In vitro Evaluation of Combination of Ibrexafungerp and Azoles against *Aspergillus* spp. Isolated from Lung Transplant Recipients

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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 class of glucan synthase inhibitor that has broad activity against *Candida*, *Aspergillus* and *Pneumocysitis*
  - Currently in a phase 2 clinical study in invasive pulmonary aspergillosis in combination with voriconazole (NCT03672292)

GOAL

- To evaluate the *in vitro* activity of IBX, either singly or in combination with isavuconazole (ISA), posaconazole (POSA) or voriconazole (VOR), against 50 *Aspergillus* isolates recovered from lung transplant recipients.

METHODS

- MICs of antifungals were determined according to CLSI M38-A2 standard.
  - Concentrations tested were from 0.015 to 16 µg/mL.
- For combination testing, fractional inhibitory concentration index determined by checkerboard method
  - FICi = MIC $_{IBX}$ (combo)/MIC$_{IBX}$ (single) + MIC$_{AZOLE}$(combo)/ MIC$_{AZOLE}$(single)) was used to classify the interaction between 2 drugs as synergy (FICi<0.5), antagonism (FICi>4) or indifference (FICi 0.5-4)

RESULTS

Fig. 1 - *Aspergillus* clinical isolates tested in this study

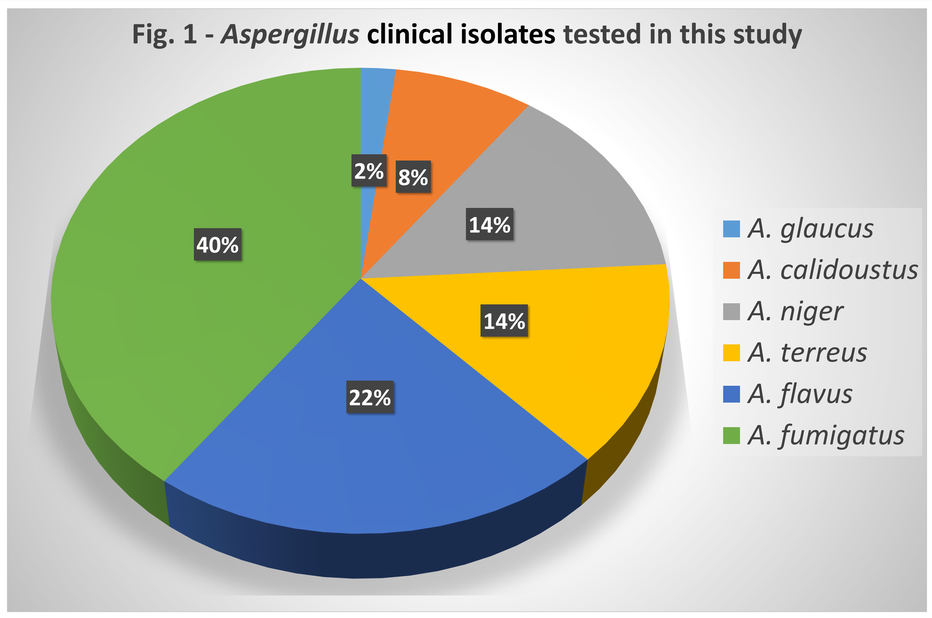


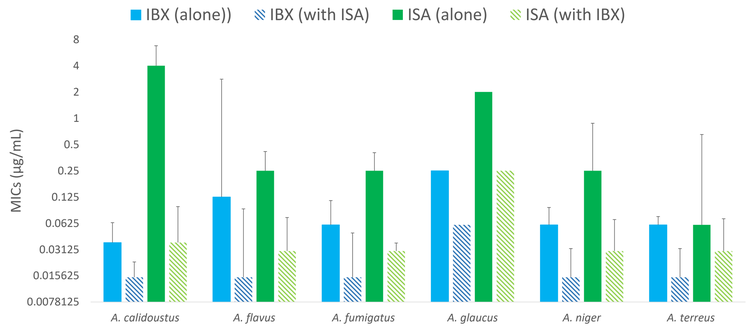
Table 1. MICs of IBX, ISA, POSA and VORI against clinical *Aspergillus* isolates

	Number of isolates	IBX		ISA		POSA		VORI	
		MIC$_{50}$	Range	MIC$_{50}$	Range	MIC$_{50}$	Range	MIC$_{50}$	Range
A. calidoustus	4	0.0375	0.015-0.06	4	0.25-16	3	0.25-16	3	0.25-8
A. flavus	11	0.125	0.03-16	0.25	0.125-0.5	0.125	0.125-0.5	0.25	0.125-0.25
A. fumigatus	20	0.06	0.015-0.125	0.25	0.06-0.5	0.06	0.03-0.125	0.125	0.06-0.125
A. glaucus	1	0.25		2		0.25		0.25	
A. niger	7	0.06	0.06-0.125	0.25	0.125-2	0.25	0.06-0.25	0.125	0.125-0.25
A. terreus	7	0.06	0.03-0.06	0.06	0.25-2	0.125	0.06-0.25	0.5	0.25-0.5

