Abstract #66614
Poster 1510

Evaluation of the In Vitro and In Vivo Antifungal Activity of APX001A/APX001 Against *Candida auris*

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Abstract

Background: *Candida auris*, an emerging multidrug-resistant yeast, causes deadly invasive infections with high mortality. *C. auris* strains often show high MICs to fluconazole and amphotericin B, and some are resistant to all 3 major antifungal classes, limiting treatment options. We tested 16 *C. auris* strains from a wide geographical area (Germany, Japan, S. Korea, and India) against 10 antifungals including APX001A, an antifungal with a novel mechanism of action (inhibition of the Gwt1 fungal enzyme). The prodrug APX001 is in clinical development and its efficacy was evaluated in an immunocompromised murine model of disseminated *C. auris*.

Methods: MICs were determined by CLSI M27-A3 method. Mice were immunocompromised for the study. Treatment was initiated 2h post challenge. IP treatment groups included a vehicle control, APX001 78mg/kg BID, 78mg/kg TID, and 104mg/kg BID, and anidulafungin 10mg/kg BID. Survival was monitored for 16d post inoculation.

Results:
Susceptibility: APX001A had significantly lower MIC_{50} and MIC_{90} values (concentration that inhibits 50 and 90% of the tested isolates, respectively) than the other tested antifungals with a MIC_{90} of 0.031µg/mL.
Efficacy: 100% mortality in the vehicle-treated control group occurred by 6d. Significant efficacy was observed in all APX001 treatment groups with 90, 100, & 80% survival observed respectively for APX001 78 mg/kg BID; 78 mg/kg TID and 104 mg/kg BID. Anidulafungin treatment resulted in 50% survival at 16d. Mice in all of the APX001 treated groups had a significantly higher % survival compared to the anidulafungin and vehicle groups.

Conclusions: APX001A was the most active antifungal agent *in vitro*. The prodrug APX001 resulted in significantly better survival than anidulafungin in a *C. auris* disseminated infection model. Thus APX001 may be a viable treatment for *C. auris* infections.

Background

- *C. auris* is an emerging multidrug-resistant yeast with high mortality
- It has been isolated in numerous countries around the globe—Japan, S. Korea, United Kingdom, India, the US, Columbia
- Entire hospital wards have been shut down by this organism due to high MICs and limited treatment options.
- It cannot be identified using traditional yeast typing techniques like Vitek or API-20C; it must be identified using DNA sequencing or MALDI-TOF.
- APX001A is a first-in-class broad spectrum antifungal with a novel mechanism of action (inhibition of the Gwt1 fungal enzyme)
- The prodrug APX001 has demonstrated broad spectrum *in vivo* activity against both yeast and moulds.
- APX001 is in clinical development for invasive fungal infections

Materials & Methods

- CLSI M27-A3 methodology was utilized to determine the minimum inhibitory concentration of 16 *C. auris* isolates (Germany, Japan, S. Korea, and India) to 10 different antifungals: flucytosine (5FC), amphotericin B (AMB), anidulafungin (AFG), caspofungin (CAS), fluconazole (FLC), itraconazole (ITC), micafungin (MFG), posaconazole (POS), voriconazole (VRC), and APX001A
- Mice were immunocompromised by intraperitoneal (IP) injection of cyclophosphamide three days before and one day after infection
- Mice were infected with 3 $\times 10^7$ of *C. auris* blastospores (via the tail vein) of a strain isolated in India, CBS # 12766. The MIC values for APX001A and anidulafungin were 0.016 µg/mL and 0.125 µg/mL, respectively vs the infecting strain
- Treatment was initiated 2h post challenge with vehicle control, APX001 78 mg/kg BID, 78 mg/kg TID, and 104 mg/kg BID, and anidulafungin 10 mg/kg BID
- Survival was monitored for 16d post inoculation
- In a second parallel experiment, mice were sacrificed 48 hr post-infection and CFU/g tissue (kidney, lung and brain) was assessed

Results

Susceptibility. APX001A had significantly lower MIC_{50} and MIC_{90} values (concentration that inhibits 50 and 90% of the tested isolates, respectively) than the other tested antifungals with a MIC_{50} of 0.004 and a MIC_{90} of 0.031µg/mL (Table 1). The drug with the next lowest MIC_{50} and MIC_{90} was anidulafungin with 0.125 µg/mL and 0.25 µg/mL, respectively.

