The novel oral glucan synthase inhibitor SCY-078 shows in vitro activity against sessile and planktonic Candida spp.

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Objective: We studied the antifungal activity of SCY-078 (an orally bioavailable 1,3-β-D-glucan synthase inhibitor), micafungin and fluconazole against the planktonic and sessile forms of 178 Candida and non-Candida isolates causing fungaemia in patients recently admitted to a large European hospital.

Methods: The in vitro activity of SCY-078, micafungin and fluconazole against the planktonic form of the isolates was assessed using EUCAST EDef 7.3 and CLSI M27-A3. Antibiofilm activity was assessed using the XTT reduction assay.

Results: SCY-078 and micafungin showed potent in vitro activity against Candida and non-Candida isolates. The in vitro activity of both drugs was similar, but SYC-078 displayed significantly lower MIC values than micafungin against Candida parapsilosis and non-Candida isolates, whereas micafungin displayed significantly lower MIC values for the remaining species (P<0.001). In contrast, SCY-078 and micafungin showed essentially the same activity against the biofilms with the exception of Candida glabrata, in which the micafungin sessile MIC values were significantly lower (P<0.001). These observations were confirmed by assessing biofilm structure by scanning electron microscopy after antifungal treatment.

Conclusions: Our study showed that the high in vitro activity of SCY-078 against invasive Candida isolates in both sessile and planktonic forms is comparable to that of micafungin.

Introduction

The antifungal armamentarium is limited by the spectrum of activity and the pharmacokinetic properties of the drugs used to treat invasive fungal infections. Echinocandins are the drugs of choice for the treatment of Candidaemia.1–2 Their mechanism of action is based on inhibition of fungal wall biosynthesis by targeting 1,3-β-D-glucan synthase.3 The three commercially available echinocandins caspofungin, micafungin, and anidulafungin have a broad spectrum of activity against the most frequent Candida species, including preformed biofilms, except for Candida parapsilosis and Candida guilliermondii, which are intrinsically less susceptible.4–7 While the incidence of echinocandin resistance in Candida is generally considered low, there has been a marked increase in some centres.6,9 Oral absorption of echinocandins is poor, thus restricting intravenous administration and preventing prescription under an outpatient regimen as prophylaxis or for long-term treatment.10 1,3-β-D-Glucan synthase inhibitors with a spectrum of activity matching that of the echinocandins but enabling oral bioavailability could obviate the need for intravenous administration and facilitate outpatient management.

SCY-078 (formerly MK-3118) is a new semi-synthetic derivative of the terpenoid enfumafungin, a potent inhibitor of 1,3-β-D-glucan synthase that is structurally different to the echinocandins.11 Administered orally, SCY-078 showed similar activity to caspofungin against Candida spp. and Aspergillus spp. isolates collected mainly in the USA.12–14 The hypothetical mechanism of action of SCY-078 anticipates antifungal activity against Candida biofilms, although this activity has been studied exclusively against planktonic forms.

We studied the antifungal activity of SCY-078, micafungin and fluconazole against a collection of yeasts causing fungaemia in patients recently admitted to a large European hospital and, for the first time, tested the activity of SCY-08 against preformed biofilms.
Materials and methods
Organisms and identification
We studied 178 isolates from patients with fungaemia admitted to Gregorio Marañón Hospital, Madrid, Spain from 2014 to 2015. All isolates were identified by amplification and sequencing of the ITS1-5.8S-ITS2 region. The distribution of isolates was as follows: Candida albicans, n = 55; C. parapsilosis, n = 33; Candida glabrata, n = 31; Candida tropicalis, n = 8; Candida krusei, n = 12; Candida spp. n = 26 (Candida dubliniensis, n = 6; Candida lusitaniae, n = 6; C. guilliermondii, n = 6; Candida fermentati, n = 3; Candida kefyr, n = 2; Candida inconspicua, n = 1; Candida pelliculosa, n = 1; Kodamariae ohmeri, n = 1), and other non-Candida yeasts, n = 13 (Rhodotorula mucilaginosa, n = 7; Trichosporon asahii, n = 2; Trichosporon dermatitidis, n = 1; Trichosporon inkin, n = 1; Trichosporon japonicum, n = 1; Axula adeninivorans, n = 1).

