İnvaziv Fungal İnfeksiyonların Tedavisinde Yeni Bir Seçenek: İtrakonazol

Dr. Ömrüm Uzun

ÖU 02/2009

YENİ

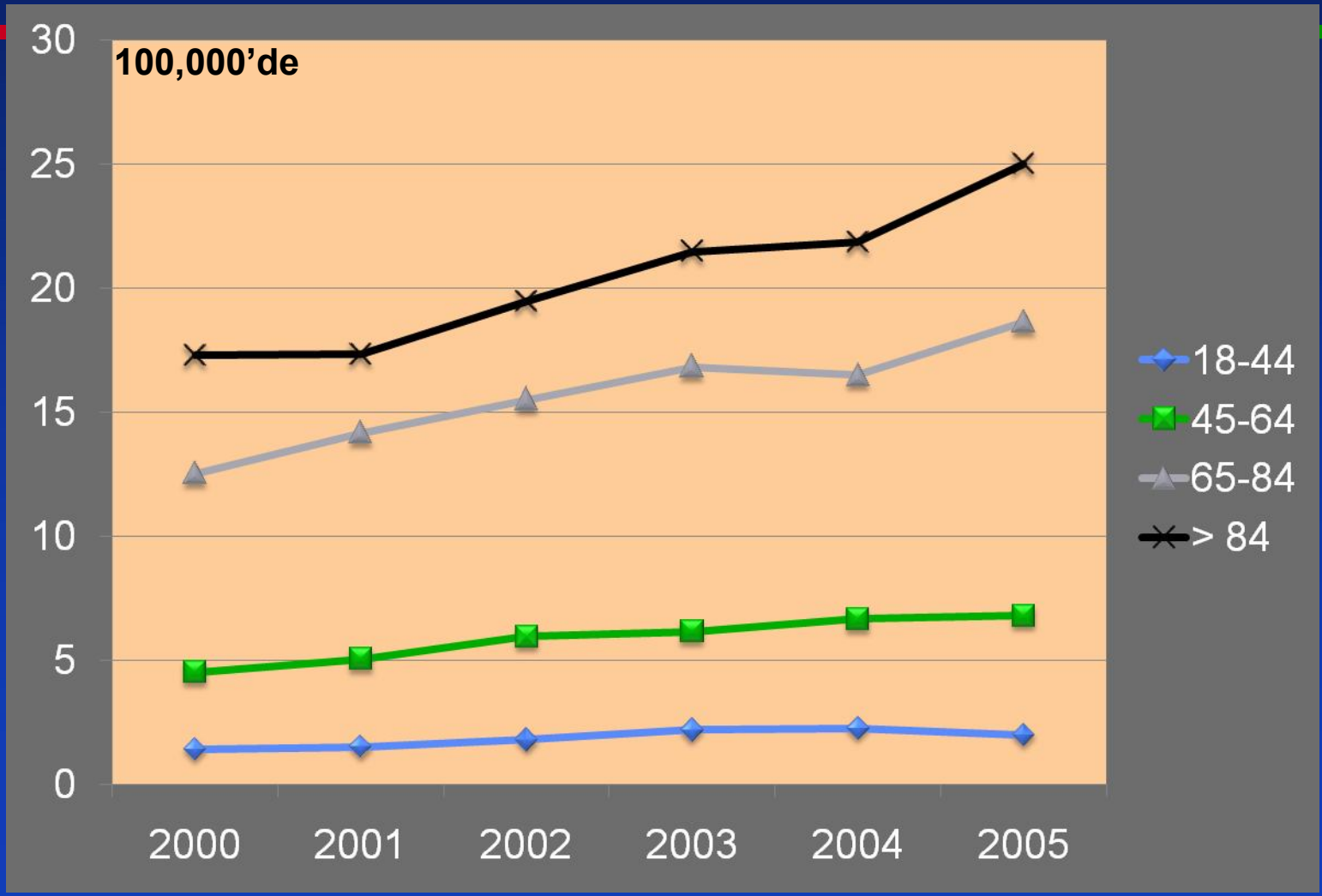
MALİ AÇIKLAMALAR

Aşağıdaki firmalardan danışman, konuşmacı, araştırma projesi ve bilimsel toplantılara katılım destekleri:

