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

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Background: *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.

Materials/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.

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 mg/mL), itraconazole and posaconazole (0.016 ug/mL), voriconazole (0.05 ug/mL), 5-flucytosine (0.08 ug/mL), terbinafine (0.1 ug/mL), caspofungin (0.4 ug/mL) and amphotericin B (2 ug/mL). The geometric means MICs/MECs against the yeast phase were, as follows: olorofim (0.0007 ug/mL), posaconazole (0.016 ug/mL), Itraconazole (0.016 ug/mL), voriconazole (0.017 ug/mL), terbinafine (0.12 ug/mL), amphotericin B (0.13 ug/mL), 5-flucytosine (0.25 ug/mL), and caspofungin (4.5 ug/mL). Olorofim was the most active antifungal agent against both mold and yeast phases of all tested *Talaromyces marneffei* isolates, exhibiting an MIC range, MIC_{50}, and MIC_{90} of 0.0005-0.002 ug/mL, 0.0005 ug/mL, and 0.0005 ug/mL, respectively.

Conclusions: In summary, 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.

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