Isavuconazole prophylaxis among solid organ transplant recipients: Effectiveness, tolerability and drug interaction with tacrolimus

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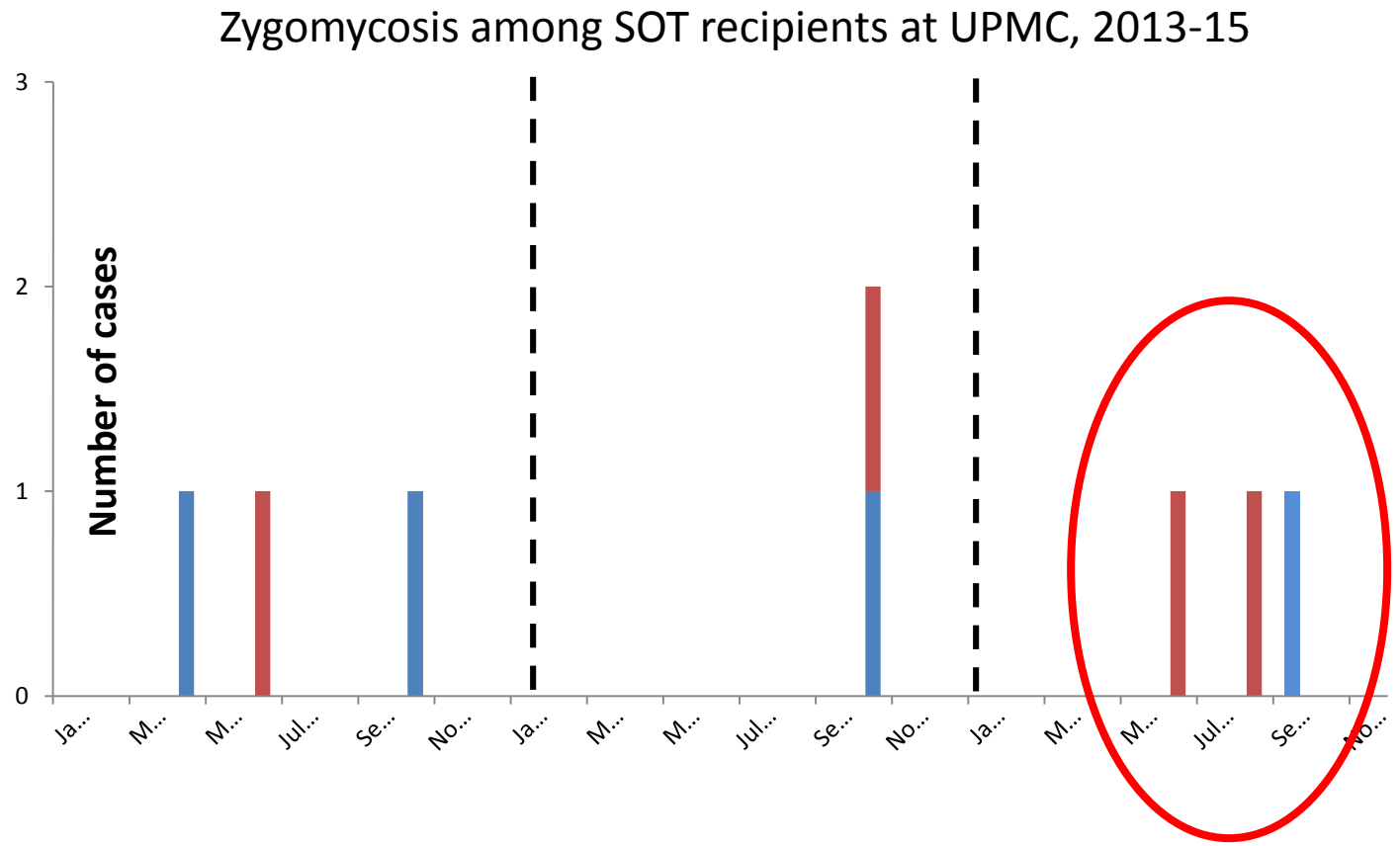
27th ECCMID
25 April 2017
Vienna, Austria

