Ibrexafungerp in combination with Azoles against Clinical Isolates of Aspergillus, including Those Resistant to Azoles

Vidya Jagadeesan, Eileen Driscoll, Binghua hao, M. Hong Nguyen

Department of Medicine, University of Pittsburgh, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA

Contact Information:
Vidya Jagadeesan, MD
Infectious Disease Fellow
3601 Fifth Avenue
Falk Medical Building, Suite 3A
Pittsburgh, PA 15213
E-mail: jagadeesanv@upmc.edu

INTRODUCTION

- Aspergillosis is the most common opportunistic mould infection. Over the past 2 decades, there has been a surge in non-*Aspergillus fumigatus* (non-Af) spp causing infections.
- This change in epidemiology might be partially attributable to increased use of broad-spectrum antifungal agents. Indeed, breakthrough infections while on azole prophylaxis or treatment have been attributed to azole-resistant non-Af species, and mortality associated with these infections is high.
- Ibrexafungerp (IBX) is a novel glucan synthase inhibitor. The purpose of our study was to evaluate the activity of IBX against clinical isolate of Aspergillus sp.

OBJECTIVE

- To evaluate the in vitro activity of IBX and anti-mould azoles against clinical isolates of Aspergillus recovered from lung transplant patients at University of Pittsburgh Medical Centre (UPMC)
- To evaluate the interaction between IBX and an anti-mould azole against clinical isolates of Aspergillus

HYPOTHESES

- Clinical Aspergillus isolates are susceptible to IBX
  - Including azole resistant *Aspergillus sp.*
- Combination of IBX and azole displays synergetic interaction in vitro
  - The combination will reduce azole MICs of resistant isolates to below the breakpoint.

METHODS

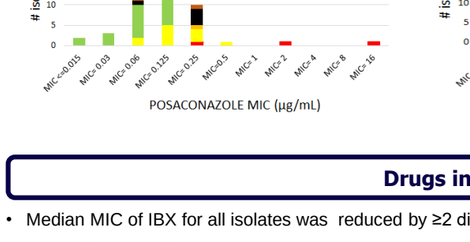
- MICs of antifungals were determined according to CLSI M38-A2 standards
- Drugs tested: IBX, CASPO, ISA, POSA, VORI. In concentrations from 0.015-16 µg/ml
- Inoculum size: 2-5 x 10^5 cfu/ml
- Testing was done in duplicates. 96 well microdilution plate was used for MIC testing
- Combination testing was done using checkerboard microdilution method
- Interaction between IBX and azole was determined using Fractional Inhibitory Concentration (FIC) index
  - FICi < 0.5 – Synergy (≥4-fold reduction in MIC for each drug when tested in combination)
  - FICi > 4 - Antagonism (≥4-fold increase in MIC for each drug when tested in combination)
  - FICi 0.5-4 – Indifference
- 50 clinical isolates were tested

Species	Number
Aspergillus calidoustus	4
Aspergillus flavus	11
Aspergillus fumigatus	2
Aspergillus glaucus	1
Aspergillus niger	7
Aspergillus terreus	7

RESULTS

MIC distribution of Ibrexafungerp and azoles

A. Ibrexafungerp (IBX) and Caspofungin (CAS) MIC



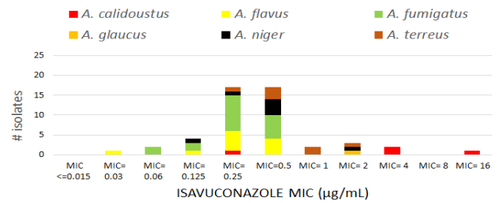
Drugs	MIC (µg/ml) 50% inhibition		
	Range	MIC_{50}	MIC_{90}
IBX	≤0.015-16	0.06	0.25
CAS	≤0.015-16	0.06	0.125

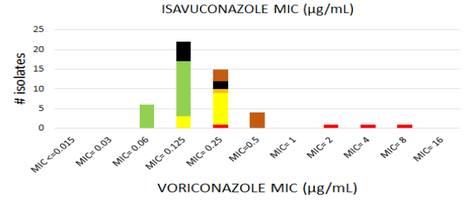
- MIC of IBX against Aspergillus isolates tested were low
- Median IBX MIC across species were within 2 dilutions
- All except 2 isolates (4%) required MIC ≥ 4 µg/mL for inhibition. Both belong to the Flavi family

