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

Frédéric Lamoth,a,b,c,d Barbara D. Alexandera,b

Division of Infectious Diseases and International Health, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USAa; Clinical Microbiology Laboratory, Department of Pathology, Duke University Medical Center, Durham, North Carolina, USAb; Infectious Diseases Service, Department of Medicine, Lausanne University Hospital, Lausanne, Switzerlandc; Institute of Microbiology, Lausanne University Hospital, Lausanne, Switzerlandd

The limited armamentarium of active and oral antifungal drugs against emerging non-Aspergillus molds is of particular concern. Current antifungal agents and the now 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.

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

<table>
<thead>
<tr>
<th>Genus/species (no.)</th>
<th>MEC&lt;sub&gt;50&lt;/sub&gt;/MEC&lt;sub&gt;90&lt;/sub&gt; (µg/ml) (range) for&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml) (range) for&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genus/species (no.)</td>
<td>SCY-078</td>
<td>CSP</td>
</tr>
<tr>
<td><em>Mucoromycotina</em> (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhizopus spp. (16)</td>
<td>16/16 (16 to &gt;16)</td>
<td>16/16 (16 &gt;16)</td>
</tr>
<tr>
<td>Mucor spp. (7)</td>
<td>16/16 (8 to &gt;16)</td>
<td>&gt;16/16 (&gt;16)</td>
</tr>
<tr>
<td>Rhizomucor spp. (2)</td>
<td>16 to &gt;16</td>
<td>&gt;16 (&gt;16)</td>
</tr>
<tr>
<td>Lichtheimia spp. (4)</td>
<td>8/16 (8–16)</td>
<td>&gt;16/16 (16)</td>
</tr>
<tr>
<td>Cunninghamella spp. (4)</td>
<td>16/16 (16)</td>
<td>&gt;16/16 (16)</td>
</tr>
<tr>
<td><em>Fusarium</em> spp. (35)</td>
<td>8/16 (8–16)</td>
<td>&gt;16/16 (8 to &gt;16)</td>
</tr>
<tr>
<td><em>Purpureocillium lilacinum</em> (30)</td>
<td>&gt;16/16 (2 to &gt;16)</td>
<td>&gt;16/16 (0.25 to &gt;16)</td>
</tr>
<tr>
<td><em>Baeomyces variotii</em> (5)</td>
<td>&lt;0.02/0.02 (&lt;0.02)</td>
<td>0.06/2 (0.03–2)</td>
</tr>
<tr>
<td><em>Soopuropis</em> spp. (8)</td>
<td>4/8 (4–8)</td>
<td>0.5/8 (0.25–16)</td>
</tr>
<tr>
<td><em>Seadosporium apiospermi</em>/&lt;br&gt;Pseudallescheria boydii (19)</td>
<td>2/4 (1–8)</td>
<td>0.5/1 (0.06 to &gt;16)</td>
</tr>
<tr>
<td><em>Seadosporium prolificans</em> (5)</td>
<td>4/4 (4)</td>
<td>16/16 (16)</td>
</tr>
</tbody>
</table>

<sup>a</sup> All drugs were tested via Clinical and Laboratory Standards Institute broth microdilution method within concentrations ranging from 0.02 to 16 µg/ml (11).

<sup>b</sup> CSP, caspofungin; MCF, micafungin; AND, anidulafungin.

<sup>c</sup> 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)90 and MIC(MEC)50 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)90 and MIC(MEC)50 values of all fungal species are represented in Table 2. Predictably, amphotericin B was the only drug displaying good universal activity against the Mucormycotina. Notably, posaconazole, the other agent with known clinical activity against this group of organisms, displayed better activity against Cunninghamhamella 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 Mucormycotina 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 (MEC90, 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 exception. It was the only agent tested with activity against C. lilacinum and L. lichtheimii. SCY-078 was the only drug to achieve a modest effect against S. prolificans (MEC90, 4 μg/ml).

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 gluscan 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.

ACKNOWLEDGMENTS

SCY-078 was provided by the sponsor, Scynexis, Inc. (Durham, NC). F.L. is supported by the Swiss National Science Foundation and the Swiss Foundation for Medical-Biological Grants (grant P3SM3-151742).

REFERENCES