- Basilea
- Erkim
- Gilead
- Janssen Cilag
- Merck
- Pfizer
- Schering

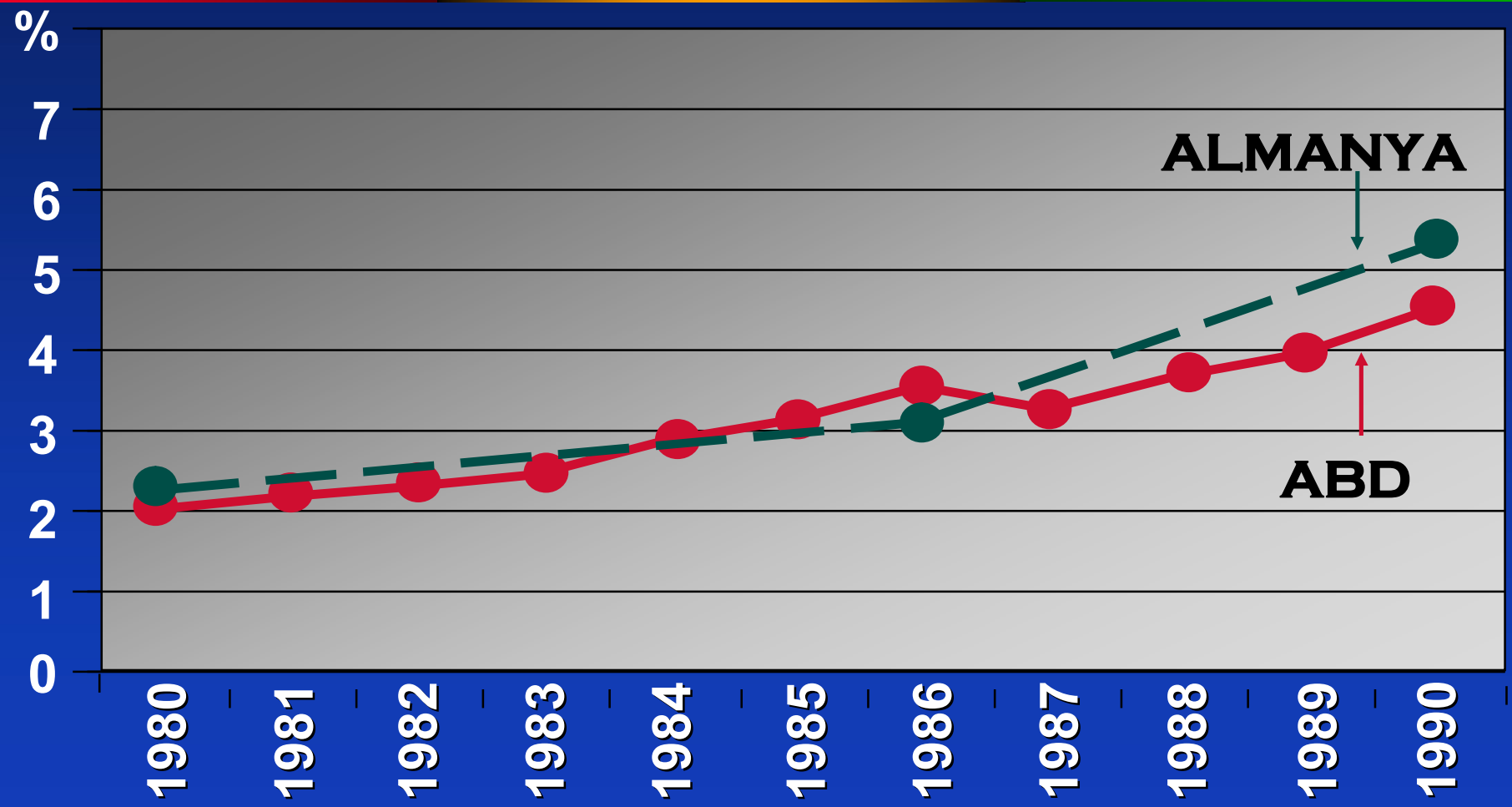
A.B.D.nde Kandidemi-ilişkili Hastaneye Yatış