B. Mould-active azole MIC

Drugs	MIC (µg/ml) 50% inhibition		
	Range	MIC_{50}	MIC_{90}
ISAVUCONAZOLE	0.03-16	0.4	2
POSACONAZOLE	≤0.015-16	0.125	0.25
VORICONAZOLE	0.06-8	0.125	0.5

- The majority of Aspergillus isolates with azole MIC ≥2µg/ml belonged to the *A. calidoustus* group





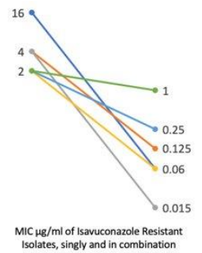
Drugs in combination

- Median MIC of IBX for all isolates was reduced by ≥2 dilutions (0.06 to ≤0.015) in combination with azoles.
- In combination with IBX,
  - MIC_{50} of ISA was 3 dilution lower in combination (0.4-->0.03)
  - MIC_{50} of POSA was ≥3 dilutions lower in combination (0.125---> ≤0.015)
  - MIC_{50} of VORI was 2 dilutions lower in combination (0.125-->0.03) with IBX for all isolates
- Applying EUCAST breakpoints for moulds, we identified 6 isolates (3 *A.calidoustus*, 1 *A. niger*, 1 *A. terreus*, 1 *A glaucus* 1), 14 isolates (3 *A.calidoustus*, 1 *A. niger*, 1 *A. terreus*, 1 *A glaucus* 1 A. *calidoustus* 4, *A. flavus* 4, *A. glaucus* 1, *A. niger* 4, A terreus 1) and 3 isolates (*A. calidoustus* 3) that were resistant to ISA, POSA and VORI respectively
- In combination with IBX, azoles MICs for resistant isolates was reduced to the susceptible range for all but one isolate

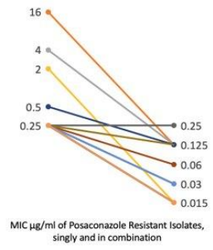
Interaction of Ibrexafungerp with azoles

ALL ISOLATES	Number of isolates in each azole group	Synergy %	Indifference %
IBREXAFUNGERP	ISA (n=36)	62	38
	POSA (n=34)	54	46
	VORI (n=36)	53	47

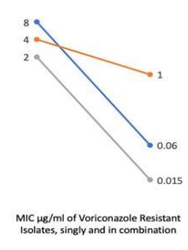
- Isolates with IBX or azole MIC <0.06 µg/ml were not included in the interaction evaluation because the MIC was too low to assess synergism: 13 isolates in IBX+ISA group, 15 isolates in the ISA+POSA group and 12 isolates in ISA+VORI group with MIC <0.06 µg/ml
- Antagonism was not observed between IBX and azole combination against any of the isolates
- Synergy was observed with IBX in combination of azole against 53-62% of <u>all</u> the isolates
- Synergy was observed with IBX in combination with azole against 40-100% of <u>azole-resistant</u> isolates
  - In combination with IBX, azoles MICs for resistant isolates (ISA MIC_{50} 3, POSA MIC_{50} 0.25, VORI MIC_{50} 4) was reduced to the susceptible range (per EUCAST: ISA ≤1 µg/ml, POSA ≤0.125 µg/ml, VORI ≤1 µg/ml) for all but one isolate in the IBX+POSA pool



MIC µg/ml of Isavuconazole Resistant Isolates, singly and in combination



MIC µg/ml of Posaconazole Resistant Isolates, singly and in combination



MIC µg/ml of Voriconazole Resistant Isolates, singly and in combination

AZOLE-RESISTANT ISOLATES	Number of azole-resistant isolates	Synergy %	Indifference %
IBREXAFUNGERP	ISA (n=5)	40%	60%
	POSA(n=12)	67%	33%
	VORI(n=2)	100%	0

CONCLUSIONS

- The majority of Aspergillus isolates from our clinical specimens at UPMC exhibited low MIC to IBX, including azole-resistant isolates
- IBX and CAS MIC of Aspergillus isolates were within a 2-fold dilution
- The in vitro results of combination of IBX and azoles against *Aspergillus* spp. are encouraging.
  - Synergy was achieved against 53 to 62% of all isolates, and 40-100% of azole-resistant isolates
  - The effect of IBX on reducing azole MICs to the susceptible range for azole-resistant *A. calidoustus* is particularly noteworthy
- Such data is especially important in lung transplant recipient in whom IA has disproportionately higher incidence and mortality rate.
- The availability of <u>oral formulation</u> is an advantage over current echinocandins
- Animal model and clinical studies are warranted to further elucidate the potential utility of IBX-azole combination therapy