Poster 1275

Evaluation of *in vitro* activity of manogepix against multidrug-resistant and pan-resistant *Candida auris* from the New York Outbreak

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ABSTRACT

Background: An ongoing *Candida auris* outbreak in the New York metropolitan area is the largest recorded to date in North America. NY *C. auris* isolates demonstrate resistance to fluconazole and variable resistance to other antifungals. Thus, there is an urgent need for new drugs with a novel mechanism of action to combat the resistance challenge. Manogepix (MGX) is a first-in-class antifungal agent that targets the fungal Gwt1 enzyme. The prodrug, fosmanogepix, is in clinical development for the treatment of invasive fungal infections.

Methods: We evaluated the susceptibility of 200 NY *C. auris* isolates (2017-2020) to MGX and 10 comparators. Testing was performed using TREK frozen broth microdilution panels for FLC, VRC, ITC, ISA, POS, AFG, CAS, and MFG. MGX MICs were evaluated by standard CLSI microdilution (M27-A3 guidelines) using a 50% reduction in fungal growth endpoint at 24 h. MICs were determined by ETEST® at 24 h for AMB and FLC. We defined pan-resistant *C. auris* as isolates with *in vitro* resistance to two or more azoles, all echinocandins, and AMB. The upper limit of wild type (UL-WT) for MGX were estimated using the Microsoft Excel spreadsheet calculator ECOFFinder.

Results: MGX demonstrated lower MICs than comparators (MIC_{50} and MIC_{90} 0.03 mg/L; range 0.004-0.06 mg/L). MGX was 8-32-fold more active that the echinocandins, 16-64-fold more active than the azoles, and 64-fold more active than AMB. No differences were found in the MGX or comparators' MIC_{50}, $MIC_{90,}$ or GEOMEAN values when subsets of clinical, surveillance, and environmental isolates were evaluated. The range of MGX MIC values for six *C. auris* pan-resistant isolates was 0.008-0.015 mg/L, and the median and mode MIC values were 0.016 mg/L, demonstrating that MGX retains activity against these isolates. The MGX WT-UL was 0.06 mg/L.

Conclusions: MGX MICs were low against *C. auris* isolates including those with variable patterns of resistance to AMB, azoles, and echinocandins. In addition, MGX retained potent activity against six pan-resistant isolates. These data support the continued clinical evaluation of fosmanogepix for the treatment of *C. auris* infections, including highly resistant isolates.

METHODS

Fungal isolates. Two hundred *C. auris* isolates were selected at random and consisted of 85 clinical, 97 surveillance, and 18 environmental isolates. The numbers of isolates evaluated from each year are as follows: 2 (2017), 58 (2018), 130 (2019), and 10 (2020). The isolation of these strains is well described **(1,2).**

Antifungal susceptibility testing. Broth microdilution antifungal susceptibility testing was performed in accordance with Reference Method M27-A3 of the Clinical and Laboratory Standards Institute using TREK frozen broth microdilution panels for FLC, VRC, ITC, ISA, POS, AFG, CAS, and MFG. MGX susceptibility testing was performed by standard CLSI guidelines as previously described for echinocandins. The concentration of MGX that led to 50% reduction in fungal growth at 24 h compared with the control was determined as the MIC. MICs of AMB for all 200 isolates and 5FC for 54 isolates were determined by Etest at 24 h. *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019 were used as quality-control isolates. The tentative susceptibility breakpoints of the Centers for Disease Control and Prevention were used to assess antifungal resistance patterns in *C. auris* (FLC, 32; AMB, 2; AFG, 4; CAS, 2; and MFG,4 mg/liter), and the Etest AMB MIC value of 1.5 mg/L was rounded up to 2.0 mg/L. Susceptibility/ resistance to VRC and other triazoles (ITA, ISA, and POS) were assessed using published reports for other *Candida* species **(3-6).** We also considered a prior publication on the epidemiological cutoff values of antifungal compounds for 122 *C. auris* isolates from India **(7)**. As the term is not used conventionally with antifungal drugs, we defined pan-resistant *C. auris* as isolates with *in vitro* resistance to two or more azoles, all echinocandins, and AMB **(8)**.

