



Treatment Options in Yeast Infections

Preliminary Slide Set

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Objective:

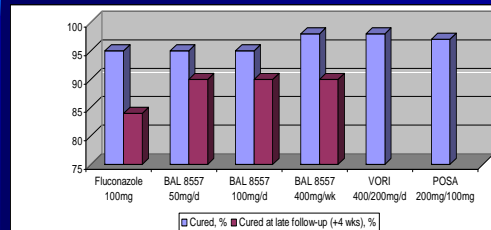
Review of various treatment options for yeast diseases
 Focusing on candidiasis

Treatment:

- Invasive Candidiasis/Candidemia
- Esophageal Candidiasis
- Biofilm Formation
- Chronic Disseminated Candidiasis
- Outlook

Proof of Principle Trials: OPC/EC

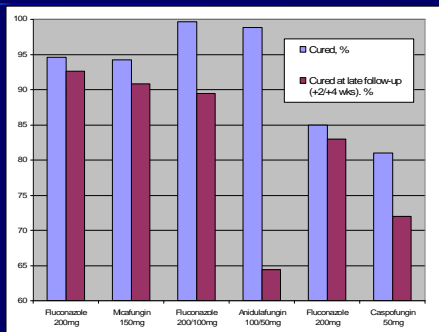
Heep M et al. ICAAC 2005
 Vazquez JA et al. CID 2006
 Alby et al. CID 2001



Cured: success and/or cure

Proof of Principle Trials: OPC/EC

de Wit HJ et al. Alimant Pharmacol Ther. 2005
 Krausz DS et al. CID 2004
 Villanueva A et al. Am J Med 2005



Chronic Disseminated Candidiasis Hepatosplenic Candidiasis

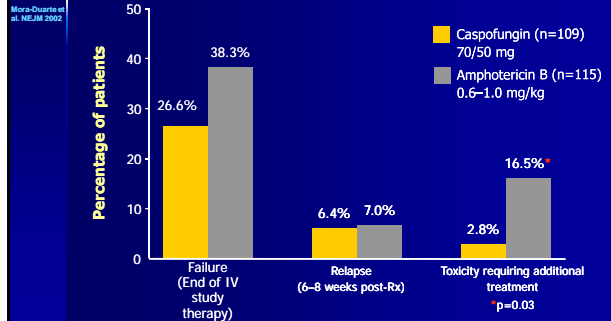


Halkic N et al. NEJM 2007

Echinocandins: Caspofungin

Clinical Data
Invasive Candidiasis

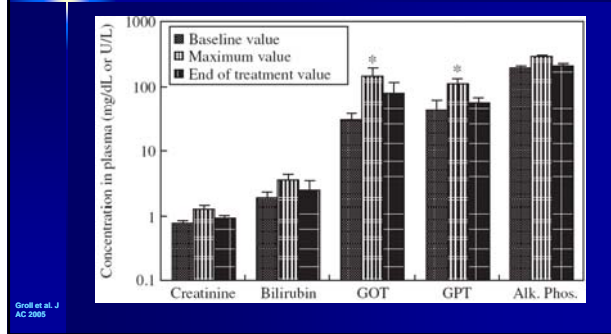
TREATMENT OF INVASIVE CANDIDIASIS: CASPOFUNGIN VS. AmB IN NON- NEUTROPENIC & NEUTROPENIC PATIENTS



TREATMENT OF INVASIVE CANDIDIASIS: CASPOFUNGIN VS. AmB IN NON- NEUTROPENIC & NEUTROPENIC PATIENTS

	Caspofungin (N=109)		Amphotericin B (N=115)	
	n	%	n	%
Neutropenic Status				
Non-neutropenic	95	(87.2)	105	(91.3)
Neutropenic (<500 μ L)	14	(12.8)	10	(8.7)
Apache II Score				
< 20	88	(80.7)	92	(80.0)
> 20	21	(19.3)	23	(20.0)
Mean	14.8		15.4	
Risk factors				
Broad Spectrum Antibiotics	90	(82.6)	102	(88.7)
CVC	80	(73.4)	90	(78.3)
Surgery	54	(49.5)	58	(50.4)
TPN	39	(35.8)	55	(47.8)
Malignancy	30	(27.5)	38	(33.0)
Transplant	6	(5.5)	1	(0.9)

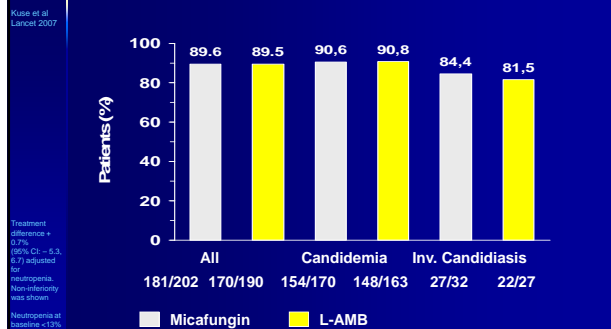
Course of laboratory parameters of renal and hepatic function during therapy with caspofungin



