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Evaluation of the antifungal activity of SCY-078 in combination with other antifungals against Aspergillus strains

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Background: High morbidity and mortality persist for invasive fungal infections due to *Aspergillus* species, and the Food and Drug Administration has approved several antifungal agents belonging to different chemical classes (polyenes, pyrimidines, azoles, and echinocandins) as therapeutic options for fungal infections. However, treatment is often complicated by high toxicity, low tolerability, narrow spectrum of activity, and drug resistance. Moreover, in spite of the recent antifungal armamentarium cure rates are unacceptably high. These difficulties have driven recent efforts to determine the efficacy of combination therapy in the treatment and management of invasive fungal infections. Most combination therapy studies are based on the rationale of combining agents that have complementary mechanisms of action. Potential benefits of using combination therapy include broad spectrum of efficacy, greater potency than either of the drugs used in monotherapy, improved safety and tolerability, and reduction in the number of resistant organisms. Further, *Aspergillus* infections require long treatment, and among approved therapies only the azoles are available orally. The objective of this study was to determine whether the combination of SCY-078, a novel glucan synthesis inhibitor that is available both orally and intravenously, with amphotericin B, isavuconazole, or voriconazole would increase their antifungal activity *in vitro*.

Material/methods: Test isolates included four wild-type *A. fumigatus* strains and 2 strains with elevated amphotericin B and azole MICs (one of which has a CYP51 mutation at F46Y). Combinations of SCY-078 plus amphotericin B, isavuconazole, or voriconazole were tested in a checkerboard assay to determine whether they have a synergistic, additive, or antagonistic effect on the respective MIC values. Combination testing was reported according to an FICI, or Fractional Inhibitory Concentration Index, which assigns a numerical value to the interaction of the two compounds. Interpretation of the FICI is as follows: Synergistic = < .5, Additive = .5 < FICI $\leq$ 4.0, Antagonistic = > 4.0.

Results: The combination of SCY-078 with all three antifungals demonstrated synergy in the majority of wild-type strains tested, and although SCY-078 retained activity against azole resistant isolates, it showed no synergistic effect against these strains. One exception was the combination of SCY-078 and amphotericin B, which was synergistic against the CYP51 mutant resistant strain.

Conclusions: The synergy of the combinations of SCY-078 and amphotericin B, isavuconazole, or voriconazole against wild-type *A. fumigatus* strains *in vitro* suggests a promising new therapeutic approach for the treatment of invasive aspergillosis.