Aspergillus isolates from patients with chronic pulmonary aspergillosis mycologically and clinically resistant to azole antifungals are sensitive to Ibrexafungerp (SCY-078)

Riina Rautemaa-Richardson, Caroline B. Moore, Katie Rawson, Lily Novak-Frazer, David Angulo, Stephen Barat, Malcolm D. Richardson

Mycology Reference Centre Manchester, National Aspergillosis Centre & Infectious Diseases, Manchester University NHS Foundation Trust; ECMM Excellence Centre; University of Manchester, Division of Infection, Immunity and Respiratory Medicine; Scynexis Inc., Jersey City, New Jersey, USA

BACKGROUND

- Ibrexafungerp (formerly MK-3118, SCY-078) is a novel and structurally distinct triterpenoid glucan synthase inhibitor whose oral availability and efficacy has already been demonstrated against a wide spectrum of *Candida* species.
- Currently the drug is being evaluated for efficacy in invasive and chronic pulmonary aspergillosis.
- Ibrexafungerp has been shown to be effective *in vitro* and *in vivo* against a broad range of *Aspergillus* species, including drug-resistant strains.
- *In vitro* activity is an important efficacy indicator of therapeutic success or failure.

OBJECTIVE

- The objective of this study was to determine the activity of Ibrexafungerp against a panel of *Aspergillus* strains isolated from the respiratory tract of patients unresponsive to or failing azole therapy, and which were previously shown to be resistant to one or more azole antifungals (itraconazole, voriconazole, posaconazole and isavuconazole) using the EUCAST E.Def 10.1 standard.

MATERIALS AND METHODS

- Patients failing azole therapy for chronic pulmonary aspergillosis were identified in the weekly departmental multi-disciplinary team meetings and their isolates selected for Ibrexafungerp sensitivity testing.
- 38 *Aspergillus fumigatus* complex with varying degrees of resistance to one or more azole antifungals were tested by measuring the minimum effective concentration (MEC) for Ibrexafungerp following the EUCAST E.Def 10.1 standard.
- Where required, isolates were sequenced (using primers to the internal transcribed spacers (ITS), beta-tubulin (bt) and calmodulin (cal) genes) to identify to the species level.

RESULTS

- The Ibrexafungerp MEC range for the 38 *Aspergillus fumigatus* isolates was 0.008 to 0.5 mg/l.
- Isolates that were deemed to be resistant to all azoles had an Ibrexafungerp MEC of <0.008 – 0.03 mg/l mg/l.
- One isolate that was resistant to all azoles and amphotericin B was sensitive to Ibrexafungerp (MEC 0.125 mg/l).

		Itraconazole	Posaconazole	Voriconazole	Isavuconazole	Amphotericin B	Ibrexafungerp (MEC) (mg/l)
Pattern 1	n=9	R	R	R	R	S	<0.008 - 0.03
Pattern 2	n=3	R	R	I	R	S	0.03 - 0.06
Pattern 3	n=3	R	I	R	R	S	0.03 - 0.125
Pattern 4	n=1	R	I	I	R	S	0.06
Pattern 5	n=1	R	R	S	R	S	0.05
Pattern 6	n=9	R	R	R	R	I	0.06 - 0.5
Pattern 7	n=9	R	R	I	R	I	<0.008 - 0.125
Pattern 8	n=11	S	S	S	S	S	0.06 - 0.5
Pattern 9	n=1	R	R	R	R	R	0.125

Antifungal MIC (mg/l): red=R, amber=I, green=S

Figure 1. Nine azole resistance patterns and corresponding Ibrexafungerp MEC values.

CONCLUSIONS

The exquisite *in vitro* activity of Ibrexafungerp against *Aspergillus fumigatus*, *A. flavus* and *A. niger* isolated from patients with chronic pulmonary aspergillosis suggests that this new compound has potential for treating patients with this condition and similar manifestations of pulmonary aspergillosis.

KEY READING

Davis et al., Ibrexafungerp: a novel oral glucan synthase inhibitor. *Medical Mycology* 2019.

Contact: riina.richardson@manchester.ac.uk www.mycologymanchester.ac.uk