Zilberberg MD, et al. Infect Control Hosp Epidemiol 2008;29:978



İnvaziv Küf Mantarı İnfeksiyonlarında Eğilim

Beck-Saque JID 1993: *Groll et al .J Infection 1996*



B. DePauw

ÖU 02/2009

İFİ Riski En Yüksek Olan Hastalar

- Hematopoietik kök hücre alıcıları
- Yoğun kemoterapi alan lösemili nötropenik hastalar
- Solid organ transplant alıcıları
- Kritik hastalar
- Yenidoğan servisinde yatan prematüre bebekler
- Uzun süreli kortikosteroid tedavisi alanlar
- AIDS'li hastalar

İFİ İnsidansındaki Artışla İlgili Faktörler

Kemoterapi alan hasta sayısındaki artış

Sağkalımın uzaması, ancak immunosupresyon süresinin uzaması

Daha agresif anti-neoplastik kemoterapi

SVK kullanımında artış
Artmış mukozit
Uzun süreli ağır nötropeni
Derin ve inatçı nötropeni

Yoğun antibiyotik kullanımı

Yüksek farkındalık ve daha iyi tanısal yöntemler

İFİ Epidemiyolojisindeki Değişiklikler

Transplant alıcılarında İK↓	FLC profilaksisi
Albicans-dışı Candida ↑	FLC profilaksisi
Kritik ve KOAH hastalarında İA ↑	Kritik hastaların daha uzun yaşaması İnvaziv girişimler Kortikosteroidler
Transplant alıcılarında geç IA ↑	Daha kısa süreli nötropeni GVHH Uzun süren immunosupresyon
Non-fumigatus Aspergillus ↑	Tanı yöntemlerindeki gelişmeler
Zigomikoz ↑	VRC profilaksisi

