Introduction/Aim

PC945 is a novel antifungal agent\textsuperscript{1,2} being developed as an inhalation therapy for the treatment of aspergillosis (Phase 2). We previously reported that topical PC945 and systemic azoles showed synergic antifungal effects in vitro and in vivo\textsuperscript{3}. This study examined the anti-fungal activity of PC945 on growth of Aspergillus fumigatus (A. fumigatus) as a combination therapy with echinocandins in vitro using a model of human alveoli.

Methods

A model of human alveoli was constructed in transwells consisting of a bilayer of human alveolar epithelial and endothelial cells. PC945 (0.1 μg/mL) was either added as monotherapy once daily on days 0, 1 and 2 to the epithelial compartment (upper chamber) mimicking inhalation treatment or was combined with caspofungin or micafungin (1 μg/mL) added to the endothelial compartment (lower chamber) mimicking oral treatment. Transwells were infected with azole sensitive (NCPF2010) A. fumigatus at a concentration of 1 x 10\textsuperscript{6} spores/mL, one hour after treatment on day 0 (Fig.1). Subsequently, levels of galactomannan in the bottom chamber, which was collected Day 1 to Day 5 post inoculation, were quantified by Platelia\textsuperscript{TM} (Biorad). Azole-resistant A. fumigatus harbouring TR34/L98H mutation was also infected in the presence of PC945 (1 μg/mL, upper) with/without caspofungin (0.1 μg/mL, lower). Figure 2 shows histology of non-infected and A. fumigatus infected controls (Day 3).

Results

Exp 1: Azole susceptible strain (NCPF2010) infection

In the in vitro model of human alveoli, caspofungin or micafungin (1 μg/mL; lower chamber) or PC945 (0.1 μg/mL; upper chamber) as monotherapy had only mild inhibitory effects on azole susceptible A. fumigatus invasion Day 1 post infection, whereas combined treatment with PC945 and caspofungin/micafungin achieved marked inhibition of fungal invasion up to Day 5 post infection (Fig.3).

Exp 2: Azole resistant strain (TR34 L98H) infection

A similar pattern was observed for the azole resistant strain TR34-L98H, with monotherapy (caspofungin,1 μg/mL, lower; PC945, 1 μg/mL, lower) monotherapy weakly inhibiting fungus invasion. In contrast, combined treatment with PC945 and caspofungin provided much greater protection than monotherapy (Fig. 4).

Conclusion

In this study, combined treatment with PC945 and echinocandins was shown to inhibit azole-susceptible and azole-resistant A. fumigatus growth to a greater extent than monotherapy using either compound. PC945 therefore has the potential to be used in combination with established antifungal drugs for the treatment of azole sensitive and resistant A. fumigatus infection in humans.

References