University of Pittsburgh

Disclosures and conflicts of interest

- Research laboratory funding from NIH
- Antifungal prophylaxis and therapeutic drug monitoring research supported by investigator-initiated awards from Astellas, Pfizer, MSD
- No financial holdings

Background



- In response, all newly transplanted patients were placed on prophylaxis with a *Zygomycetes*-active agent pending investigation by our Infection Control team, the PA DoH and the CDC

Choosing an antifungal agent

Posaconazole	Characteristic	Isavuconazole
No	FDA approval for treatment of zygomycosis	Yes
Solution, IV, PO (SR)	Formulation	IV, PO (SR)
Yes	Inter-patient variability	?
Yes	Need for therapeutic drug monitoring	No
$$$	Cost	$$$

Caveats about isavuconazole (ISA)

- Off-label use as prophylaxis in SOT
  - Unknown efficacy and tolerability
- Unknown interactions with calcineurin inhibitors
  - Tacrolimus (TAC) dose reduction with ISA?
- Unstudied in patients immediately after liver transplantation
  - Half-life prolonged by greater than 100 hours in patients with mild to moderate liver dysfunction

Antimicrob Agents Chemother. 2009;53(11): 4885-90
J Clin Pharm Ther. 2015 [Epub ahead of print]

UPMC SOT Fungal Prophylaxis			
Organ Type	**Pre-Outbreak**	**Post-Outbreak**	**Protocol adjustment**
Kidney	None	ISA X 1 month	d/c'ed
Pancreas	Universal fluconazole	ISA X 1 month	Returned to pre-outbreak
Liver	Tiered approach -No risk: None -Yeast risk: Fluconazole -Mold risk: Voriconazole	ISA X 1 month	Tiered approach with ISA for mould risk
Heart	Targeted voriconazole	ISA X 1 month	Continued with post-outbreak
Lung	Universal voriconazole	ISA X 4 months	Continued with post-outbreak

- ISA Dosing
  - 372 mg for six doses beginning post-SOT day 0, then 372 mg daily
  - Transition to PO as soon as the patient was able to tolerate

Objectives

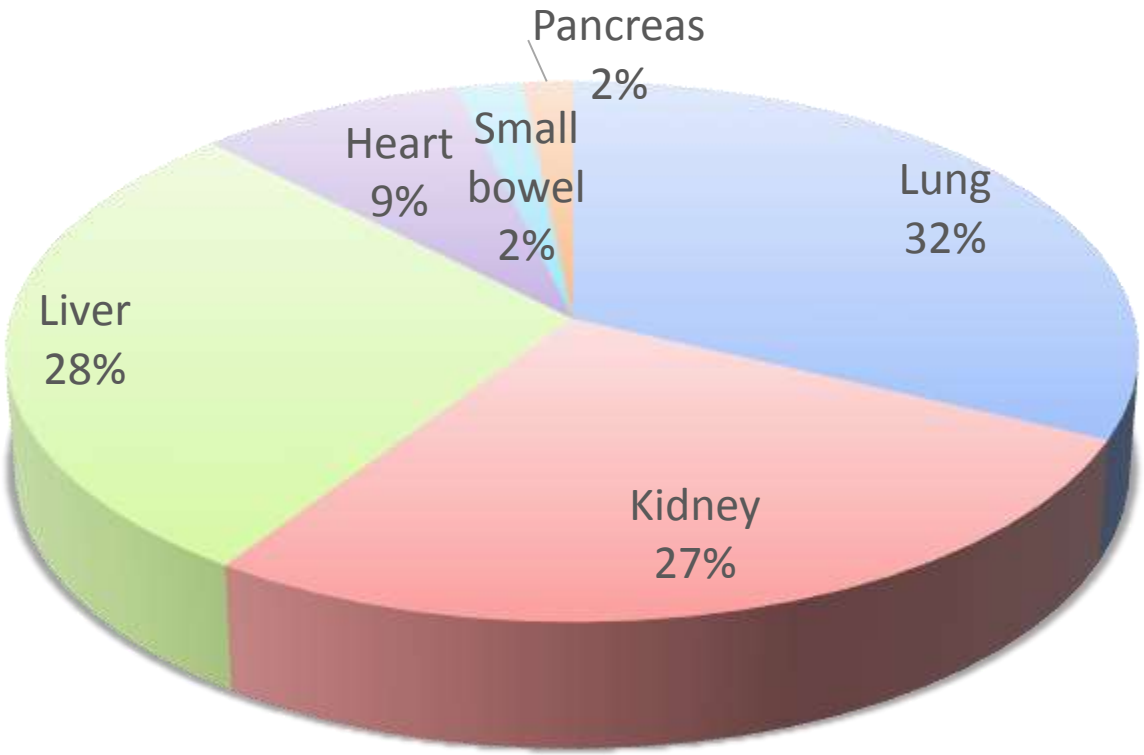
- To evaluate the efficacy and tolerability of ISA prophylaxis among SOT patients
- To evaluate the interaction between ISA and TAC
- To evaluate ISA serum trough levels

