Evaluation of the *In vitro* Activity of Olorofim Against *Fusarium* Species

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BACKGROUND & OBJECTIVE

- Invasive infections caused by *Fusarium* species are often associated with significant morbidity and mortality in highly immunocompromised patients, and treatment options are limited.
- Several species are often resistant to treatment with clinically available antifungals.
- Olorofim (formerly F901318; F2G Ltd.) is a member of the orotomide class of antifungal agents that inhibits fungal pyrimidine biosynthesis and has potent activity against a variety of filamentous fungi.
- We evaluated the *in vitro* activity of olorofim against a selection of various *Fusarium* isolates.
- The *in vitro* activity was also measured for the clinically available antifungals amphotericin B, posaconazole, and voriconazole.

MATERIALS & METHODS

- Clinical isolates (n = 111) of *Fusarium* species in the collection of the University of Texas Health Science Center Fungus Testing Laboratory were used.
- Susceptibility testing was performed by broth microdilution according the CLSI M38 reference standard.
- MICs for olorofim were determined after 48 hours of incubation using the 50% and 100% inhibition endpoint, while those of the control agents (amphotericin B, posaconazole, and voriconazole) were determined using the 100% inhibition endpoint.

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RESULTS

- Olorofim demonstrated *in vitro* activity against *F. oxysporum* species complex (FOSC, MIC range 0.125-0.25 mg/L and 0.5 – 1 mg/L at the 50% and 100% endpoints, respectively), *F. fujikuroi* (≤0.015 mg/L and ≤0.015-0.125 mg/L), *F. verticillioides* (0.06-0.125 mg/L and 0.06-0.25 mg/L), and *F. proliferatum* (≤0.015->8 mg/L and 0.06->8 mg/L) (Table).
- At the 50% inhibition endpoint, olorofim demonstrated *in vitro* activity against some isolates of the *F. solani* species complex (FSSC, now members of the genus *Neocosmospora* 0.5->8 mg/L) and the *F. incarnatum-equiseti* species complex (FIESC, 0.25->8mg/L).
- In contrast, when the 100% inhibition endpoint was used, limited to no *in vitro* activity was observed against these species complexes (4->8 mg/L), nor was activity observed against *F. dimerum* using either endpoint (>8 mg/L).
- Olorofim activity against some of the rarer species of *Fusarium* was mixed, with the growth of some species being inhibited at low MICs (i.e., *F. brachygibbosum, F. decemcellulare, F. redolens,* and *F. thapsinum*; 0.06-0.25 mg/L at 50% inhibition and 0.25-0.5 mg/L at 100% inhibition).
- In contrast, limited to no activity was also observed against other rarer species (i.e., *F. delphinoides, F. nygamai, F. pallidoroseum, F. petroliphilum,* and *P. pseudensiforme*; 0.25-8 mg/L at 50% inhibition and ≥8 mg/L at 100% inhibition).
- The MIC ranges for the control agents were also wide and differed across *Fusarium* species. The most consistent activity was observed with amphotericin B.

Table. MIC values (mg/L) and geometric mean (GM) MICs for olorofim, amphotericin B, posaconazole, and voriconazole against *Fusarium* species with at least 6 isolates included.

Antifungal	Olorofim 50%		Olorofim 100%		Amphotericin B		Posaconazole		Voriconazole	
Species/Spp. Complex	Range	GM MIC	Range	GM MIC	Range	GM MIC	Range	GM MIC	Range	GM MIC
FSSC (n = 29)	0.5 - >8	1.07	4 - >8	>8	1 - 4	1.86	>16	>16	4 - >16	>16
FOSC (n = 14)	0.12 - 0.25	0.24	0.5 - 1	0.53	2 - 4	2.69	2 - >16	4.64	2 - 16	4.88
FIESC (n = 16)	0.25 - >8	5.19	>8	>8	1 - 4	2.00	1 - >16	2.48	1 - 8	4.56
F. fujikuroi (n = 6)	≤0.015	≤0.015	≤0.015 - 0.125	0.043	2 - 4	2.52	0.5 - 2	1.26	0.25 - 4	2.52
F. proliferatum (n = 21)	≤0.015 - >8	0.028	0.03 - >8	0.113	2 - 8	3.87	1 - >16	>16	2 - 16	9.44
F. verticillioides (n = 6)	0.03 - 0.125	0.077	0.06 - 0.5	0.221	2 - 16	3.56	0.5 - 1	0.707	1 - 2	1.78

CONCLUSIONS

- Olorofim demonstrated *in vitro* activity against some clinical isolates of *Fusarium* species.
- This activity appeared to be species-dependent, and was also dependent on the endpoint used (50% vs. 100% inhibition of growth).
- Further worked is needed to determine how the *in vitro* activity observed against *Fusarium* species in this study may translate into *in vivo* efficacy, especially for more common species for which there were differences between the activity of olorofim at the different of growth inhibition endpoints.

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