Antifungal susceptibility testing
Antifungal susceptibility testing was performed using the microdilution broth procedures CLSI M27-A3 and EUCAST EDef 7.3. The following antifungals were used: fluconazole (Pfizer Pharmaceutical Group, New York, NY, USA); SCY-078 (formerly MK-3118, SCYNEXIS Inc., Jersey City, NJ, USA) and micafungin (LGMD Pharma, Nashville, TN, USA). C. krusei ATCC 6258 and C. parapsilosis ATCC 22019 isolates were used as quality control strains. A stock of 5 mL of the citrate salt of SCY-078 dissolved in DMSO was prepared in glass vials and stored at −70 °C until preparation of the microtitre trays on the day when antifungal susceptibility testing was performed.

(i) CLSI M27-A3 procedure
The antifungal agents were tested at concentrations ranging from 0.007 to 8 mg/L (micafungin and SCY-078) and 0.062 to 64 mg/L (fluconazole).

(ii) EUCAST EDef 7.3 procedure
The antifungal agents were tested at concentrations ranging from 0.015 to 8 mg/L (micafungin and SCY-078) and 0.125 to 64 mg/L (fluconazole). For non-fermentative species, antifungal susceptibility testing was assessed with shaking and incubation at 30 °C for 48 h before determining the optical density.

Inoculated trays were incubated at 35 °C, and the MIC was visually (CLSI) or spectrophotometrically (EUCAST) determined after 24 h of incubation. The MIC for the three drugs was defined as the lowest concentration of drug that resulted in visual inhibition of ≥50% of growth in comparison with a drug-free control; given the lack of a predefined endpoint for determination of the MIC80 MIC, the 100% growth inhibition endpoint was also used for SCY-078.

Biofilm formation and antifungal susceptibility
Biofilms were formed according to the method proposed by Pierce and colleagues. Briefly, the preformed biofilms were treated with concentrations ranging from 0.015 to 16 mg/L (micafungin and SCY-078) or 0.125 to 128 mg/L (fluconazole). Trays were incubated at 37 °C for 24 h, the antifungal was removed and the plates were washed three times with PBS. A solution of XTT 0.5 mg/mL and menadione 0.1 mM (Sigma-Aldrich) was added, and the plates were incubated in darkness for 2 h. Reduction of XTT was assessed spectrophotometrically at 490 nm (Multiskan FC Microplate Photometer, Thermo Scientific).

The sessile MICs (SMIC50 and SMIC90) were defined, respectively, as a 50% and 80% reduction in the metabolic activity of the biofilm treated with the antifungal compared with the control well.

Scanning electron microscopy (SEM)
Four isolates (C. albicans, n = 1; C. parapsilosis, n = 1; C. glabrata, n = 1; C. tropicalis, n = 1) were randomly selected for SEM analysis to study the impact of micafungin and SCY-078 on the biofilm structure (JEOL-JSM 6400, JEOL, Tokyo, Japan). Briefly, preformed biofilms of each isolate were incubated for 24 h at 37 °C with 100 µL RPMI solution containing a drug concentration equal to the SMIC50 or antifungal-free RPMI solution as a control. Both exposed and control samples were prepared for SEM according to our previously reported protocol.

Data analysis
The activity of micafungin, micafungin and SCY-078 overall and by species was shown as geometric mean, MIC50, MIC90, and ranges of MICs for both planktonic and sessile forms. Comparisons between micafungin and SCY-078 (50% inhibition endpoint) against planktonic and sessile forms were performed using the Wilcoxon matched-pairs test.

For calculation of agreement between MICs of SCY-078 based on EUCAST and CLSI (50% inhibition endpoint), off-scale MICs obtained using the CLSI procedure (0.007 mg/L) were transformed to the next 2-fold dilution according to the scale used for EUCAST (0.015 mg/L). MIC discrepancies of no more than ± 2-fold dilutions were used to calculate the essential agreement between both methods, as previously reported.

