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Molecular characterisation of Fusarium oxysporum species complex isolates from the United States and susceptibility profile of the investigational antifungal olorofim

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Background: Fusariosis is one of the most serious non-*Aspergillus* mold infections among immunocompromised patients, and members of the *Fusarium oxysporum* species complex (FOSC) are major etiologic agents of this opportunistic infection. Recently, members of the FOSC have been distinguished into more than 20 phylogenetic species. Our objective was to evaluate the species distribution and antifungal susceptibility profiles of FOSC isolates in the U.S, including the investigational agent olorofim.

Materials/methods: 49 clinical FOSC isolates received by the Fungus Testing Laboratory at the UT Health Science Center San Antonio for identification and antifungal susceptibility testing were included. Identification was performed by DNA sequencing and phylogenetic analysis of translation elongation factor 1-alpha (*TEF1α*) and RNA polymerase II second largest subunit (*RPB2*). Antifungal susceptibility testing was performed by CLSI M38 broth microdilution. MICs for olorofim were determined after 48 hours of incubation at the 50% and 100% inhibition endpoints, while those of amphotericin B, posaconazole, voriconazole, itraconazole, and isavuconazole were determined at 100% inhibition

Results: Of the 49 isolates, 40 were identified to the species level, including 20 *F. veterinarium*, 12 *F. nirenbergiae*, 5 *F. fabacearum*, 2 *F. triseptatum*, and 1 *F. cugenangense*. Nine isolates were unnamed species. Olorofim demonstrated good *in vitro* activity against FOSC isolates (MIC range 0.03 - 0.5 and 0.06 - >4 mg/L at 50% and 100% inhibition, respectively). Of the antifungals, olorofim also had the lowest GM MIC values (0.107 and 0.559 mg/L at 50% and 100% inhibition) followed by amphotericin B (1.59 mg/L), posaconazole (6.11 mg/L), voriconazole (6.94 mg/L), and itraconazole and isavuconazole (>16 mg/L for each). Interestingly, olorofim GM MICs were higher against *F. nirenbergiae* (0.177 and 1.19 mg/L at 50% and 100% inhibition) compared to *F. veterinarium* (0.081 and 0.391 mg/L; $p < 0.01$).

Conclusions: Olorofim demonstrated potent *in vitro* activity against FOSC isolates, and this activity was maintained regardless of the specific species. Interestingly, differences in olorofim activity was observed between the two most prevalent species, *F. veterinarium* and *F. nirenbergiae*. Further studies are needed to determine how these findings may translate into *in vivo* efficacy.

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