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Antifungal Activity of SCY-078 and Standard Antifungal Agents against 178 Clinical Isolates of Resistant and Susceptible *Candida* Species

Wiley A. Schell,[a] A. M. Jones,[b] Katyna Borroto-Esoda,[c] Barbara D. Alexander[a]

Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA[a]; Computational Genomics Unit, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA[b]; Scynexis, Inc., Jersey City, New Jersey, USA[c]

ABSTRACT SCY-078 *in vitro* activity was determined for 178 isolates of resistant or susceptible *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida krusei*, *Candida lusitaniae*, and *Candida parapsilosis*, including 44 *Candida* isolates with known genotypic (*FKS1* or *FKS2* mutations), phenotypic, or clinical resistance to echinocandins. Results were compared to those for anidulafungin, caspofungin, micafungin, fluconazole, and voriconazole. SCY-078 was shown to have excellent activity against both wild-type isolates and echinocandin- and azole-resistant isolates of *Candida* species.

KEYWORDS *Candida*, antifungal agents, antifungal resistance

Candida species are the most common cause of invasive fungal infections. Invasive *Candida* infections are seen worldwide among immunocompromised and nonimmunocompromised hosts and are associated with high mortality and morbidity rates, as well as excess costs (1–8). Resistance to currently available azole and echinocandin antifungals is increasing, and the emergence of resistance to both azoles and echinocandins within the same isolate (multidrug resistance), particularly in *Candida glabrata*, is a major public health concern (9). Such multidrug resistance threatens the implementation of effective early treatment, leading to increased mortality rates.

Derivatives of the natural product enfumafungin are potent inhibitors of fungal glucan synthase (GS) but are structurally distinct from the echinocandins and constitute a new class of GS inhibitor compounds (10). SCY-078 (formerly MK-3118), a semisynthetic compound derived from enfumafungin, has been formulated as both oral and intravenous preparations and exhibits *in vitro* and *in vivo* activity against azole- and echinocandin-resistant isolates of *Candida* species (11–13).

In this retrospective study, we determined the *in vitro* antifungal activity of SCY-078, anidulafungin (ANF), caspofungin (CAS), micafungin (MCF), fluconazole (FLC), and voriconazole (VRC) against 178 *Candida* strains recovered from clinical specimens between 2009 and 2013. The isolates were divided into three groups. Group 1 consisted of 44 isolates known to have genotypic (detection of *FKS* mutations by nucleic acid sequencing), phenotypic (MIC indicating resistance to one or more echinocandins), or clinical (failure to clear blood after ≥5 days of directed antifungal therapy or microbiologically documented recurrent infection with continuing antifungal therapy) echinocandin resistance, based on prior studies (14, 15). Isolates in group 1 were *Candida glabrata* ($n = 34$), *Candida parapsilosis* ($n = 6$), *Candida tropicalis* ($n = 2$), *Candida albicans* ($n = 1$), and *Candida krusei* ($n = 1$) (see Tables S1 and S2 in the supplemental material). Among the *C. glabrata* isolates in group 1, 79% harbored an *FKS* mutation and the majority demonstrated *in vitro* resistance to the echinocandins. Group 2 consisted

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Address correspondence to Barbara D. Alexander, barbara.alexander@dm.duke.edu.

TABLE 1 MIC results for paired *Candida glabrata* isolates

Isolate type and antifungal drug	MIC (μg/ml)[a]					
	Range	Geometric mean	Median	Mode	MIC_{50}	MIC_{90}
Resistant *C. glabrata* isolates ($n = 34$)[b]						
SCY-078	0.25–4	0.72	0.5	0.5	0.5	4
FLC	1–128	12	16	4	16	128
ANF	≤0.015 to 4	0.29	0.37	0.03	0.25	2
MCF	≤0.015 to 4	0.16	0.18	≤0.015	0.12	2
CAS	≤0.015 to 16	0.3	0.5	≤0.015	0.5	8
VRC	≤0.015 to 8	0.5	0.5	0.5	0.5	4
Matched *C. glabrata* isolates ($n = 34$)[c]						
SCY-078	0.25–1	0.38	0.5	0.25	0.5	0.5
FLC	4–128	14	12	16	8	128
ANF	≤0.015 to 0.12	0.04	0.06	0.03	0.03	0.12
MCF	≤0.015 to 0.12	0.019	≤0.015	≤0.015	≤0.015	0.06
CAS	≤0.015 to 0.25	0.025	≤0.015	≤0.015	≤0.015	0.06
VRC	0.06–16	0.61	0.5	0.5	0.5	4

[a]All drugs were tested with the Clinical and Laboratory Standards Institute broth microdilution method at concentrations ranging from 0.015 to 16 μg/ml, except for fluconazole, which ranged in concentration from 0.125 to 128 μg/ml. ANF, anidulafungin; CAS, caspofungin; FLC, fluconazole; MCF, micafungin; VRC, voriconazole.