Ethics
This study was approved by the local ethics committee (Comité Ético de Investigación Clínica del Hospital Gregorio Marañón (CEIC-A1), study number 98/16).

Results
In vitro activity of SCY-078 against clinical isolates
Table S1 (available as Supplementary data at JAC Online) shows the frequencies of MIC distributions of SYC-078 against the species studied using the CLSI M27-A3 and EUCAST EDef 7.3 procedures at the two endpoints (50% and 100% growth inhibition). The in vitro activity of SCY-078, micafungin and fluconazole is shown in Table 1. SCY-078 and micafungin showed potent in vitro activity against Candida and non-Candida isolates; since SCY-078 and micafungin showed systematically lower MICs than fluconazole, only SCY-078 and micafungin were compared.

SCY-078 demonstrated significantly lower geometric mean MIC values than micafungin against C. parapsilosis (0.206 versus 0.458 mg/L, respectively) and non-Candida isolates (4.66 versus 9.33 mg/L, respectively) by EUCAST. This phenomenon was also observed with the CLSI procedure. By contrast, micafungin demonstrated significantly lower MIC values than SCY-078 for the remaining species (MIC range 0.008–0.053 versus 0.29–0.556 mg/L, respectively), regardless of the microdilution procedure used (Table 1). C. albicans and non-Candida isolates showed the highest and lowest susceptibility, respectively, to both SCY-078 and micafungin.

SCY-078 and micafungin showed attenuated activity against the Candida isolates with mutations in the fks genes compared with the wild-type isolates. However, differences were observed...
between the drugs both in the overall susceptibility of the isolates and in the impact of fks mutations. The MIC50 of micafungin against echinocandin-resistant isolates increased by a mean of 15-fold (range 4–133) compared with the wild-type isolates. By contrast, the individual MICs of SCY-078 increased by only 2-fold (range 1–32). Individual mutations in fks genes had different effects on the activity of the two compounds. The F641S mutation in the one C. albicans isolate tested appeared to have a greater effect on the activity of SCY-078 than on that of micafungin; among the C. glabrata isolates, mutations in fks genes had a greater impact on the activity of micafungin than on that of SCY-078 (Table 2).

We did not find cross-resistance between SCY-078 and fluconazole in the panel of fluconazole-resistant isolates. The geometric mean MIC of SCY-078 against this set of isolates was higher than the overall MIC owing to the high proportion of C. krusei (Table 1).

Overall essential agreement between CLSI and EUCAST was 90.3%, but no differences were found between the species.
However, agreement was stronger for C. albicans, C. parapsilosis and non-Candida spp. than for C. tropicalis and other Candida spp. (Table 3).

### In vitro activity of SCY-078 against biofilms

The antibiofilm activity of the three drugs tested is shown in Table 4. SCY-078 showed significantly higher activity against the biofilms than fluconazole \((P<0.001)\). In contrast to the in vitro results described above, SMIC\(_{50}\) values for SCY-078 and micafungin were essentially the same against the biofilms generated by the different Candida spp. with the exception of C. glabrata, in which micafungin had significantly lower SMIC values \((P<0.001)\).

The impact of SCY-078 and micafungin exposure on the preformed biofilm structure was assessed by SEM (Figure 1). C. albicans biofilms had swollen blastospores and thin hyphae after exposure to micafungin (Figure 1b) and SCY-078 (Figure 1c).

### Discussion

Our study demonstrated that SCY-078 was highly active in vitro against invasive Candida and non-Candida yeast isolates in both sessile and planktonic forms and that its activity was comparable...
Table 4. Antifungal activity of fluconazole, micafungin and SCY-078 against the biofilms of the 178 isolates studied

