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Antifungal Activities of SCY-078 (MK-3118) and Standard Antifungal Agents against Clinical Non-*Aspergillus* Mold Isolates

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The limited armamentarium of active and oral antifungal drugs against emerging non-*Aspergillus* molds is of particular concern. Current antifungal agents and the new orally available beta-1,3-D-glucan synthase inhibitor SCY-078 were tested *in vitro* against 135 clinical non-*Aspergillus* mold isolates. Akin to echinocandins, SCY-078 showed no or poor activity against *Mucoromycotina* and *Fusarium* spp. However, SCY-078 was highly active against *Paecilomyces variotii* and was the only compound displaying some activity against notoriously panresistant *Scedosporium prolificans*.

Invasive mold infections are a major threat for patients with chemotherapy-induced neutropenia or long-term immunosuppressive therapy following allogeneic hematopoietic stem cell or solid-organ transplantation. While *Aspergillus* spp. account for the majority of cases, invasive mold infections due to non-*Aspergillus* molds are increasing and are associated with a particularly high mortality rate (1, 2). *Mucoromycotina* (previously referred to as zygomycetes), *Fusarium* spp., *Scedosporium* spp., *Paecilomyces* spp., and *Scopulariopsis* spp. are well-recognized opportunistic fungal pathogens that often exhibit high MICs *in vitro* and clinical resistance to currently available antifungal drugs (3–7). Amphotericin B, while not active against all of these species, often remains the only therapeutic choice but is associated with toxicity. The lack of oral drug formulations is another major problem in the management of these infections, which require prolonged courses of antifungal treatment.

TABLE 1 Patient demographic characteristics and origins of clinical isolates

Patient characteristic or source of isolate	No. (%)
Patient characteristics	123
Solid-organ transplant recipients	47 (38)
Lung	41
Other	6
Allogeneic hematopoietic stem cell transplant recipients	13 (11)
Neutropenia secondary to hematological malignancies	21 (17)
Other[a]	37 (30)
Unknown[b]	5 (4)
Sources of isolates	135
Respiratory sample[c]	72 (53)
Sinus/nose	18 (13)
Skin/soft tissue	24 (18)
Eye	12 (9)
Blood	6 (4)
Other[d]	3 (2)

[a] Solid tumor (4), chronic pulmonary disease (5), diabetes mellitus (4), auto-immune disease (1), or no specific underlying conditions (23).
[b] No clinical data available (isolate referred from outside hospital for identification).
[c] Bronchoalveolar lavage fluid or endotracheal suction (44), sputum (7), lung tissue (11), bronchial tissue (6), or pleural fluid (4).
[d] Intraperitoneal abscess (2) or ear (1).

SCY-078 (formerly MK-3118) is a semisynthetic derivative of the natural product enfumafungin, a potent inhibitor of fungal beta-1,3-D-glucan synthases (8, 9). This compound is structurally different from the echinocandins and has the advantage of having oral bioavailability. Its *in vitro* activity against *Candida* spp. and *Aspergillus* spp. was recently demonstrated (10–12).

We retrospectively tested the *in vitro* antifungal activities of standard antifungal agents (amphotericin B, voriconazole, itraconazole, posaconazole, caspofungin, micafungin, and anidulafungin) and SCY-078 against a collection of 135 selected clinical isolates representing the most clinically relevant non-*Aspergillus* fungal pathogens, including *Rhizopus* spp. (16), *Mucor* spp. (7), *Rhizomucor* spp. (2), *Cunninghamella* spp. (4), *Lichtheimia* spp. (previously *Absidia* spp.) (4), *Fusarium* spp. (35), *Scedosporium apiospermum*/*Pseudallescheria boydii* complex (19), *Scedosporium prolificans* (5), *Purpureocillium lilacinum* (previously *Paecilomyces lilacinus*) (30), *Paecilomyces variotii* (5), and *Scopulariopsis* spp. (8). All isolates were recovered from clinical specimens at Duke University Hospital (Durham, NC, USA) between 2009 and 2013. The ATCC strain *P. variotii* MYA3630 was used as a control strain. Antifungal susceptibility testing was performed by broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M38-A2 procedure (13). SCY-078 powder was provided by Scynexis Inc. (Durham, NC). According to CLSI recommendations, the MICs (the concentration at which no hyphal growth was detected) were assessed for amphotericin B and azole compounds, and the minimal effective concentrations (MECs) (the concentration at which hyphal growth was significantly altered, with formation of blunted colonies) were determined for