[b]*C. glabrata* isolates with known *FKS1* or *FKS2* mutations or phenotypic or clinical resistance (see the supplemental material).

[c]*C. glabrata* isolates without known resistance, matched to the resistant isolates by year of recovery.

of 34 *C. glabrata* isolates matched to the *C. glabrata* isolates in group 1 by year of recovery but lacking known clinical, phenotypic, or genotypic echinocandin resistance (Table S1). Group 3 consisted of 101 consecutive *Candida* isolates from unique episodes of bloodstream infections that occurred in 2013 at Duke University Hospital, including *C. albicans* ($n = 33$), *C. albicans/dubliniensis* not further identified ($n = 5$), *C. tropicalis* ($n = 12$), *C. glabrata* ($n = 23$), *C. krusei* ($n = 6$), *C. parapsilosis* ($n = 19$), and *Candida lusitaniae* ($n = 3$) (Table S3).

Tests were performed in the broth microdilution format, as described by the Clinical and Laboratory Standards Institute (16, 17). SCY-078 powder (100% pure) was provided by Scynexis, Inc. (Jersey City, NJ), and a stock solution of 1,600 μg/ml was prepared in pure dimethyl sulfoxide (DMSO). ANF, MCF, CAS, and VRC were purchased in the form of frozen noncolorimetric microtiter plates (Trek Diagnostics, Inc., Independence, OH). FLC was purchased as a powder (99% pure; Alfa Aesar, Inc., Ward Hill, MA). Drugs were tested at concentrations ranging from 0.015 μg/ml to 16 μg/ml, except for FLC, which ranged in concentration from 0.125 μg/ml to 128 μg/ml. Inoculum concentrations were verified by quantitative culture. MIC_{50} endpoints (≥50% inhibition) were determined visually at 24 h (SCY-078 and echinocandins) and 48 h (azoles). *C. parapsilosis* ATCC 22019 was used as the quality control strain. For species for which 10 or more isolates were tested, summary statistics, including MIC ranges, geometric means, medians, modes, and the MICs that encompassed 50% and 90% of the isolates tested, were calculated for each species with each drug. For interpretation of summary statistics, results that fell between standard 2-fold dilution values were rounded to the next highest 2-fold dilution (e.g., a median MIC of 0.18 μg/ml would be rounded to 0.25 μg/ml and a value of 0.75 μg/ml would be rounded to 1.0 μg/ml).

Results for the 34 resistant *C. glabrata* isolates and the 34 paired control isolates are shown in Table 1. As expected, echinocandin MICs for the *C. glabrata* isolates with genotypic, phenotypic, or clinical resistance were higher than those for the *C. glabrata* matched controls. For SCY-078, the MIC_{90} for resistant isolates was 4 μg/ml, compared with 0.5 μg/ml for the controls, although the median SCY-078 MICs were the same for the two groups (0.5 μg/ml). The median ANF, MCF, and CAS MICs were 3, 4, and 5 dilutions higher, respectively, for the resistant *C. glabrata* group than for the control

group. SCY-078 MICs for individual isolates tended to be 3 to 5 dilutions higher than those for the echinocandins, but in general the SCY-078 MICs trended in agreement (tested high versus low) with those for the echinocandins (Tables S1 and S2). An exception was the *C. glabrata* isolates with S663P mutations, for which SCY-078 MICs tended to be 1 to 3 dilutions lower than echinocandin MICs. All 44 *Candida* isolates with known *FKS1* or *FKS2* mutations or phenotypic or clinical resistance identified in prior studies were inhibited by SCY-078 at concentrations of ≤4 μg/ml (*C. glabrata* geometric mean MIC, 0.72 μg/ml; non-*C. glabrata* geometric mean MIC, 0.24 μg/ml) at 24 h of incubation, and 38/44 isolates (86%) were inhibited by SCY-078 at concentrations of <2 μg/ml (Table 1; also see Tables S1 and S2).