<table>
<thead>
<tr>
<th>Species</th>
<th>Antifungal</th>
<th>SMIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>SMIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>range</th>
<th>GM percentile 50</th>
<th>percentile 90</th>
<th>range</th>
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</thead>
<tbody>
<tr>
<td>C. albicans (n = 55)</td>
<td>micafungin</td>
<td>0.028</td>
<td>&lt;0.015</td>
<td>1</td>
<td>(≤0.015–32)</td>
<td>0.75</td>
<td>&lt;0.015–32</td>
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<td></td>
<td>SCY-078</td>
<td>0.073</td>
<td>0.031</td>
<td>8</td>
<td>(≤0.015–32)</td>
<td>1.007</td>
<td>&lt;0.015–32</td>
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<td></td>
<td>fluconazole</td>
<td>158.58</td>
<td>≥256</td>
<td>≥256</td>
<td>(0.25–256)</td>
<td>≥256</td>
<td>≥256</td>
</tr>
<tr>
<td>C. parapsilosis (n = 33)</td>
<td>micafungin</td>
<td>1.13</td>
<td>2</td>
<td>8</td>
<td>(≤0.015–8)</td>
<td>8</td>
<td>16</td>
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<tr>
<td></td>
<td>SCY-078</td>
<td>0.738</td>
<td>0.25</td>
<td>≥32</td>
<td>(0.062–32)</td>
<td>11.81</td>
<td>≥32</td>
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<td></td>
<td>fluconazole</td>
<td>8.9</td>
<td>4</td>
<td>≥256</td>
<td>(0.5–256)</td>
<td>162.4</td>
<td>≥256</td>
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<tr>
<td>C. glabrata (n = 31)</td>
<td>micafungin</td>
<td>0.026</td>
<td>&lt;0.015</td>
<td>0.25</td>
<td>(≤0.015–1)</td>
<td>0.072</td>
<td>&lt;0.015–2</td>
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<td></td>
<td>SCY-078</td>
<td>0.229</td>
<td>0.25</td>
<td>0.25</td>
<td>(0.125–16)</td>
<td>0.431</td>
<td>0.25–16</td>
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<tr>
<td></td>
<td>fluconazole</td>
<td>61.4</td>
<td>≥256</td>
<td>≥256</td>
<td>(2–256)</td>
<td>245.5</td>
<td>≥256</td>
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<tr>
<td>C. tropicalis (n = 8)</td>
<td>micafungin</td>
<td>0.369</td>
<td>0.25</td>
<td>8</td>
<td>(≤0.015–8)</td>
<td>4.8</td>
<td>≥32</td>
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<td></td>
<td>SCY-078</td>
<td>0.497</td>
<td>0.125</td>
<td>≥32</td>
<td>(≤0.015–32)</td>
<td>2.3</td>
<td>≥32</td>
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<td></td>
<td>fluconazole</td>
<td>≥256</td>
<td>≥256</td>
<td>≥256</td>
<td>(≥256)</td>
<td>≥256</td>
<td>≥256</td>
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<tr>
<td>C. krusei (n = 12)</td>
<td>micafungin</td>
<td>0.138</td>
<td>0.125</td>
<td>0.5</td>
<td>(0.062–0.5)</td>
<td>0.187</td>
<td>0.125–0.5</td>
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<tr>
<td></td>
<td>SCY-078</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>(0.25)</td>
<td>0.567</td>
<td>0.5–16</td>
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<tr>
<td></td>
<td>fluconazole</td>
<td>191.8</td>
<td>≥256</td>
<td>≥256</td>
<td>(64–256)</td>
<td>241.6</td>
<td>≥256</td>
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<tr>
<td>Candida spp. (n = 26)</td>
<td>micafungin</td>
<td>0.314</td>
<td>0.125</td>
<td>≥32</td>
<td>(≤0.015–32)</td>
<td>1.7</td>
<td>2</td>
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<tr>
<td></td>
<td>SCY-078</td>
<td>1.2</td>
<td>1</td>
<td>(≥32)</td>
<td>(0.031–32)</td>
<td>4.9</td>
<td>8</td>
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<tr>
<td></td>
<td>fluconazole</td>
<td>135.1</td>
<td>≥256</td>
<td>≥256</td>
<td>(1–256)</td>
<td>249.2</td>
<td>≥256</td>
</tr>
<tr>
<td>Non-Candida (n = 13)</td>
<td>micafungin</td>
<td>15.2</td>
<td>≥32</td>
<td>≥32</td>
<td>(≥32)</td>
<td>≥32</td>
<td>(≥32)</td>
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<tr>
<td></td>
<td>SCY-078</td>
<td>9.8</td>
<td>16</td>
<td>(≥32)</td>
<td>(≤0.125–32)</td>
<td>27.3</td>
<td>(4–32)</td>
</tr>
<tr>
<td></td>
<td>fluconazole</td>
<td>103.4</td>
<td>≥256</td>
<td>≥256</td>
<td>(0.25–256)</td>
<td>≥256</td>
<td>≥256</td>
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<tr>
<td>Fluconazole-resistant Candida isolates (n = 24)</td>
<td>micafungin</td>
<td>0.146</td>
<td>0.125</td>
<td>≥32</td>
<td>(≤0.015–32)</td>
<td>0.33</td>
<td>0.125–32</td>
</tr>
<tr>
<td></td>
<td>SCY-078</td>
<td>0.272</td>
<td>0.25</td>
<td>1</td>
<td>(0.031–16)</td>
<td>1.33</td>
<td>0.5–32</td>
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<td></td>
<td>fluconazole</td>
<td>128</td>
<td>≥256</td>
<td>≥256</td>
<td>(8–256)</td>
<td>221.5</td>
<td>≥256</td>
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<tr>
<td>fks-mutant Candida isolates (n = 9)</td>
<td>micafungin</td>
<td>0.212</td>
<td>0.25</td>
<td>2</td>
<td>(≤0.015–2)</td>
<td>1.9</td>
<td>1</td>
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<tr>
<td></td>
<td>SCY-078</td>
<td>0.627</td>
<td>0.25</td>
<td>≥32</td>
<td>(≤0.015–32)</td>
<td>1.9</td>
<td>1</td>
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<tr>
<td></td>
<td>fluconazole</td>
<td>94.1</td>
<td>≥256</td>
<td>≥256</td>
<td>(4–256)</td>
<td>≥256</td>
<td>≥256</td>
</tr>
<tr>
<td>Overall (n = 178)</td>
<td>micafungin</td>
<td>0.147</td>
<td>0.062</td>
<td>≥32</td>
<td>(≤0.015–32)</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SCY-078</td>
<td>0.317</td>
<td>0.25</td>
<td>16</td>
<td>(≤0.015–32)</td>
<td>2.04</td>
<td>4</td>
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<td></td>
<td>fluconazole</td>
<td>76.2</td>
<td>≥256</td>
<td>≥256</td>
<td>(0.25–256)</td>
<td>229.5</td>
<td>≥256</td>
</tr>
</tbody>
</table>