Methods

- Prospective, observational study of consecutive patients undergoing SOT at UPMC 10/1/15 through 7/31/2016 who received ISA prophylaxis
  - For liver and lung transplantation, the efficacy and tolerability of ISA was retrospectively compared with voriconazole
- Interaction between TAC with ISA
  - TAC concentration/dose (C/D) while on ISA *versus* off ISA
- ISA trough level determination
  - HPLC/MS

Results

- 187 patients were enrolled



Results - Efficacy

- 3% (6/187) developed an IFI
  - No breakthrough zygomycosis
  - *Candida*: 3
    - *C. albicans*, 1
    - *C. glabrata*, 2
  - Moulds: 3
    - 1 invasive *Aspergillus fumigatus* pneumonia and chest wall infection
    - 1 invasive *Aspergillus fumigatus* pneumonia andendobronchial infection
    - 1 *Cladophialophora* endobronchial infection

Results - Efficacy

	ISA	VORI	P-values
Lung transplant	7% (4/60)	4% (10/93)	NS (0.57)
Liver transplant	4% (2/53)	6% (20/314)	NS (0.75)

Other organ transplant – no IFI

Results – Premature discontinuation

	ISA	VORI	P-values
Lung transplant	28% (7/60)	27% (25/93)	NS (1.0)
Toxicity	12% (7/60)	27% (25/93)	**0.03**
GI side effect	10% (6/60)	14% (13/93)	NS (0.62)
Hepatotoxicity	2% (1/60)	11% (10/93)	**0.051**
Neurotoxicity	0%	3% (3/93)	0.28
D/c on enteral feed	17% (10/60)	0%	0.054

Results – Premature discontinuation

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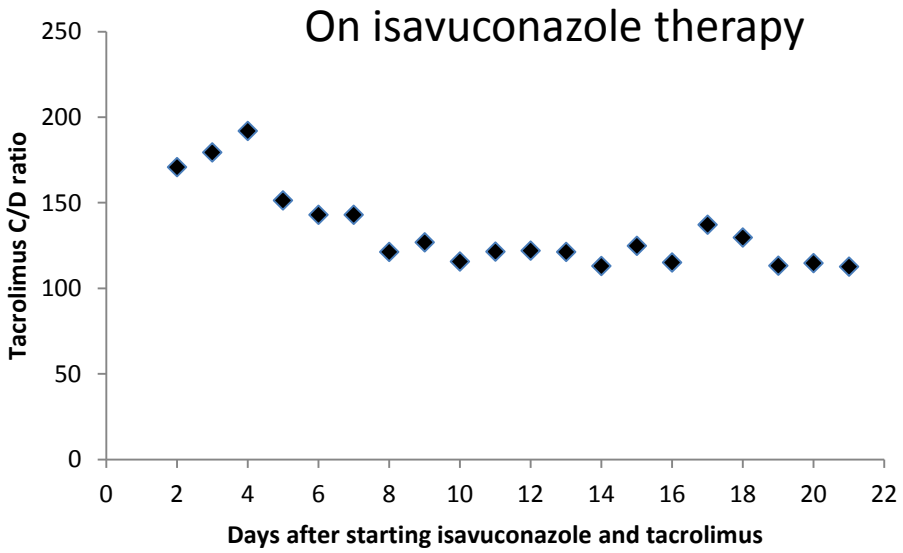
GI side effect	10% (6/60)	14% (13/93)	NS (0.62)
Hepatotoxicity	2% (1/60)	11% (10/93)	**0.051**
Neurotoxicity	0%	3% (3/93)	NS (0.28)
D/c on enteral feed	17% (10/60)	0%	0.054
Liver transplant	3% (2/60)	10% (30/314)	NS (0.13)
Toxicity	3% (2/60)	10% (30/314)	NS (0.13)
GI side effect	2% (1/60)	6% (20/314)	NS (0.22)
Hepatotoxicity	2% (1/60)	3% (10/314)	NS (1.0)

