activity of olorofim against clinical isolates of *Scedosporium* species and *Lomentospora prolificans* using EUCAST and CLSI methodologies. *J Antimicrob Chemother* 2020; **75**: 3582–5.