Amfoterisin B-deoksikolat

SEÇENEKLER

POLİEN'LER

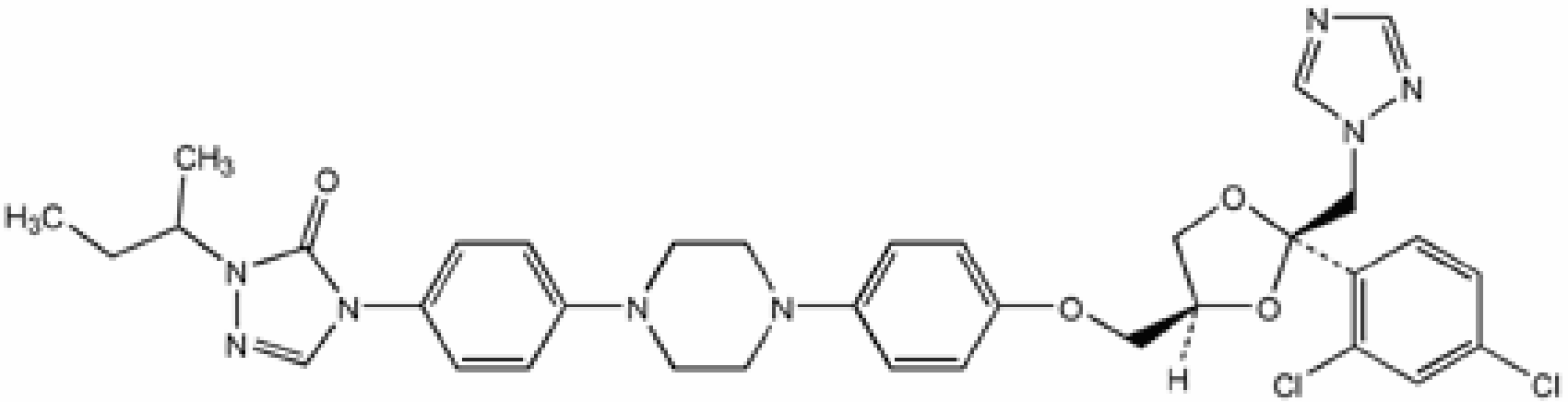
- AmB-d
- Lipid AmB
- İV nistatin

AZOLLER

- Flukonazol
- İtrakonazol
- Vorikonazol
- Posakonazol
- Ravukonazol

EKİNOKANDİNLER

- Kaspofungin
- Anidulafungin
- Mikafungin



itraconazole


SPOR
OX

Maya Türlerine In Vitro Etkinlik

Johnson E, et al. Int J Antimicrob Agents 2008:32:511

1763 maya izolatı

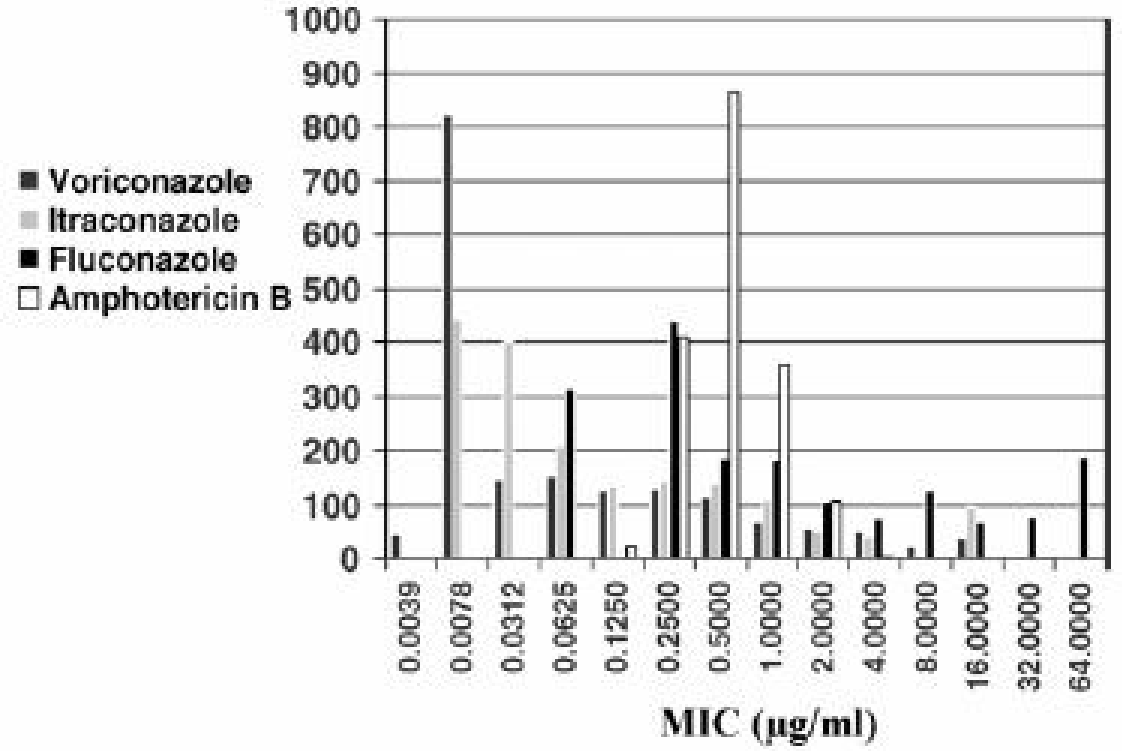
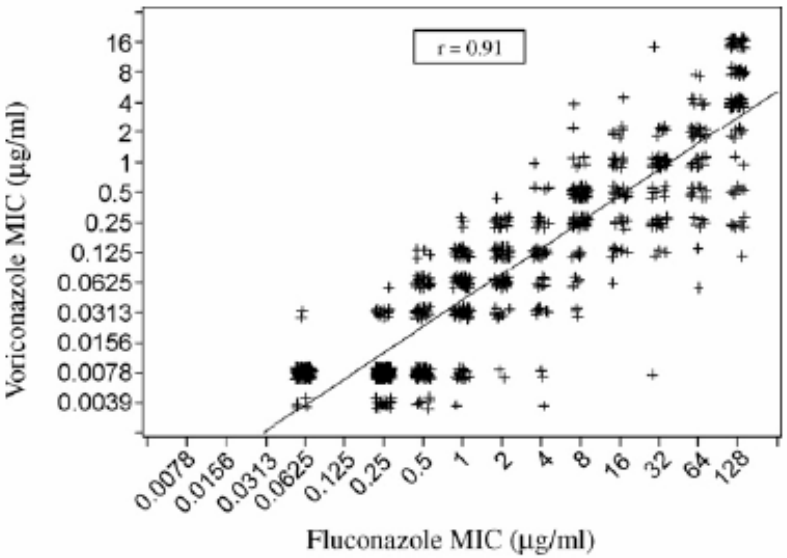
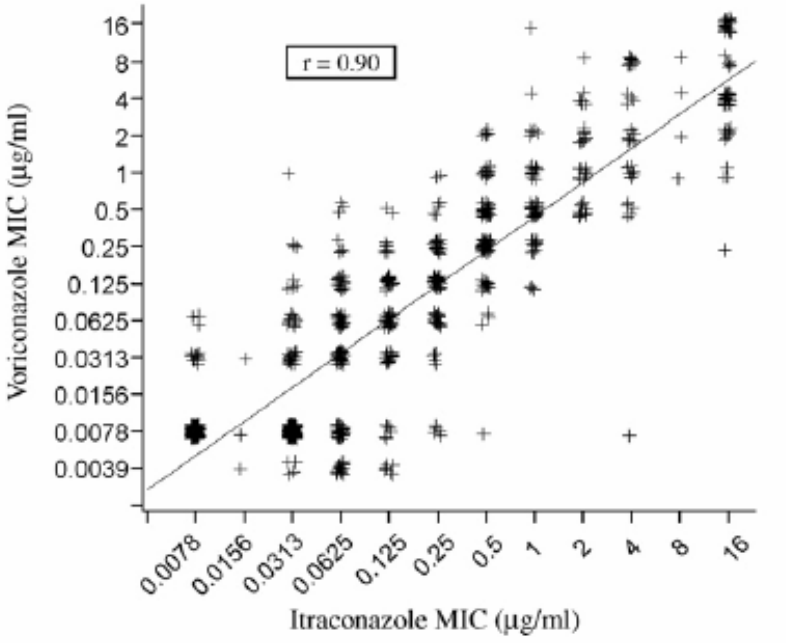