A reduction of 50% and 80% in metabolic activity (SMIC<sub>50</sub> and SMIC<sub>90</sub>, respectively) is shown. Statistically significant values (P < 0.05) are underlined.

Antifungal activity of SCY-078 against Candida spp. biofilms

to that of micafungin. We showed that the antifungal activity of SCY-078 was high (comparable to micafungin) against the most common Candida species and even higher against C. parapsilosis and non-Candida isolates. SCY-078 was also highly active against fluconazole-resistant Candida isolates. Previous studies demonstrated that the activity of SCY-078 was comparable to that of caspofungin against C. albicans, C. glabrata and C. parapsilosis, findings which we confirmed in the present study.

Although the number of isolates that are resistant to echinocandins is low, recent reports have documented the emergence of resistance, which can complicate the management of patients, particularly in infections caused by species or isolates with attenuated in vitro activity against azoles. The presence of mutations in the fks genes may lead to various degrees of echinocandin resistance, which, while not a class effect, can involve specific echinocandins depending on the position of the mutation.

Considering the mechanism of action of SCY-078, the presence of fks mutations may have an impact on its activity against Candida, although data remain very limited. A previous report showed that SCY-078 was more active than caspofungin against isolates with mutations in the fks genes. We used micafungin instead of caspofungin owing to problems of inter-laboratory reproducibility of caspofungin when studied by CLSI or EUCAST methods. These problems have not been reported for micafungin. Moreover, most of our mutant isolates were C. glabrata, and micafungin has previously proven more active than caspofungin and anidulafungin against this species.