QC testing. *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019 were used as quality-control (QC) isolates. MGX was tested seven times against two QC strains, and MIC values for *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019 were within recommended CLSI ranges The WT-UL for MGX was estimated using the Microsoft Excel spreadsheet calculator ECOFFinder **(9,10).**

RESULTS

Table 1. MGX is highly potent against 200 NY *C. auris* isolates[a]

Antifungal	GM	Mode	MIC_{50}	MIC_{90}	Range
MGX	0.02	0.03	0.03	0.03	0.004 to 0.06
AFG	0.33	0.50	0.25	1.0	0.03 to 8
CAS	0.14	0.25	0.12	0.25	0.016 to >16
MFG	0.16	0.12	0.12	0.25	0.06 to 4
FLC	246	256	256	256	32 to >256
ISA	0.71	1	1	1.0	0.03 to 2
ITC	0.58	1	0.5	1.0	0.125 to 1
POS	0.20	0.25	0.25	0.5	0.03 to 1
VRC	1.67	2	2	2	0.06 to 4
AMB	1.35	2	1	2	0.125 to 32
5FC	0.14	0.06	0.064	32	0.023 to 32

[a]All values are mg/liter.

Figure 1. WT-UL of MGX for NY isolates estimated using ECOFFinder

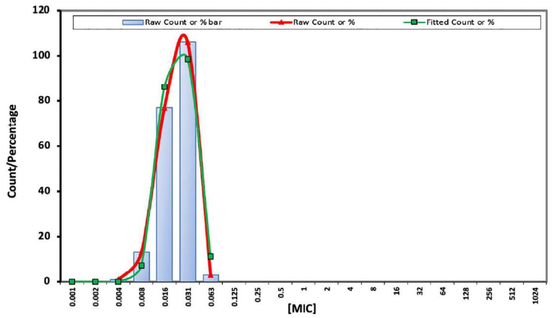

Table 2. *C. auris* MIC distributions for MGX and comparators

	No. of isolates by MIC (mg/liter)[a]																								
Antifungal	0.001	0.002	0.004	0.008	0.016	0.023	0.03	0.047	0.06	0.064	0.094	0.125	0.25	0.38	0.5	0.75	1	2	3	4	8	16	24	32	64	128	≥256
MGX	**0**	**0**	1	13	77		**106**		3			0	0		0												
AFG				0	0		1		9			35	63		**71**		6	4		10	1	0					
CAS				0	6		25		27			61	**64**		4		2	3		2	0	5		1[b]			
MFG				0	0		0		25			130	25		3		3	4		10	0						
FLC												0	0		0		0	0		0	0	0		2	1	3	194
ISA			0	0	0		2		1			3	5		69		**118**	2		0	0						
ITC				0	0		0		0			2	43		66		**88**	1		0	0	0					
POS				0	0		15		26			19	**80**		59		1	0		0	0	0					
VRC				0	0		0		1			1	1		3		44	**140**		10	0	0					
AMB												1	3	3	3	37	60	**79**	8			2	3	1			
5FC						1		7		**23**	12	5												6			

[a]Modal MIC values are indicated by underlining and bold font. Shaded values indicate non-wild-type MIC values.
[b]CAS value >16 mg/liter.

Table 3. MGX maintains potency against pan-resistant *C. auris* isolates

	MIC (mg/liter) by antifungal agent										
C. auris strain	FLC	VRC	ITC	ISA	POS	AFG	CAS	MFG	AMB	5FC	MGX
17-24	256	2	0.5	0.5	0.25	4	>16	4	2	0.064	0.016
18-2	256	2	1	1	0.25	8	2	4	2	0.064	0.016
19-42	256	2	1	1	0.25	4	16	4	2		0.016
19-43	256	2	1	1	0.25	4	16	4	2		0.016
19-4	256	2	0.5	0.5	0.25	4	2	4	2		0.016
20-1	256	2	0.5	1	0.25	4	4	4	2		0.008

CONCLUSIONS

- MGX demonstrated ≥ 8 fold lower MICs than all comparators
- The local epidemiological cutoff value (ECV) for MGX was 0.06 mg/L, which defines the UL-WT for this collection of strains
- All *C. auris* isolates were within the population of wild-type (WT) strains
- No differences in MIC_{50}, MIC_{90}, or geometric mean (GM) values for MGX or comparators were observed when subsets of clinical, surveillance, and environmental isolates were evaluated
- The range of MGX MIC values for six *C. auris* pan-resistant isolates was 0.008 to 0.015 mg/L demonstrating MGX retains activity against these isolates.
- These data support further clinical evaluation of fosmanogepix for the treatment of *C. auris* infections, including highly resistant isolates

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