Introduction

Invasive mold infections caused by Aspergillus spp., Fusarium spp., Scedosporium spp., and Mucorales spp. are important causes of morbidity and mortality in immunocompromised patients. Response of these infections to single agent therapy is often inadequate. Combination antifungal therapy provides a potential strategy by which to improve antifungal activity and improve clinical outcome.

The development and discovery of SCY-078 (SCY) (isavuconazole) as a new antifungal agent has the potential to enhance the activity of current antifungal therapy. SCY-078 acting through inhibition of lanosterol 14α-demethylase is a potent antifungal agent and has been found effective against Aspergillus spp., Fusarium spp., and Mucorales spp. In vitro combination studies conducted in our laboratory were analyzed by the Lowe additivity model. The combined effects of antifungal agents were quantified after 24 and 48 h.

Materials and Methods

Isolates of molds were obtained in lyophilized powder form and prepared according to the manufacturer’s instructions. The median inhibitory concentration (MIC) was claimed. The combination of antifungal triazoles and echinocandins provides the most rational mechanistic basis for this approach. Antifungal triazoles inhibit ergosterol biosynthesis through inhibition of lanosterol C14-demethylase, while echinocandins inhibit cell wall synthesis through inhibition of 1,3-β-D-glucan synthase has the potential to enhance antifungal activity and improve clinical outcome.

Table 1. Minimal inhibitory concentrations (MIC) of SCY-078 (SCY) and isavuconazole (ISA) against different mould isolates

Table 2. In vitro interactions between SCY-078 (SCY) and isavuconazole (ISA) on different mould isolates (after 24 h incubation)

Results

These results indicate that the combination of SCY plus ISA may be more effective than either agent alone against different molds. The combination of antifungal triazoles and echinocandins provides the most rational mechanistic basis for this approach. Antifungal triazoles inhibit ergosterol biosynthesis through inhibition of lanosterol C14-demethylase, while echinocandins inhibit cell wall synthesis through inhibition of 1,3-β-D-glucan synthase has the potential to enhance antifungal activity and improve clinical outcome.

Table 3A. Comparison of standard combination studies and our study for the combinations of SCY-078 (SCY), isavuconazole (ISA), and amphotericin B (AMB) against medically important filamentous fungi.

Table 3B. Comparison of standard combination studies and our study for the combinations of SCY-078 (SCY) and isavuconazole (ISA) against different mould isolates.

Table 3C. In vitro interactions between SCY-078 (SCY) and isavuconazole (ISA) on different mould isolates (after 48 h incubation).

Conclusions/Summary

In vitro SCY-078 and isavuconazole are synergistically active against A. fumigatus, A. flavus, A. terreus, M. circinelloides, S. apiospermum, and F. solani hyphae.

These results indicate that the combination of SCY-078 plus isavuconazole may be more effective than either agent alone in treatment of invasive aspergillosis, as well as other invasive mold infections, and warrant further investigation.