Results for 101 consecutive *Candida* isolates recovered from blood samples in 2013 are shown in Table 2 and Table S3. SCY-078 MIC_{90} values for *C. albicans* ($n = 33$), *C. tropicalis* ($n = 12$), *C. glabrata* ($n = 23$), and *C. parapsilosis* ($n = 19$) were 0.12 μg/ml, 0.25 μg/ml, 1 μg/ml, and 0.25 μg/ml, respectively. MIC ranges for *C. albicans/dubliniensis* not further identified ($n = 5$), *C. krusei* ($n = 6$), and *C. lusitaniae* ($n = 3$) were 0.12 μg/ml, 0.5 to 4 μg/ml, and 1 to 2 μg/ml, respectively. SCY-078 MICs for *C. krusei* and *C. lusitaniae* were 2 to 4 dilutions and 3 to 5 dilutions higher, respectively, than those for the other *Candida* species. SCY-078 MICs were consistently low (≤0.5 μg/ml) for azole-resistant *C. albicans*, *C. tropicalis*, and *C. parapsilosis* isolates. SCY-078 MICs were typically 1 to 3 dilutions lower than ANF and MCF MICs for *C. parapsilosis*.

Fksp subunits of the β-1,3-D-glucan synthase enzyme complex are encoded by the *FKS1*, *FKS2*, and *FKS3* genes. These genes are the targets of echinocandin antifungal compounds. For most *Candida* species, acquired reduced susceptibility to echinocandins involves amino acid substitutions in two hot spot regions of *FKS1* and *FKS2*. Amino acid substitutions in these genes can decrease the sensitivity of glucan synthase to echinocandins by several log units, with the degree of impact being dependent on the specific amino acid substitution and its location (18–20). SCY-078 also acts on β-1,3-glucan synthase, but it represents a new class of antifungal compounds, structurally distinct from the echinocandins, and it is thought to interact differently with the enzyme target. Indeed, this study confirms good *in vitro* activity of SCY-078 against *C. glabrata* isolates with a S663P mutation, which is the most prevalent mutation yielding high-level echinocandin resistance (21). For *C. glabrata* isolates with a S663P mutation, SCY-078 MICs were 1 to 3 dilutions lower than those for the echinocandins. Thus, SCY-078 represents a potential treatment option for the most prevalent echinocandin-resistant *C. glabrata* isolates.

The naturally occurring high MICs exhibited by echinocandins against *C. parapsilosis* and *Candida guilliermondii* have been recognized since these antifungal agents were first introduced. Epidemiological cutoff values (ECVs) that capture ≥97.5% of the wild-type population for ANF and MCF are 8 and 4 μg/ml, respectively, for *C. parapsilosis* and 8 and 2 μg/ml, respectively, for *C. guilliermondii* (22). Naturally occurring substitutions in the HS1 region of FKS1 in *C. parapsilosis* and *C. guilliermondii* are thought to be responsible for the intrinsically high echinocandin MICs. The changes in FKS1 appear to decrease the sensitivity of glucan synthase for the drugs, resulting in elevated MIC values (20, 23). Our data show a lower SCY-078 MIC_{90} for *C. parapsilosis* (0.25 μg/ml), compared with echinocandins, suggesting that the naturally occurring changes in FKS1 that result in higher *C. parapsilosis* MICs for echinocandins do not affect the capacity of SCY-078 to inhibit glucan synthase in this pathogen.

SCY-078 MICs for the few isolates of *C. lusitaniae* ($n = 3$) (MIC range, 1 to 2 μg/ml) and *C. krusei* ($n = 6$) (MIC range, 0.5 to 4 μg/ml) tested in this study were higher than those for the other *Candida* species. As with *C. parapsilosis* and the echinocandins, a naturally occurring substitution (as yet unidentified) may be responsible for reduced activity of SCY-078 with glucan synthase in *C. lusitaniae* and *C. krusei*; whether this will translate into clinical failure is unknown.