Echinocandins: Micafungin

Clinical Data
Candidemia/Invasive Candidiasis

Comparison of Micafungin and Liposomal Amphotericin B for Invasive Candidiasis Overall Treatment Success at EOT (PPS)



Comparison of Micafungin and Liposomal Amphotericin B for Invasive Candidiasis

Treatment Success by Species at EOT (PPS)

Kuse et al
Lancet 2007

Species	Micafungin n = 202	L-AMB n = 190
C. albicans	76/86 (88.4%)	75/84 (89.3%)
Non-C. albicans	113/126 (89.7%)	100/112 (89.3%)
<i>C. tropicalis</i>	48/52 (92.3%)	41/43 (95.3%)
<i>C. parapsilosis</i>	33/37 (89.2%)	26/30 (86.7%)
<i>C. glabrata</i>	19/23 (82.6%)	12/15 (80.0%)
<i>C. krusei</i>	5/6 (83.3%)	6/7 (85.7%)
Other species†	10/11 (90.9%)	9/9 (100.0%)

†
C. guilliermondii, C.
ferrousii, C.
lusitanae, C.
saccharicola, C.
zosteromyces, C.
ecorossii, C.
spirogramma, C.
reptans

Comparison of Micafungin and Liposomal Amphotericin B for Invasive Candidiasis

Treatment-related AE's (ITT)

Kuse et al
Lancet 2007

AE's (> 3%)	Micafungin n = 264	L-AMB n = 267
Fever*	8.7%	13.5%
Chills*	0.8%	6.4%
Back pain*	0.4%	4.5%
Nausea	4.5%	3.7%
LFT abnormal	4.2%	1.9%
Vomiting	3.4%	3.4%
Hypokalemia	6.8%	12.0%
Creatinine increased	1.9%	6.4%

* Included in infusion-related adverse events (pre-defined endpoint)

LFT, liver function test.

Anidulafungin

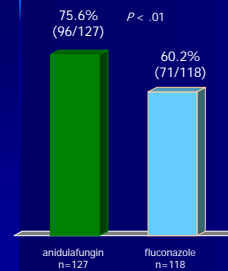
Clinical Data

Candidemia/Invasive Candidiasis

Invasive Candidiasis or Candidemia - ANID 200/100 vs FLU 800/400

Primary Efficacy Analysis

Kucolnik A et al
NEJM 2007
356: 2419-28



- Difference in success rates = 15.4% (95% CI: 3.85, 26.99)
- Lower limit of CI > 0
- Anidulafungin was found to be superior to fluconazole

* in the Micro ITT population

Invasive Candidiasis or Candidemia ANID 200/100 vs FLU 800/400

Secondary Endpoints

Kucolnik A et al
NEJM 2007
356: 2472-82

End Point	Global Success		Absolute Percent Difference between Treatments (95% CI)
	Fluconazole Group (N=118)	Anidulafungin Group (N=127)	
End of intravenous therapy	71 (60.2)	96 (75.6)	15.4 (3.9 to 27.0)
End of all therapy	67 (56.8)	94 (74.0)	17.2 (5.5 to 29.0)
2-Week follow-up	58 (49.2)	82 (64.6)	15.4 (3.1 to 27.7)
6-Week follow-up	52 (44.1)	71 (55.9)	11.8 (-0.6 to 24.3)

Newer Agents

Next Generation of Azoles

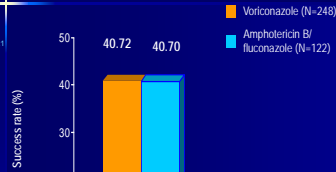
Voriconazole

Clinical Data:

Candidemia/Invasive Candidiasis

Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial

Kulberg BJ et al. Lancet. 2006 Oct 22; 368(9549):1435-42.



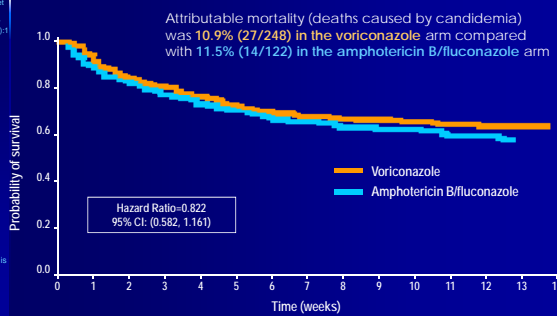
- The difference in response rate was 0.04% (stratified by region)
- The 95% confidence intervals around this difference were not less than -15% (-10.55%, 10.63%)
- This met the predefined criterion for non-inferiority

Note: Patients can have more than one site of infection. Includes patients with both candidemia and 'other' deep tissue Candida infection.

Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial

Kaplan-Meier Survival Curve (MITT Population)

Kulberg BJ et al. Lancet. 2006 Oct 22; 368(9549):1435-42.



Note: the hazard ratio is stratified by region.

New Directions

- Efungumab/Mycograb: recombinant antibody fragment targets *Candida albicans* hsp90 (received no approval by EMEA)
- Antimicrobial peptides
- Newer azoles: Isavuconazole (BAL8557)
- More echinocandins: Aminocandin
- Calcineurin inhibitors