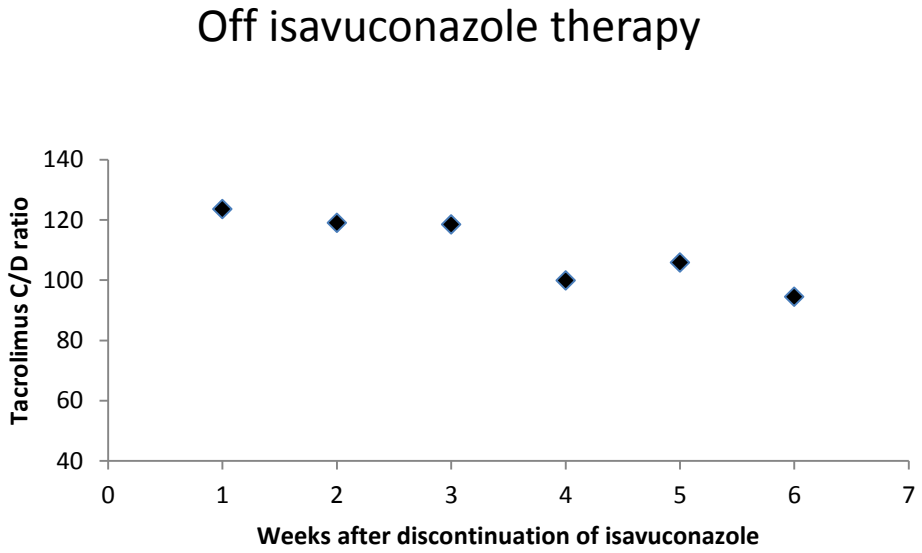
Other SOT

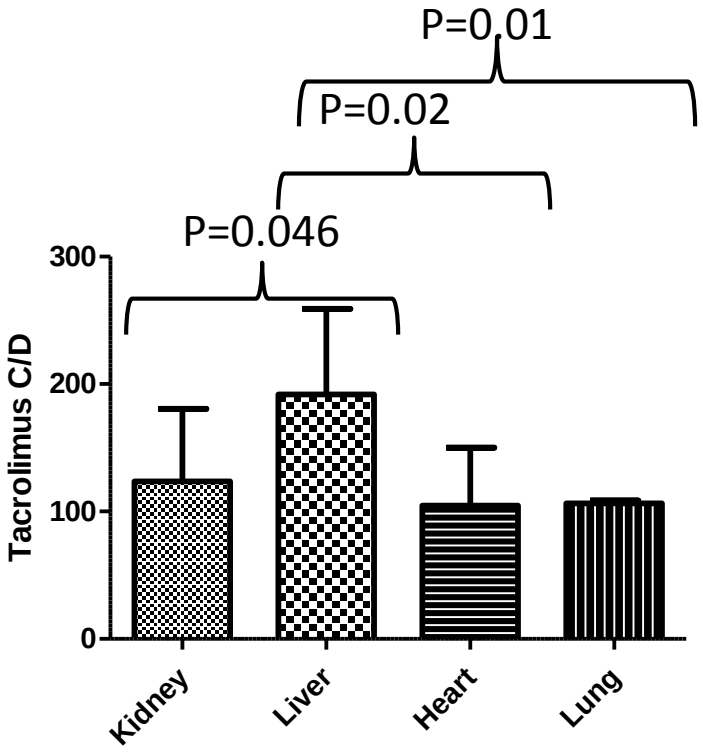
- Premature discontinuation (GI) = 1.4% (1/74)

