Antifungal susceptibility profiles of Olorofim (formerly F901318), and currently available systemic antifungals against mold and yeast phases of Talaromyces marneffei

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Introduction

Talaromyces marneffei is a thermal dimorphic fungus and is the etiologic agent of talaromycosis, a life-threatening disease which affects immunocompromised host especially those with HIV infection. The fungus is endemic in Southeast Asia and is known to be associated with bamboo rats. Talaromycosis is initially treated with amphotericin B but its use is limited due to toxic side effects. Therefore, the need for new antifungals to treat talaromycosis is urgent. Olorofim is a novel fungicidal drug which targets dihydroorotate dehydrogenase in the de novo pyrimidine biosynthesis pathway. It is highly active against Aspergillus and other filamentous Ascomycetes. However, the in vitro efficacy of olorofim against T. marneffei has yet to be reported. We therefore aimed to evaluate the susceptibility of T. marneffei to olorofim and other currently available systemic antifungals in its yeast as well as in mold phases.

Methods

We tested 32 clinical and environmental T. marneffei strains recovered from southern China against 8 different antifungals according to the Clinical and Laboratory Standards Institute M38-A2 and M27-A3 guidelines. The final concentration ranges of antifungal agents were 0.0313-16 μg/mL for amphotericin B, itraconazole, voriconazole, posaconazole, and terbinafine; 0.031-32 μg/mL for 5-flucytosine and caspofungin; and 0.00025-0.25 μg/mL for olorofim. The mold conidial suspensions were obtained from T. marneffei strains which have been cultured on malt extract agar for 7-14 days at 25°C. The yeast suspensions were obtained from T. marneffei strains which have been cultured on brain heart infusion agar for 4-5 days at 37°C.

Results

The geometric means of the minimum inhibitory concentrations/minimum effective concentrations (MICs/MECs) of the antifungals against mold phase of all T. marneffei strains were (in increasing order): olorofim (0.0005 μg/mL), itraconazole and posaconazole (0.016 μg/mL), voriconazole (0.05 μg/mL), 5-flucytosine (0.08 μg/mL), terbinafine (0.14 μg/mL), caspofungin (1.35 μg/mL) and amphotericin B (1.92 μg/mL).

The geometric means MICs/MECs against the yeast phase were, as follows: olorofim (0.0007 μg/mL), posaconazole and itraconazole (0.016 μg/mL), voriconazole (0.017 μg/mL), 5-flucytosine (0.12 μg/mL), amphotericin B (0.13 μg/mL), and caspofungin (4.5 μg/mL).

Olorofim was the most active antifungal agent against both mold and yeast phases of all tested Talaromyces marneffei isolates, exhibiting an MIC range, MIC50 and MIC90 of 0.00025-0.002 μg/mL, 0.0005 μg/mL, and 0.0005 μg/mL, respectively.

Conclusion

- Overall, olorofim demonstrated potent and consistent activity against all T. marneffei strains in vitro, and its activity was maintained in two different growth phases.
- Further studies are warranted to evaluate the in vivo efficacy of olorofim against this fungus.