Note - Azole MIC ≥2 µg/mL was observed vs 75% of *A. calidoustus*

RESULTS

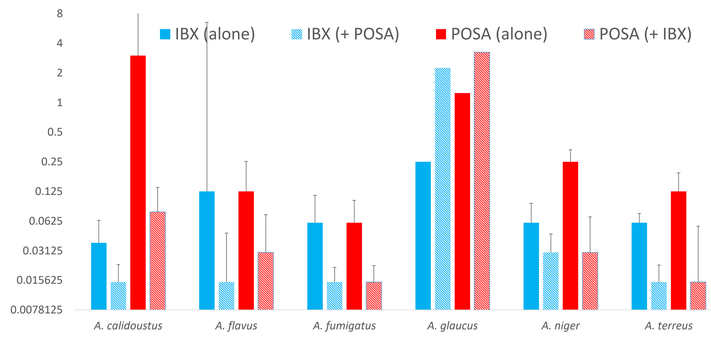
Figure 2. Effect of combination of IBX and an azole on individual drug MIC



SUMMARY OF DATA:

- 12, 14, 1 and 5 isolates exhibited IBX, ISA and POSA MIC <0.06 µg/mL, thus FICi cannot be determined.
- Synergy was observed with
  - IBX+ISA in 62%
  - IBX+POSA in 54%
  - IBX+VOR in 53%
- Among isolates exhibiting either IBX or azole MICs <0.06 µg/mL, the beneficial effect of the combination was still observed:
  - the MIC of the ISA, POSA and VORI was reduced by ≥ 4-fold in 75%, 50% and 75% of the isolates, respectively, when tested in combination with IBX

Note: Median MIC of azoles were reduced by ≥4-fold when combined with IBX. Median IBX MICs for *Aspergillus* spp. other than *A. calidoustus* were also reduced by ≥4-fold when combined with an azole. Median IBX MIC for *A. calidoustus* was too low to assess synergy.



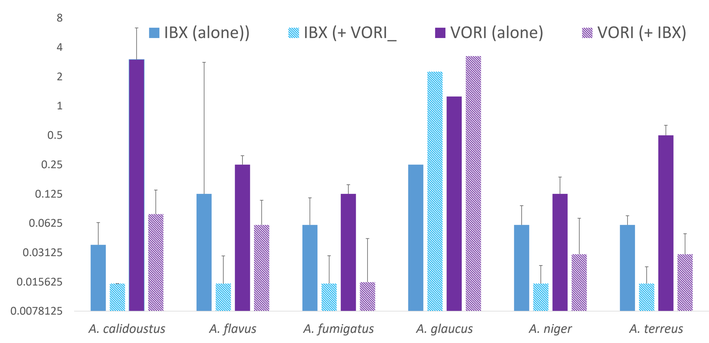


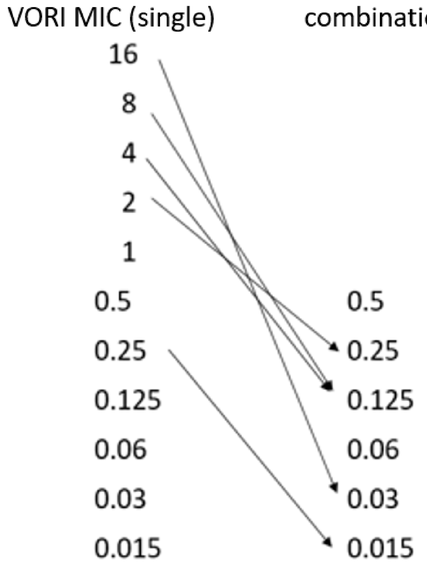
Figure 3. Interaction between IBX and VORI vs 5 *A. calidoustus* isolates

1A. VORI MICs for *A. calidoustus* isolates when VORI was given alone (left) and after combination with IBX (right). Note that 4 isolates exhibited VORI MIC ≥2 µg/mL

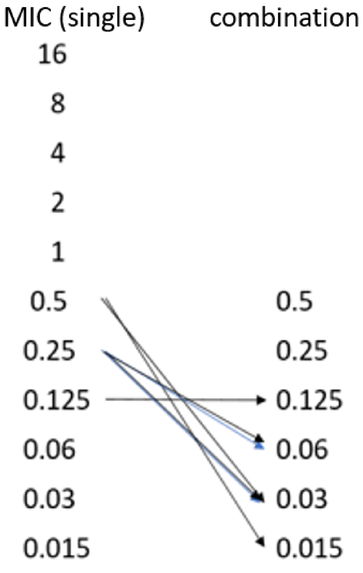
1B. IBX MICs for *A. calidoustus* when IBX was given alone (left panel) and after combination with VORI (right panel). Note that the interaction between IBX and VORI was synergistic in 80% (4/5) of isolates tested

Note: For *A. calidoustus*, ISA, POSA and VOR MICs in combination with IBX decreased from the range of 4-16 µg/mL to ≤0.0015-0.125 µg/mL for all azoles

1A.



1B.



CONCLUSIONS

- The *in vitro* results with combinations of IBX and azoles against *Aspergillus* spp. are encouraging.
  - Synergy was achieved against 53 to 62% of isolates.
  - Antagonism was not observed for this combination
  - The effect of IBX on reducing azole MICs to low range for azole-resistant *A. calidoustus* and *A. terreus* is particularly noteworthy
- Animal model and clinical studies are warranted to further elucidate the potential utility of IBX-azole combination therapy
- Such data are especially important in lung transplant recipients since azoles are the agents used most commonly as antifungal prophylaxis, but IFI and breakthrough IFIs are ~8-12% and ~3-5%, respectively
  - Mortality rates among lung transplant recipients with invasive aspergillosis are high despite azole treatment