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TABLE 2 Antifungal activities of SCY-078 and standard antifungal agents against non-*Aspergillus* clinical isolates (n = 135)

Genus/species (no.)	MEC_{50}/MEC_{90} (μg/ml) (range) for[a,b]:				MIC_{50}/MIC_{90} (μg/ml) (range) for[a,c]:			
	SCY-078	CSP	MCF	AND	AMB	VCZ	POS	ITZ
Mucoromycotina (33)								
Rhizopus spp. (16)	16/16 (16 to >16)	>16/>16 (>16)	>16/>16 (>16)	>16/>16 (>16)	0.5/2 (0.125–2)	16/>16 (8 to >16)	>16/>16 (0.5 to >16)	>16/>16 (2 to >16)
Mucor spp. (7)	16/>16 (8 to >16)	>16/>16 (>16)	>16/>16 (>16)	>16/>16 (8 to >16)	0.5/1 (0.125–4)	>16/>16 (8 to >16)	>16/>16 (1 to >16)	>16/>16 (2 to >16)
Rhizomucor spp. (2)	16 to >16	>16	>16	8 to >16	0.25–1	>16	2 to >16	>16
Lichtheimia spp. (4)	8/16 (8–16)	>16/>16 (>16)	>16/>16 (>16)	8/16 (8–16)	1/2 (0.5–2)	>16/>16 (>16)	1/>16 (1 to >16)	>16/>16 (2 to >16)
Cunninghamella spp. (4)	16/16 (16)	>16/>16 (>16)	>16/>16 (>16)	16/16 (8–16)	4/4 (2–4)	>16/>16 (16 to >16)	1/2 (1–2)	4/>16 (4 to >16)
Fusarium spp. (35)	8/16 (8–16)	>16/>16 (8 to >16)	>16/>16 (2 to >16)	>16/>16 (8 to >16)	2/4 (1 to >16)	>16/>16 (2 to >16)	>16/>16 (2 to >16)	>16/>16 (>16)
Purpureocillium lilacinum (30)	>16/>16 (2 to >16)	>16/>16 (0.25 to >16)	>16/>16 (0.06 to >16)	>16/>16 (0.06 to >16)	>16/>16 (16 to >16)	0.25/0.5 (0.125–0.5)	1/1 (0.25–2)	>16/>16 (4 to >16)
Paecilomyces variotii (5)	<0.02/<0.02 (<0.02)	0.06/2 (0.03–2)	<0.02–0.03 (<0.02–0.03)	<0.02–0.03 (<0.02–0.03)	0.5/2 (0.125–2)	>16/>16 (16 to >16)	0.5/>16 (0.25 to >16)	>16/>16 (1 to >16)
Scopulariopsis spp. (8)	4/8 (4–8)	0.5/8 (0.25–16)	1/>16 (<0.02 to >16)	8/>16 (<0.02 to >16)	8/>16 (2 to >16)	>16/>16 (16 to >16)	>16/>16 (>16)	>16/>16 (>16)
Scedosporium apiospermum/ *Pseudallescheria boydii* (19)	2/4 (1–8)	0.5/1 (0.06 to >16)	1/2 (0.25 to >16)	8/8 (2–16)	8/>16 (2 to >16)	1/1 (0.5–2)	>16/>16 (2 to >16)	>16/>16 (>16)
Scedosporium prolificans (5)	4/4 (4)	16/16 (16)	>16/>16 (>16)	8/16 (8–16)	>16/>16 (8 to >16)	>16/>16 (>16)	>16/>16 (>16)	>16/>16 (>16)

[a] All drugs were tested via Clinical and Laboratory Standards Institute broth microdilution method within concentrations ranging from 0.02 to 16 μg/ml (11).
[b] CSP, caspofungin; MCF, micafungin; AND, anidulafungin.
[c] AMB, amphotericin B; VCZ, voriconazole; POS, posaconazole; ITZ, itraconazole.

echinocandins and SCY-078 (13); reading was performed at 24 h or 48 h according to genus (13). MIC(MEC)$_{50}$ and MIC(MEC)$_{90}$ values (i.e., concentrations that inhibit 50% and 90% of isolates, respectively) were determined for each species. The study was approved by the Duke Hospital Institutional Review Board.

