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The activity of novel orotomide antifungal F901318 against Australian isolates of Scedosporium spp. and Lomentospora prolificans

Chayanika Biswas[1], Sharon Chen[2], Catriona Halliday[1], Monica Slavin[3], Michael Birch[4], Derek Law*[4]

[1]*Westmead Hospital*

[2]*Westmead Hospital; Centre for Infectious Diseases and Microbiology - Public Health and Marie Bashir Institute for Infectious Diseases and Biosecurity*

[3]*Peter Maccallum Cancer Centre; Infectious Diseases*

[4]*F2g Ltd*

Background: Infections caused by *Scedosporium* spp. and *Lomentospora* (formerly *Scedosporium*) *prolificans* are the second commonest non-*Aspergillus* mould infections in Australia. Treatment is problematic because these fungi, in particular *L. prolificans,* are intrinsically resistant to currently available antifungals. New antifungal agents are urgently required . F901318 is an antifungal agent with a novel mechanism of action currently entering Phase 2 clinical development. The objective of this study was to compare the *in vitro* potency of F901318 against Australian clinical isolates of *Scedosporium* and *L. prolificans* in comparison with standard antifungals.

Material/methods: Twenty clinical *Scedosporium* isolates (10 *S. apiospermum,* 7 *S. aurantiacum,* 3 *S. boydii*) and 30 *L. prolificans* were studied. Each isolate was identified by morphologic assessment and sequencing of the ITS gene region. Susceptibility testing of F901318 and isavuconazole was performed according to the CLSI M38-A2 reference standard. For testing of other agents (amphotericin B, posaconazole, voriconazole, itraconazole, fluconazole, micafungin, caspofungin and anidulafungin) Sensititre plates were used. Four *Aspergillus fumigatus* isolates were included as controls.

Results: table shows MIC data for some of the drugs tested in this study. F901318 demonstrated the most potent *in vitro* activity of the agents tested. F901318 was active against all isolates of *L.*

prolificans strains with MICs falling into a very narrow range (0.125-0.5mg/L). In contrast, the *L. prolificans* isolates showed a high level of resistance to the other agents tested. F901318 MICs against the three species of *Scedosporium* also fell into a narrow range (0.125-0.5mg/L). The activity of standard antifungals was variable with only voriconazole and itraconazole generally active against *Scedosporium* spp. but not against *L. prolificans*.

	n		**F901318**	**AMB**	**CASP**	**POSA**	**VORI**	**ITRA**	**ISAV**
Scedosporium apiospermum	*10*	GMean	0.15	3.06	1.44	0.55	0.12	0.34	5.28
		Range	0.125-0.5	2-16	0.12-16	0.25-128	0.06-0.5	0.25-0.5	2-8
Scedosporium aurantiacum	*7*	GMean	0.25	9.75	4.42	0.37	0.11	0.61	8
		Range	0.125-0.5	2-16	2-16	0.12-1	0.03-0.25	0.12-32	4-16
Scedosporium boydii	*3*	GMean	0.20	6.35	8	0.5	0.12	0.5	5.04
		Range	0.125-0.25	4-8	8	0.5	0.03-0.25	0.12-32	4-8
Lomentospora prolificans	*30*	GMean	0.26	11.31	7.64	16	5.66	32	16.76
		Range	0.125-0.5	4-16	4-16	16	0.5-16	32	8-32

Conclusions: In this study, F901318 demonstrated potent *in vitro* activity against all 20 strains representing three species of *Scedosporium* and 30 strains of *L. prolificans*, and was the only agent to show consistently low MICs against the latter. F901318 MICs for *Scedosporium* and *Lomentospora* spp. were very similar to those obtained for 4 *A. fumigatus* isolates, where animal models show potent F901318 *in-vivo* activity. The results in a large panel of Australian *L. prolificans* clinical isolates corroborate preliminary findings from Europe and US, highlighting the poor activity of approved antifungals, and underscore the urgent need for new and effective treatment options.