Poster P056

Frequency of paradoxical and trailing effects with rezafungin, anidulafungin, caspofungin and micafungin against *Candida* species

Lajos Forgács[1], Zoltán Tóth[1], Jeffrey B. Locke[2], Fruzsina Nagy[1], Bence Balázs[1], Eszter Prépost[1], Gábor Kardos[1], Renátó Kovács[1], Adrienn Szekely[3], Andrew M. Borman[3], László Majoros[1]

[1]Department of Medical Microbiology, Faculty of Medicine, University of Debrecen, Hungary,
[2]Cidara Therapeutics, Inc., 6310 Nancy Ridge Dr., Suite 101, San Diego, CA 92121, USA.
[3]UK National Mycology Reference Laboratory (MRL), Public Health England South-West, Bristol, UK

L. Majoros
major@med.unideb.hu

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INTRODUCTION

Echinocandins demonstrate excellent efficacy and fungicidal activity against *Candida* species *in vivo*. However, echinocandins can exhibit some disconnected growth phenomena *in vitro*, such as paradoxical effect (PE) and trailing effect (TE). PE and TE can significantly alter the determination/interpretation of MIC values and impact other *in vitro* assays (1,2). Rezafungin is a next-generation echinocandin capable of attaining high concentrations and exposures *in vivo,* exceeding those measured for the three approved echinocandins, due to its long half-life and front-loaded dosing regimen (3). Given the relevance of evaluating higher drug concentrations for rezafungin and that rezafungin PE/TE trends have not yet been characterized, herein we compared the occurrence of PE and TE for rezafungin with data generated in parallel for caspofungin, micafungin and anidulafungin against clinically important *Candida* species.

METHODS

We tested 349 non-duplicate Hungarian clinical isolates belonging to 12 species (Table). Sixteen *C. auris* isolates were from the National Mycology Reference Laboratory (UK). All isolates were identified with MALDI Biotyper (Bruker, Bremen, Germany). MICs were determined by BMD method according to CLSI (M27 Ed4) in RPMI-1640 (4). We used tissue culture–treated microtiter test plates (TPP Techno Plastic Products AG, Switzerland, catalogue number 92097). Rezafungin pure powder was provided by Cidara Therapeutics (San Diego, CA). Caspofungin, micafungin and anidulafungin were purchased from Molcan Corporation (Richmond Hill, ON, Canada). Concentration ranges of antifungals were 0.06-32 mg/L. MICs were read visually after 24 and 48h. PE was defined as visible growth occurring at higher but not at lower supra-MIC concentrations (5). TE was defined when yeasts show reduced but observable growth in supra-MIC concentrations.

RESULTS

Echinocandins MICs distributions and the most frequent concentration ranges (where appropriate) where PE was noticed for the 13 *Candida* species

Species (n)	Drug	Number of isolates inhibited at each MIC value (mg/L)									
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32
C. albicans (100)	RZF	99	1								
	ANF	100									
	CSF	9	5	52	34						
	MCF	98	2								
C. glabrata (30)	RZF	17	12	1							
	ANF	30									
	CSF		1	11	18						
	MCF	30									
C. parapsilosis (26)	RZF				5	11	10				
	ANF				4	10	12				
	CSF				4	16	6				
	MCF				3	14	9				
C. tropicalis (50)	RZF	50									
	ANF	50									
	CSF	2	9	24	15						
	MCF	50									
C. krusei (30)	RZF	16	14								
	ANF	14	13	2	1						
	CSF			2	6	22					
	MCF		9	21							
C. kefyr (16)	RZF	9	7								
	ANF	15	1								
	CSF			12	4						
	MCF	12	4								
C. lusitaniae (27)	RZF	3	17	7							
	ANF	26	1								
	CSF		1	4	12	10					
	MCF	9	11	6	1						
C. guilliermondii (16)	RZF				3	12	1				
	ANF				3	11	2				
	CSF				9	6	1				
	MCF				7	7	2				
C. dubliniensis (22)	RZF	22									
	ANF	22									
	CSF	2	8	10	2						
	MCF	22									
C. auris (16)	RZF	4	6	6							
	ANF	11	5								
	CSF			4	7	5					
	MCF		6	10							
C. orthopsilosis (8)	RZF			3	2	3					
	ANF		1	1	3	3					
	CSF				3	5					
	MCF			1	4	3					
C. metapsilosis (11)	RZF			2	9						
	ANF		4	5	2						
	CSF		1	5	5						
	MCF		1	6	4						
C. inconspicua (13)	RZF	13									
	ANF	13									
	CSF	2	4	7							
	MCF	13									

