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Antifungal drug treatment

The novel orotomide F901318 demonstrates potent in vitro antifungal activity against Lomentospora and Scedosporium species

Annette Fothergill[1], Michael Birch[2], Derek Law[2], Nathan Wiederhold*[1]

[1]*Ut Health Science Center San Antonio, San Antonio, United States*

[2]*F2g Ltd, Manchester, United Kingdom*

Background: *Scedosporium* species and *Lomentospora* (formerly *Scedosporium*) *prolificans* are increasing causes of invasive fungal infections in immunocompromised hosts. Many isolates of these species are resistant to available antifungals, and treatment options are limited. F901318 is the most advanced analog of the orotomide class of antifungal agents with a novel mechanism of action and is currently under clinical development. The objective of this study was to assess the *in vitro* potency of F901318 against *Scedosporium* species and *L. prolificans*.

Material/methods: Sixty-six *Scedosporium* isolates and 7 *Lomentospora prolificans* clinical isolates were used in this study. This included 43 *S. apiospermum,* 15 *S. boydii*, 6 *S. aurantiacum*, 2 *S. dehoogii*, and 7 *L. prolificans* isolates. The species identification of each isolate was confirmed by morphologic assessment and DNA sequence analysis of the ITS region and calmodulin gene. *In vitro* susceptibility testing was performed according to the methods in the CLSI M38-A2 reference standards. For F901318, amphotericin B, posaconazole, and voriconazole MICs were read after 72 hours of incubation as the lowest concentration that resulted in 100% inhibition of growth. For caspofungin the MEC was read as the lowest concentration that resulted in morphologic changes (i.e., short, stubby hyphae with abnormal branching). The MIC50, MIC90, and geometric mean (GM) MIC/MEC were determined, and differences in GM MIC values were assessed for significance by ANOVA.

Results: F901318 demonstrated the most potent *in vitro* activity of all the agents included in this study. Against *S. apiospermum* and *boydii* the F901318 GM MICs (0.079 and 0.046 mg/L, repectively) were significantly lower than those observed with amphotericin (3.404 and 5.595 mg/L), posaconazole (1.937 and 1.823 mg/L), voriconazole (0.784 and 0.630 mg/L), and caspofungin (5.703 and 7.639 mg/L) ($p < 0.001$ for all comparisons). MIC50 and MIC90 values for F901318 were also lower for *S. apiospermum* and *S. boydii* than those of the comparator agents. Against *S. aurantiacum* and *S. dehoogii* isolates the F901318 MIC range (0.12 – 0.5 mg/L) was also lower than the MIC/MEC ranges for the other antifungals (0.5 - >8 mg/L). The activity of F901318 also maintained against *L. proflicans* isolates (range 0.12 – 0.25 mg/L) in contrast to that observed with the other antifungals, none of which demonstrated *in vitro* activity against this multidrug resistant species.

Conclusions: F901318, a novel member of the orotomide class of antifungals, demonstrated potent *in vitro* activity against *Scedosporium* species and *L. prolificans*. This activity was maintained against isolates that had significantly reduced susceptibility to the other antifungals included in this study, including *L. prolificans,* for which treatment options are limited. Further studies are warranted to evaluate the in vivo efficacy of F901318 against *Scedosporium* species and *L. prolificans*.