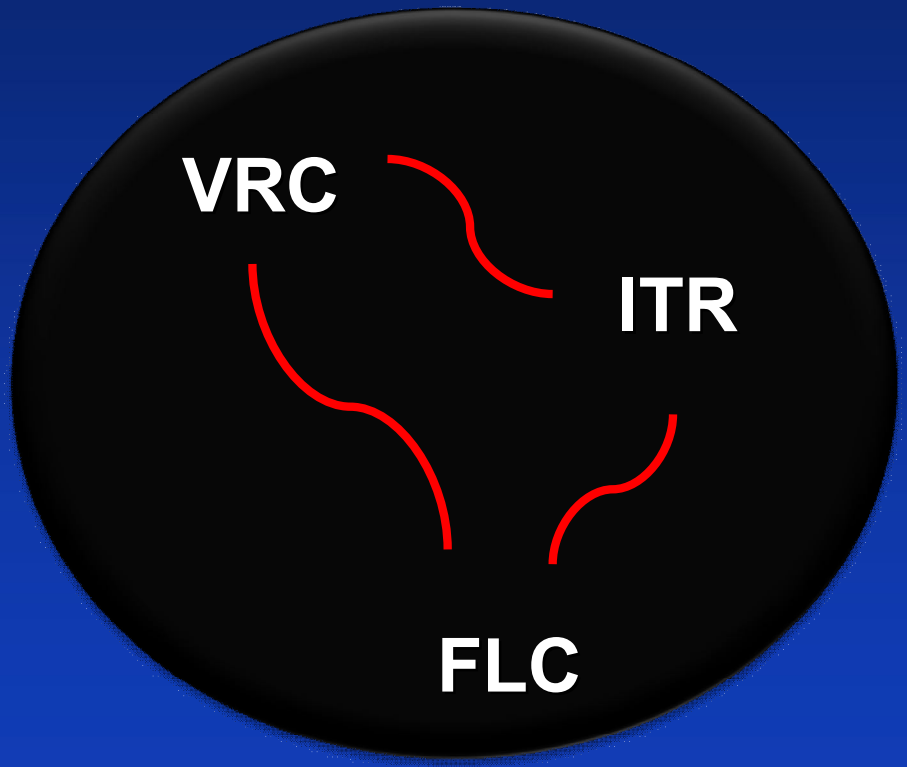
Fig. 2. Distribution of voriconazole, itraconazole, fluconazole and amphotericin B minimum inhibitory concentrations (MICs) for all isolates tested.

