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Abstract (poster session)

Inter-laboratory comparison of treatment response in a murine model of invasive candidiasis using two Candida albicans isolates

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Objective: Murine models of invasive candidiasis are frequently used in the preclinical evaluation of investigational antifungals as these models are typically robust and inexpensive. However, there have been few inter-laboratory studies of outcome variability with the same model. Our objective was to conduct an inter-laboratory comparison of treatment response between two laboratories (UTHSCSA and University of Manchester) using a murine model of invasive candidiasis with two different C. albicans clinical isolates. Methods: Immunocompetent 30 gram outbred ICR or CD1 mice were inoculated intravenously with C. albicans SC5314 or ATCC 90028 (target starting inocula 1.5 x 105 and 1.5 x 106 cells/mouse, respectively). Antifungal therapy began 1 day later and continued for 5 days. Treatment groups consisted of control, fluconazole (FLC) 10 mg/kg PO QD, and caspofungin (CFG) 1 mg/kg IP QD. Treatment continued until day 5 and mice were followed off therapy until day 21 to assess survival. Kidneys and brains were collected on day 8 in the fungal burden arm. Fungal burden was assessed by colony-forming units (CFU), and survival was assessed by Kaplan-Meier analysis. Each laboratory evaluated both isolates and conducted the experiments independently. Results: Antifungal response, as measured by reductions in kidney fungal burden and improvements in survival, was very similar between the two laboratories (Table). CFG significantly improved survival and reduced fungal burden in mice infected with SC5314, while modest reductions in fungal burden and survival improvements were observed with FLC. Similarly, both laboratories also reported significant improvements in survival and reductions in fungal burden for each antifungal in mice challenged with ATCC 90028. Interestingly, there were significant differences in median survival and fungal burden in the brains of untreated mice infected with ATCC 90028. These may have been due to differences between laboratories in the number of viable C. albicans cells used to challenge the mice or the subjective criteria used to judge moribund animals. Conclusions: Antifungal treatment response was highly reproducible between these two laboratories. Both CFG and FLC were effective at improving survival and reducing fungal burden against two C. albicans clinical isolates. These results demonstrate that our murine model of invasive candidiasis provides a useful and reproducible tool for evaluating therapeutic agents.

Isolate	**SC5314 (target starting inoculum 1.5 x 10^5 cells/mouse)**							
Outcome	Kidney Tissue Log_{10} CFU/g (mean SD)		Brain Tissue Log_{10} CFU/g (mean SD)		Median Survival		Percent Survival	
Institution	Manchester	UTHSCSA	Manchester	UTHSCSA	Manchester	UTHSCSA	Manchester	UTHSCSA
Control	4.71 (0.59)	5.46 (0.62)	1.52 (0.10)	1.50 (0.14)	9.5 days	7.5 days ($p = 0.033$)	20%	0%
FLC	2.13 (0.60)	2.73 (0.65)	1.48 (0.04)	1.48 (0.13)	>21 days	20 days	65%	30%
CFG	2.13 (0.60)	2.01 (1.21)	1.52 (0.08)	1.42 (0.04)	>21 days	>21 days	95%	100%
Isolate	**ATCC 90028 (target starting inoculum 1.5 x 10^6 cells/mouse)**							
Outcome	Kidney Tissue Log_{10} CFU/g (mean SD)		Brain Tissue Log_{10} CFU/g (mean SD)		Median Survival		Percent Survival	
Institution	Manchester	UTHSCSA	Manchester	UTHSCSA	Manchester	UTHSCSA	Manchester	UTHSCSA
Control	5.01 (0.41)	5.85 (0.50)	2.00 (0.53)	3.66 (0.32) ($p < 0.05$)	4 days	10 days ($p < 0.001$)	5%	20%
FLC	3.28 (0.85)	3.59 (0.57)	1.97 (0.79)	2.95 (0.62) ($p < 0.05$)	14 days	16 days	10%	30%
CFG	1.58 (0.47)	2.69 (0.64)	1.69 (0.31)	2.71 (0.67) ($p < 0.05$)	15 days	>21 days	30%	60%

p-value UTHSCSA vs. Manchester data