	Invasive Candidiasis and Candidemia (n=56)	Mucocutaneous Candidiasis (not VVC) (n=32)	Vulvovaginal Candidiasis (n=14)	Invasive Pulmonary Aspergillosis (n=10)	Chronic Pulmonary Aspergillosis (n=1)
Complete, Partial Response, or Clinical Improvement	35 (62.5%)	17 (53.1%)	10 (71.4%)	4 (40%)	0
Stable Disease	13 (23.2%)	11 (34.3%)	1 (7.1%)	1 (10%)	1 (100%)
Clinical Improvement Criteria Not Met (VVC only)	-	-	2 (14.3%)	-	-
Progression of Disease	4 (7.1%)	3 (9.4%)	0	4 (40%)	0
Indeterminate	4 (7.1%)	0	1 (7.1%)	1 (10%)	0
Deaths	0	1 (3.1%)	0	0	0

P057

All- cause mortality in patients with invasive Candidiasis or candidemia from an interim analysis of a Phase 3 Open-label Study (FURI)

Juergen Prattes[1,2], Thomas King[3], Nkechi Azie[3], David Angulo[3]
[1]Medical University of Graz, Department of Internal Medicine, Division of Infectious Diseases, Excellence Center for Medical Mycology (ECMM), Graz, Austria
[2]Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), University of Cologne and University Hospital Cologne, Cologne, Germany
[3]SCYNEXIS, Inc., Jersey City, USA

Poster session 1, September 21, 2022, 12:30 PM - 1:30 PM

Background: There are limited oral treatment options for patients with high-mortality fungal infections such as candidemia or invasive candidiasis who fail currently available antifungals or have an infection caused by resistant organisms. Ibrexafungerp is an investigational broad-spectrum glucan synthase inhibitor with activity against *Candida* species, including azole- and echinocandin-resistant strains. A Phase 3 open-label, single-arm study of ibrexafungerp (FURI; NCT03059992) is ongoing for the treatment of patients intolerant of, or with invasive fungal disease refractory to, standard antifungal therapy. We present an interim analysis of all-cause mortality within 30 days post-treatment from the FURI study by fungal disease type for patients with candidemia or invasive candidiasis, who completed therapy up until October 2021.

Methods: FURI patients are eligible for enrolment if they have proven or probable: severe mucocutaneous candidiasis or invasive candidiasis, or candidemia, with documented evidence of failure, intolerance, or toxicity related to a currently approved standard-of-care antifungal treatment; or patients who cannot receive approved oral antifungal options (eg, due to susceptibility), and continued IV antifungal therapy is clinically undesirable or unfeasible. Patients were followed through 30 days post-treatment for all-cause mortality.

Results: Out of the 113 patients who completed therapy in the FURI study through October 2021, 56 (50%) had invasive candidiasis or candidemia and were treated with ibrexafungerp. The most common infections in this group were candidemia (15/56, 26.8%), intra-abdominal infection (13/56, 23.2%), and bone infection (10/56, 17.9%).

Overall survival within 30 days post-treatment in this group of 56 patients was 94.6%. Of the 56 patients with candidemia or invasive candidiasis, three (5.3%) died within 30 days after completion of treatment with ibrexafungerp, a fourth died at 31 days, a fifth died at 50 days, and a sixth died at 56 days. The mean age of the expired patients was 56 years. All 4 patients had candidemia (3 with *C. parapsilosis* and 1 with *C. albicans*), and 2 had intra-abdominal candidiasis, (both with *C. glabrata*). The average time on therapy with ibrexafungerp was 15.7 days. The mean time to death post-treatment for these patients was 27 days (median, 21 days). In five cases, the deaths were due to causes other than the underlying fungal disease. For the other case, the cause of death was not disclosed.

Conclusions: Analysis of all-cause mortality in these patients from the FURI study indicates that oral ibrexafungerp provides a favorable therapeutic response in patients with challenging fungal diseases and limited treatment options.