The origins of isolates and characteristics of patients from whom they were obtained are shown in Table 1. MIC(MEC)$_{50}$ and MIC(MEC)$_{90}$ values of all fungal species are represented in Table 2. Predictably, amphotericin B was the only drug displaying good universal activity against the *Mucoromycotina*. Notably, posaconazole, the other agent with known clinical activity against this group of organisms, displayed better activity against *Cunninghamella* and *Lichtheimia* spp. (7/8 strains had an MIC of ≤2 μg/ml) than against *Rhizopus* spp. or *Mucor* spp., for which the MIC was >16 μg/ml for 56% and 71% of strains tested, respectively. Similarly, amphotericin B was the only active drug against most *Fusarium* spp., although relatively high MICs (≥4 μg/ml) were observed in 40% of cases. The echinocandins and SCY-078 had little activity against the *Mucoromycotina* or *Fusarium* spp.

SCY-078 and the echinocandins had negligible effect against *P. lilacinum* but were very active against *P. variotii* (MEC, <0.02 to 0.03 μg/ml), including the MYA3630 control strain (MEC, <0.02 μg/ml). Also akin to echinocandins, SCY-078 displayed variable activity against *Scopulariopsis* spp., for which the triazoles showed no activity.

Amphotericin B was poorly active against the two species of *Scedosporium* while voriconazole, caspofungin, micafungin, and SCY-078 showed variable activity against *S. apiospermum*. SCY-078 was the only drug to achieve a modest effect against *S. prolificans* (MEC$_{90}$, 4 μg/ml).

The new orally available beta-glucan synthase inhibitor SCY-078 exhibited *in vitro* antifungal activity against non-*Aspergillus* molds comparable to that of echinocandins, with one important exception. It was the only agent tested with activity against *S. prolificans*, a notoriously panresistant mold for which there are no good treatment options. While the degree of activity was modest (MEC$_{90}$, 4 μg/ml), this discovery warrants further investigation into the potential role of SCY-078 for treating *S. prolificans* infections. Also from a clinical perspective, the good activity of SCY-078 against *P. variotii* is of particular interest. *P. variotii* has been associated with disseminated infections, including fungemia and peritonitis in patients undergoing peritoneal dialysis (14–16). Amphotericin B is, to date, the treatment of choice for this pathogen, with itraconazole considered a second-line oral agent (17). Among our collection of isolates and consistent with previous reports (18), voriconazole showed no activity and posaconazole and itraconazole displayed only variable activity against *P. variotii* isolates, while SCY-078 appears to be a good candidate for the management of *P. variotii* infections. Overall, this study further supports the potential utility of this compound as an alternative to the standard first-line intravenous drugs in the long-course treatment of certain invasive fungal infections for which oral therapeutic options are limited. The pharmacokinetic and pharmacodynamic profile of SCY-078 has been recently studied in a murine model of invasive candidiasis (19). A maximum concentration of drug in serum (C_{max}) of 2.66 μg/ml was achieved for an oral dose of 200 mg/kg of body weight. Whether higher serum concentrations can be achieved and well tolerated *in vivo* is unknown. Pharmacodynamic analyses showed that the area under the concentration-time curve (AUC)/MIC index was a good predictor of therapeutic response in terms of reduction of the fungal burden.

This analysis of a large collection of clinical isolates highlights the growing concern of antifungal resistance among non-*Aspergillus* molds, which account for an increasing proportion of invasive mold infections. Although the correlation between *in vitro* susceptibility and clinical outcomes is still unclear for these molds, our data raise some concerns with respect to current practices in the management of non-*Aspergillus* mold infections. For instance, the use of posaconazole for the treatment of "mucormycosis" should be carefully considered, as posaconazole activity appears to vary significantly among the various genera capable of causing this infection. Further, while voriconazole is the current recommended first-line therapy of fusariosis (17), most of the *Fusarium* isolates in this collection exhibited high MICs to all triazoles tested. While our data are center specific, our institution is a major, high-volume oncology and transplant center and our institutional practices follow national guidelines/recommendations with regard to antifungal prophylaxis and treatment, thus enhancing the generalizability of the results and raising an alarm for similar institutions. Certainly, studies that correlate outcomes of mold infections based on *in vitro* susceptibility results are desperately needed. SCY-078 represents a much anticipated oral glucan synthase inhibitor and its *in vitro* activity against several important non-*Aspergillus* molds is promising. Further, *in vivo* analyses of the pharmacokinetics, safety profile, and efficacy of this drug are warranted to better define the role of SCY-078 for the treatment of invasive mold infections.

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