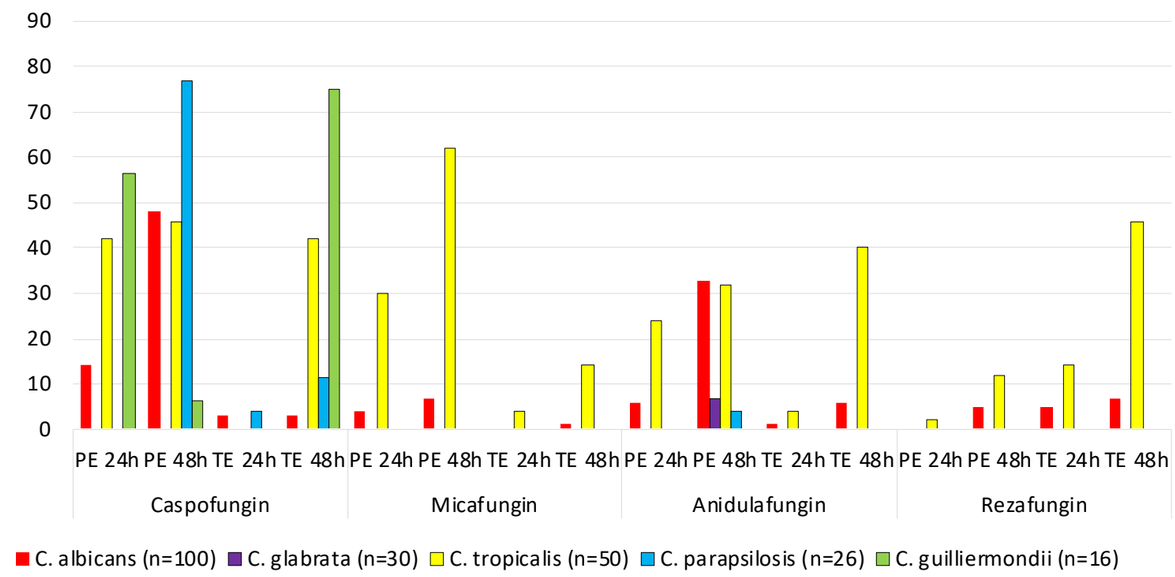
RZF – rezafungin; ANF – anidulafungin; CSF – caspofungin; MCF – micafungin. Grey shadowing: the most frequent concentrations where PE occurred

RESULTS (cont'd)

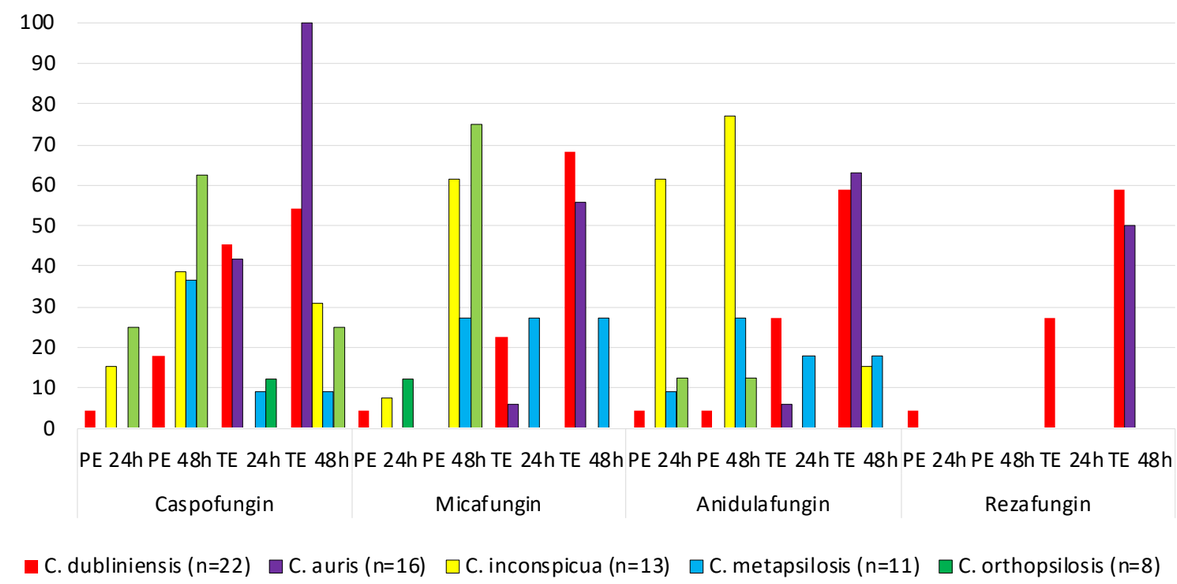
Neither PE nor TE was observed in the case of *C. krusei* with the three licensed echinocandins as well as rezafungin.

PE after 24 hours that turned to TE after 48 hours was observed with CSF in 13 *C. tropicalis* and 6 *C. albicans* and with ANF in 3 and 5 isolates, respectively. A similar phenomenon was observed with CSF in 9 *C. guilliermondii* isolates.

Frequency (%) of paradoxical effect (PE) and trailing effect (TE) among common *Candida* species and *C. guilliermondii*



Frequency (%) of paradoxical effect (PE) and trailing effect (TE) among rare *Candida* species



CONCLUSIONS

- PE or TE was widely observed among *Candida* species and were echinocandin- and species-dependent.
- Rezafungin induced PE with the lowest frequency (3.1%), while the PE with caspofungin, anidulafungin and micafungin were higher (31.4, 21 and 15.8%, respectively).
- PE with caspofungin, micafungin or anidulafungin occurred most frequently in cases of *C. tropicalis*, *C. albicans*, *C. orthopsilosis, C. metapsilosis* and *C. inconspicua*.
- Slightly higher rates of TE were observed for caspofungin (16.3%), anidulafungin (14.9%) and rezafungin (14.6%) compared to micafungin (10.0%).
- This study is the first to characterize PE and TE trends for rezafungin and helps to inform future *in vitro* work with this novel echinocandin.

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