P059

The overexpression of efflux pump gene cdr1B resulting in voriconazole- and isavuconazole- resistance in *Aspergillus fumigatus* recovered from a patient with chronic pulmonary aspergillosis in China

Tianyu Liang[1], Qiqi Wang, Shiyang Pan[2], Fang Ni[2], Ruoyu Li[1], Zhe Wan[1], Wei Liu[1]

[1]Department of Dermatology and Venerology, Peking University First Hospital, National Clinical Research Center for Skin and Immune Diseases, Research Center for Medical Mycology, Peking University, Beijing, China, Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, Beijing, China., Beijing, China
[2]Department of Clinical Laboratory, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

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Objectives: Triazole resistance in the pathogenic *Aspergillus fumigatus* has been increasing worldwide, posing a growing therapeutic challenge. To date, triazole resistance in clinical isolates of *A. fumigatus* causing pulmonary aspergillosis has been mainly attributed to the mutations in the cyp51A gene or its promoter, followed by mutations in cyp51B and hmg1 gene encoding 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. From chronic pulmonary aspergillosis (CPA) patient, we isolated a strain of *A. fumigatus* (BMU10672) with resistance to voriconazole (VRC) and isavuconazole (ISZ), which was caused by overexpression of efflux pump Cdr1B.

Methods: Antifungal susceptibility testing of the isolate of *A. fumigatus* BMU10672 was performed using the broth microdilution method (CLSI M38-A3), E-test and disk diffusion method. The promoter region and open reading frame of the cyp51A, cyp51B, and hmg1 gene were amplified and sequenced. Then, the expression levels of cyp51A, cyp51B, and efflux pump gene cdr1B with or without being exposed to VRC or ISZ were quantified using real-time PCR, compared with triazole-susceptible *A. fumigatus* Af293. And the function of efflux pump Cdr1B was tested by efflux pump substrate (Nile red) accumulation assay and efflux pump inhibitor (FK520) assay.

Results: The minimum inhibitory concentration (MIC) of itraconazole (ITC), VRC, posaconazole (POS), ISZ and amphotericin B (AMB), and the minimal effective concentration (MEC) of caspofungin (CAS) against *A. fumigatus* BMU10672 was 1 μg/ml, 2 μg/mL, 0.5 μg/mL, 2 μg/mL, 1 μg/mL and 0.125 μg/mL, respectively. The results of E-test and disk diffusion assay were consistent with those of the broth microdilution method (Figs. 1a and b). Together, these results indicate that *A. fumigatus* BMU10672 is resistant to VRC and ISZ, while being susceptible to ITC, POS, AMB, and CAS. Sequencing of the cyp51A, cyp51B and hmg1 gene of *A. fumigatus* BMU10672 were all intact. The basal and VRC- or ISZ- induced expression levels of efflux pumps gene cdr1B in *A. fumigatus* BMU10672 were all higher (> 4-fold) than those in triazole-susceptible *A. fumigatus* Af293. However, no differences in basal and VRC- or ISZ- induced expression levels of cyp51A gene and cyp51B gene were observed between *A. fumigatus* BMU10672 and Af293. The efflux pump substrate Nile red accumulation assay showed the *A. fumigatus* BMU10672 accumulated less Nile red than Af293, confirming that Cdr1B was active at exporting Nile red, while efflux pumps inhibitor FK520 can increase the accumulation of the Nile red in *A. fumigatus* BMU10672 (Fig. 1c). Inhibition of efflux pumps activity by inhibitor FK520 resulted in a MIC reduction of 4-fold in VRC and ISZ MICs, and 2-fold in ITC and POS, against *A. fumigatus* BMU10672 (Figs. 1a and b).

Conclusion: Overexpression of efflux pumps gene cdr1B resulting in VRC- and ISZ- resistance in the clinical isolate of *A. fumigatus* BMU10672.