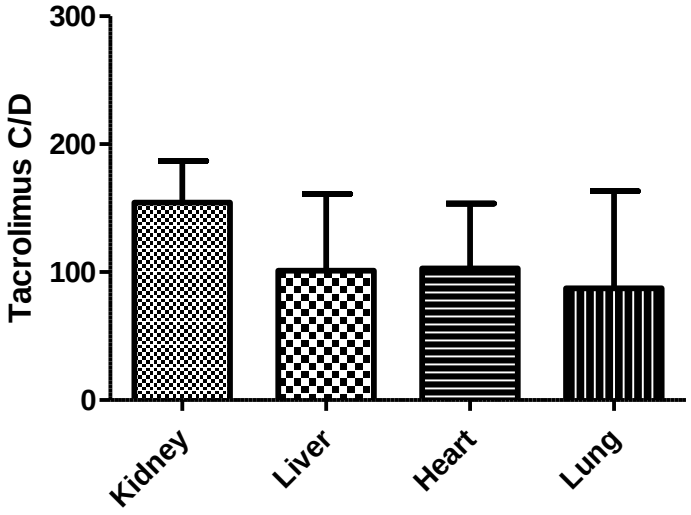
Results - TAC C/D

- 59 patients who had ≥5 and ≥3 TAC levels performed while on (total levels n=641) and off (n=459) ISA prophylaxis, respectively