However, we did not find differences between the MICs of SCY-078 and micafungin, although the presence of fks mutations affected both drugs to differing extents. This observation was particularly notable for C. glabrata, where the MIC values for micafungin increased up to 71-fold as compared with a maximum 16-fold increase in the MIC values for SCY-078. We found that in a small number of strains with fks mutations, MIC values varied depending on the fks mutation, as previously reported for the three echinocandins. Future analysis of the potential impact of the specific mutation on the activity of SCY-078 based on a larger number of isolates should be done.

We performed antifungal susceptibility testing based on the two reference microdilution methods developed by CLSI and EUCAST. Both procedures are very similar and differ with respect to preparation of the inoculum and the concentration of glucose used. The EUCAST method tended to yield MICs than CLSI, regardless of the species studied; however, essential agreement between both methods (defined as a ± 2-fold dilutions) was high (90.3%), and both methods were suitable and comparable for antifungal susceptibility testing of SCY-078, as previously reported.

Many episodes of candidaemia are biofilm-related infections. In a recent population-based study on candidaemia conducted in...
Figure 1. SEM images of the activity of micafungin and SCY-078 against biofilms formed by different species of Candida. A concentration equal to SMIC₈₀ was tested. Original magnification ×2000. (a) C. albicans, untreated control. (b) C. albicans treated with micafungin (0.031 mg/L). (c) C. albicans treated with SCY-078 (0.062 mg/L). (d) C. parapsilosis, untreated control. (e) C. parapsilosis treated with micafungin (8 mg/L). (f) C. parapsilosis treated with SCY-078 (16 mg/L). (g) C. tropicalis, untreated control. (h) C. tropicalis treated with micafungin (16 mg/L). (i) C. tropicalis treated with SCY-078 (16 mg/L). (j) C. glabrata, untreated control. (k) C. glabrata treated with micafungin (0.015 mg/L). (l) C. glabrata treated with SCY-078 (0.25 mg/L).
Spain, almost one-third of the episodes of candidaemia were catheter-related. Current guidelines recommend catheter removal in patients with candidaemia; however, this approach is not always possible. The in vitro activity of the echinocandins against Candida biofilms is an outstanding characteristic of this group of antifungals and antifungal treatment with echinocandins may prevent the need for catheter removal. As SCY-078 and the echinocandins share the same target, activity against biofilms is expected. SCY-078 was active in vitro against preformed mature C. albicans, C. parapsilosis, C. tropicalis, and C. glabrata. In addition, SEM analysis showed that SCY-078 induced changes in the biofilm structure similar to that of micafungin, the echinocandin that was most active against the biofilm. The geometric mean MIC for an 80% reduction of the metabolic activity was 0.5 mg/L, a concentration that can easily be reached in serum. Moreover, the geometric mean of the SMIC90 for all the species tested showed that a concentration of 2.1 mg/L was sufficient to reduce the metabolic activity of the isolates tested by 80%, thus highlighting for the first time the considerable potential of SCY-078 as an antibiofilm drug. Future studies should be performed in different geographic areas to confirm the marked in vitro activity of SCY-078 we report here.

In a murine model of invasive candidiasis caused by C. albicans, C. parapsilosis, or C. glabrata, Lepak et al. demonstrated that the AUC/MIC was the best pharmacodynamic target predicting clinical response. Considering an AUC equal to 0.68 µg·h/mL obtained after administration of a dose of 3.125 mg/kg and the species-independent pharmacodynamic target of 0.7, an MIC ≤1 mg/L obtained by CLSI would predict a clinical response. In our collection, an MIC of ≥2 mg/L for SCY-078 was achieved in only one C. glabrata isolate with a delf658 substitution in HS1 of fks2 (Table 2), and the pharmacodynamic target would have been reached in the remaining mutants and wild-type isolates. The impact of this pharmacodynamic target for the remaining species should be studied in the future.

We conclude that SCY-078 is a promising drug with high antifungal activity against both the planktonic and biofilm forms of Candida that is similar to that of micafungin. Future clinical studies on the efficacy of SCY-078 in patients with invasive candidiasis are warranted.

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Supplementary data

Table S1 is available as Supplementary data at JAC Online.

References

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