SCY-078 targets the same enzyme complex as the echinocandins and has shown good activity *in vitro* and *in vivo*. However, direct comparisons of its MIC values with those of other compounds must be made cautiously. Different compounds may

TABLE 2 MIC results for 101 consecutive *Candida* isolates from unique episodes of bloodstream infection

Species and antifungal drug	MIC (μg/ml)					
	Range[a]	Geometric mean	Median	Mode	MIC_{50}	MIC_{90}
C. albicans (*n* = 33)						
SCY-078	0.06–0.25	0.08	0.06	0.06	0.06	0.12
FLC	≤0.125 to 128	1	0.5	0.25	0.5	>128
ANF	≤0.015 to 1	0.02	≤0.015	≤0.015	≤0.015	0.03
MCF	≤0.015 to 1	0.02	≤0.015	≤0.015	≤0.015	0.06
CAS	≤0.015 to 0.5	0.02	≤0.015	≤0.015	≤0.015	0.06
VRC	≤0.015 to >16	0.08	0.03	≤0.015	0.03	>16
C. albicans/dubliniensis not further identified (*n* = 5)						
SCY-078	0.12					
FLC	≤0.125 to 0.25					
ANF	≤0.125 to 0.03					
MCF	≤0.015 to 0.03					
CAS	≤0.015 to 0.03					
VRC	≤0.015					
C. glabrata (*n* = 23)						
SCY-078	0.25–1	0.35	0.25	0.25	0.25	1
FLC	2 to >128	11	8	8	8	64
ANF	0.03–1	0.04	0.03	0.03	0.03	0.06
MCF	≤0.015 to 0.5	0.02	≤0.015	≤0.015	≤0.015	≤0.015
CAS	≤0.015 to 0.5	0.02	≤0.015	≤0.015	≤0.015	0.03
VRC	0.03–8	0.3	0.25	0.25	0.25	1
C. krusei (*n* = 6)						
SCY-078	0.5–4					
FLC	64–128					
ANF	0.03–0.25					
MCF	0.03–0.25					
CAS	0.06–0.5					
VRC	0.5–1					
C. parapsilosis (*n* = 18)						
SCY-078	0.25–0.5	0.26	0.25	0.25	0.25	0.25
FLC	0.25–4	0.8	2	1	1	2
ANF	0.06–2	0.92	1	1	1	2
MCF	0.5–2	0.98	1	2	1	2
CAS	0.06–0.5	0.22	0.25	0.25	0.25	0.5
VRC	≤0.015 to 0.12	0.02	0.03	0.03	0.03	0.06
C. tropicalis (*n* = 12)						
SCY-078	0.03–0.5	0.1	0.12	0.12	0.12	0.25
FLC	0.25–1	0.5	0.5	0.5	0.5	1
ANF	≤0.015	≤0.015	≤0.015	≤0.015	≤0.015	≤0.015
MCF	≤0.015 to 0.06	0.02	≤0.015	≤0.015	≤0.015	0.06
CAS	≤0.015 to 0.06	0.01	≤0.015	≤0.015	≤0.015	0.03
VRC	≤0.015	0.03	0.04	0.06	0.03	0.06
C lusitaniae (*n* = 3)						
SCY-078	1–2					
FLC	0.5–2					
ANF	0.12–0.25					
MCF	0.12					
CAS	0.12–0.25					
VRC	≤0.015					

[a]Only ranges are reported when the number of isolates tested was less than 10.

produce different ranges of MIC results *in vitro* and yet have comparable efficacy *in vivo* as a result of differences in bioavailability and in pharmacokinetic (PK)/pharmacodynamic (PD) parameters. Furthermore, *in vitro* testing variables (e.g., media and pH) can affect antifungal agents differently, thereby influencing MIC values. Presently, no

interpretive breakpoints or ECVs are available for SCY-078. Although SCY-078 MICs tended to be 3 to 5 dilutions higher than echinocandin MICs overall, results for individual isolates generally corresponded (high versus low MICs), except as discussed above.

Preclinical studies of SCY-078 in murine models of candidiasis have determined the area under the concentration-time curve (AUC)/MIC to be the PK/PD parameter most predictive of outcome (13, 24). Relative to the MICs determined here, the amount of SCY-078 required for efficacy for this group of isolates should be achievable in humans, based on preclinical and phase 1 and phase 2 clinical data. However, we await data from the clinical trials to establish a definitive breakpoint for susceptibility.

In summary, our data suggest that, although SCY-078 targets the same fungal site as the echinocandins, it is structurally distinct and distinguishes itself by having activity against species of *Candida* in which resistance to standard antifungal compounds can be intrinsic or acquired. SCY-078 shows strong potential for the treatment of *Candida* infections, including azole- and echinocandin-resistant isolates. Thus, SCY-078 may represent the first oral option for multidrug-resistant *Candida* infections. This information should prove useful in the design of future trials to assess the clinical efficacy of SCY-078 in human patients with invasive *Candida* infections.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01102-17.

SUPPLEMENTAL FILE 1, PDF file, 0.5 MB.

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