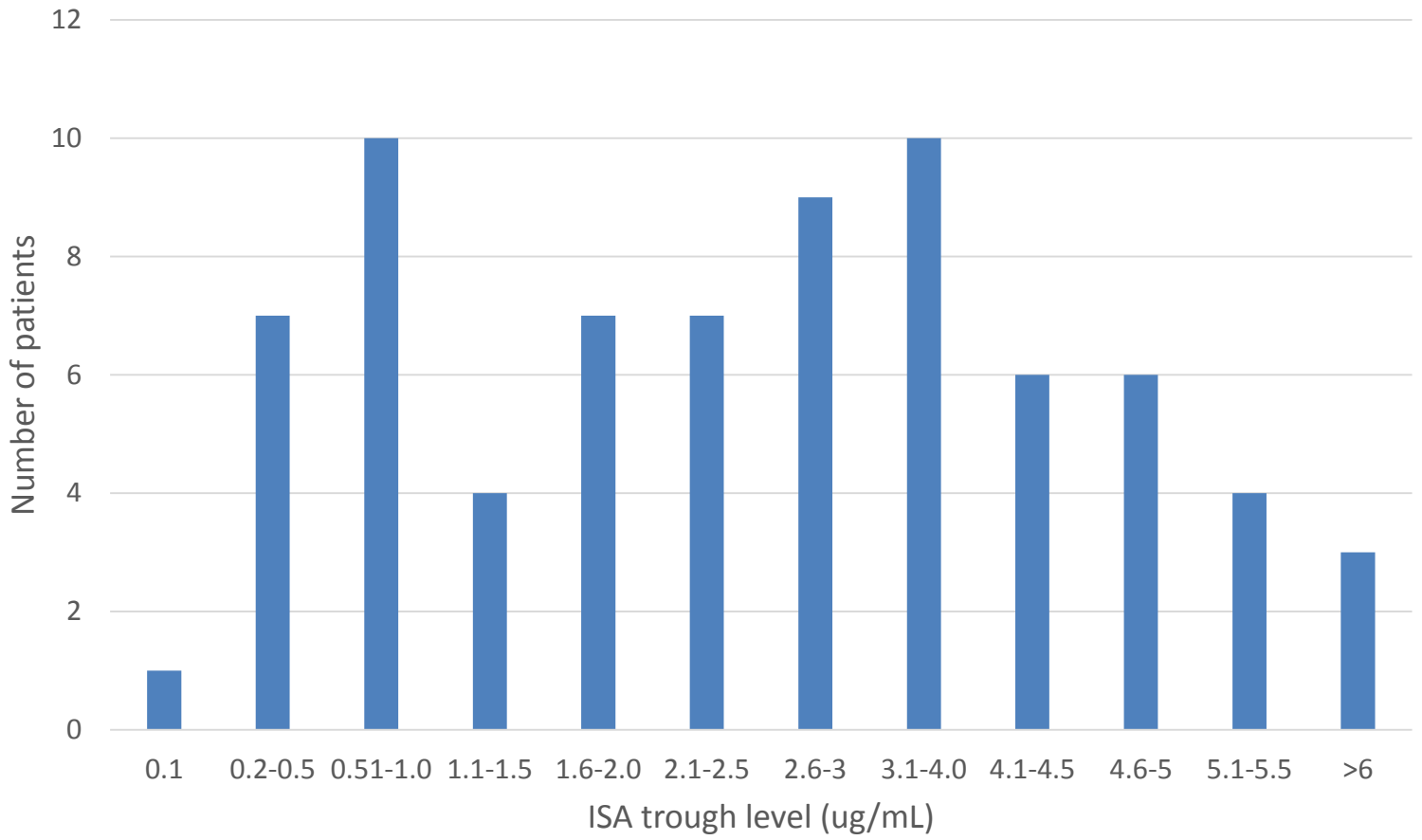


- **TAC C/D on ISA**
  - C/D was higher among liver transplant patients than other organs
- **Median TAC C/D on ISA was higher than C/D off ISA**
  - Only significant differences were noted among liver transplant recipients (median decreased from 200 to 100; p=0.04)
- **TAC C/D off ISA**
  - No differences in C/D by type of SOT (p=0.59)

Factors associated with TAC C/D

Factors	On ISA	Off ISA
	Univariate	Univariate
	P-values	P-values
Age	NS	NS
Sex	NS	NS
Race	NS	NS
Liver transplant	0.0004 (OR 6.1 (2.9-8.3))	NS

Results – Serum trough ISA levels



- Median ISA trough = 2.8 ug/mL (range: 0.1 – 8.4 ug/mL)
- No significant difference in troughs between IV or oral administration (p=0.89)
- No overall difference in troughs by type of SOT
  - Troughs were lower among CF lung transplant patients vs other patients (p=0.009)
  - Trend toward higher troughs within 21 days of liver transplant (p=0.063)

Discussion

- ISA is effective antifungal prophylaxis among SOT patients
  - Breakthrough mould infections in high-risk patients (lung transplant)
    - 2/3 patients had positive lung culture positive for *A. fumigatus* at the time of transplant
    - All 3 patients with breakthrough mould infections had > grade 2 ischemia reperfusion injury.
    - 1/3 patient had ISA trough level <0.1

Discussion

- Toxicity requiring premature discontinuation of ISA was highest for lung > liver >>> other organs
- In lung transplant patients, the rate of ISA discontinuation due to toxicity was lower than the rate of voriconazole discontinuation
  - Most toxicity was due to GI symptoms
  - Hepatotoxicity is less for ISA than voriconazole
- Inter-patient variability exists in ISA levels
  - Lowest troughs in CF patients
  - Highest troughs early following liver transplant

Conclusions

- Clinical recommendations
  - No “routine” reduction in TAC doses when given in conjunction with ISA
    - TAC doses to be adjusted by levels
    - More cautious dose adjustments in liver transplant patients with elevated MELD
- Ongoing studies
  - Focus on lung and liver transplants
  - Need for therapeutic drug monitoring of ISA?
  - Efficacy and tolerability of ISA prophylaxis
  - Population PK evaluations
  - Detailed serum and ELF PK
  - Genomic epidemiology of clinical and environmental Mucorales

Acknowledgements

- **Neil Clancy, MD**
- **Ryan Rivosecchi, PharmD**
- **Venkat Venkataramanan, PharmD**
- Ryan K. Shields, PharmD
- Palash Samanta, MD
- Bonnie Falcone, PharmD
- Abhinar Humar, MD
- UPMC Transplant ID team
  - EJ Kwak, MD, Fernanda Silveira, MD, Tatiana Bogdanovich, MD, Rima Abdel Massih, MD

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