Survival. Vehicle-treated group succumbed to the infection with 100% mortality occurring on day 5 (Fig 1). Percent survival for mice in the APX001 78mg/kg BID, APX001 78 mg/kg TID, APX001 104 mg/kg BID, and anidulafungin 10 mg/kg BID groups were 90%, 100%, 80%, and 50%, respectively. Mice in all of the APX001 treated groups had a significantly higher percent survival when compared to the anidulafungin and vehicle groups (Table 2). The anidulafungin treated mice also had a significantly higher percent survival when compared to the vehicle group.

CFU reduction. Both APX001 and AFG demonstrated a significant decrease in kidney and lung CFU at 48 hr. Only APX001 demonstrated a reduction in brain CFU, consistent with brain penetration observed in ^{14}C APX001 distribution studies (Poster 1513).

Table 1: Susceptibility of 16 *C. auris* isolates to 10 antifungal agents

	APX001A	5FC	AMB	AFG	CAS	FLC		ITC	MFG	POS	VRD
	24h	48h	48h	24h	24h	24h	48h	48h	24h	48h	48h
	50%	50%	100%	50%	50%	50%	50%	50%	50%	50%	50%
Range	0.002-0.063	0.5-1	2-4	0.125-0.25	0.25-1	1->64	2->64	<0.063-1	0.25-2	0.25-1	<0.063-2
MIC_{50}	0.004	0.5	4	0.125	0.5	16	>64	0.5	1	0.25	0.5
MIC_{90}	0.031	1	4	0.25	1	>64	>64	1	1	0.5	2

Figure 1. Percent survival for mice in all treatment groups

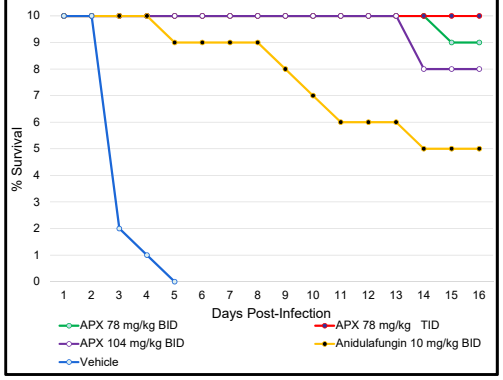

Figure 2. Kidney, Lung and Brain CFU 48 hrs Post-Infection

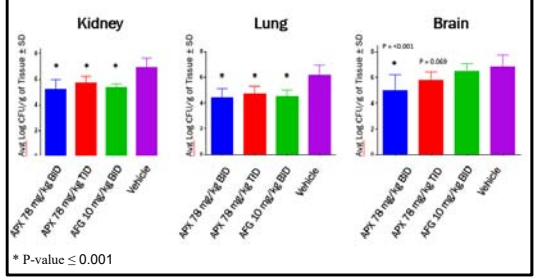

Table 2. Survival comparison for mice infected with *C. auris*. *P*-value of ≤ 0.05 was considered significant.

Group	Significant?	*P*-value
APX001 78 mg/kg BID vs. AFG 10mg/kg BID	Yes	0.011
APX001 78 mg/kg TID vs. AFG 10mg/kg BID	Yes	0.006
APX001 104 mg/kg BID vs. AFG 10mg/kg BID	Yes	0.034
APX001 78 mg/kg BID vs. Vehicle	Yes	<0.0001
APX001 78 mg/kg TID vs. Vehicle	Yes	<0.0001
APX001 104 mg/kg BID vs. Vehicle	Yes	<0.0001
AFG 10 mg/kg BID vs. Vehicle	Yes	<0.0001

Summary

- APX001A was the most active antifungal agent *in vitro* with an MIC_{50} that was 10 times lower than the next lowest drug, anidulafungin
- The prodrug APX001 resulted in significantly longer survival than anidulafungin in a *C. auris* disseminated infection model
- Both APX001 and AFG demonstrated a significant decrease in kidney and lung CFU at 48 hr. However, only APX001 demonstrated a reduction in brain CFU, consistent with brain penetration observed in ^{14}C APX001 distribution studies (Poster 1513).
- Brain penetration may have contributed to better overall survival in this model
- APX001 may be a viable treatment for *C. auris* infections

Acknowledgments

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