Maya Türlerine In Vitro Etkinlik

Johnson E, et al. Int J Antimicrob Agents 2008:32:511







Aspergillus ve *Rhizopus* türlerine Antifungallerin In vitro Etkisi

Arıkan S et al. Med Mycol 2008;46:567.

Table 1 MICs of posaconazole, voriconazole, itraconazole, and amphotericin B against clinical *Aspergillus* and *Rhizopus* isolates

Test isolates (number tested) Incubation time	Posaconazole CLSI microdilution		Posaconazole Etest		Voriconazole CLSI microdilution		Itraconazole CLSI microdilution		Amphotericin B CLSI microdilution	
	GM	Range	GM	Range	GM	Range	GM	Range	GM	Range
Aspergillus (Total, *n* =82)										
24 h	0.96	0.5–1	0.02	0.002–0.03	0.49	0.125–1	0.93	0.25–2	1.82	0.5–4
48h	1.01	0.5–2	0.02	0.0075–0.125	0.80	0.125–2	1.13	0.25–2	2.51	1–8
A. fumigatus (43)										
24 h	0.94	0.5–1	0.01	0.002–0.03	0.45	0.125–1	1	0.5–2	1.73	1–4
48 h	0.97	0.5–2	0.03	0.0075–0.125	0.72	0.125–2	1.21	0.5–2	2.39	2–8
A. flavus (29)										
24 h	1	1	0.02	0.0075–0.03	0.65	0.25–1	0.83	0.25–1	2.2	1–4
48 h	1.02	1–2	0.06	0.03–0.125	1	0.5–2	0.98	0.25–2	2.93	2–4
A. niger (7)										
24 h	0.91	0.5–1	0.01	0.002–0.03	0.30	0.125–0.5	0.91	0.5–2	1.21	0.5–2
48 h	1.22	1–2	0.07	0.06–0.125	0.67	0.25–1	1.35	0.5–2	1.81	1–2
A. terreus (2)										
24 h	–	1	–	0.0075–0.03	–	0.5	–	1	–	2
48 h	–	1	–	0.015–0.125	–	1	–	1	–	2–4
A. nidulans (1)										
24 h	–	1	–	0.03	–	0.125	–	1	–	2
48 h	–	1	–	0.125	–	0.25	–	1	–	2
R.oryzae (*n* =11)										
24 h	1.13	1–2	ND	ND	15.02	8 →8	2	2	2.57	2–4
48h	1.55	1–2	ND	ND	15.02	8 →8	3.75	2–8	3.53	2–8

GM, Geometric mean; ND, not determined.

EU-CAST Yöntemine Göre In Vitro Duyarlılık

Lass-Flörl C et al. AAC 2008;52:3637

TABLE 1. MFC ranges for the various antifungal agents against yeasts

Species	No. of isolates	MFC range (μg/ml)					
		AMB	l-AMB	CPF	ITC	VRC	POS
Candida species							
Candida albicans	59	2–4	0.5–2	0.15–1	0.06–8	0.06–8	0.12–8
Candida glabrata	18	0.5–8	0.5–4	0.15–4	4–>8	4–>8	4–>8
Candida parapsilosis	18	4–8	1–4	0.25–8	0.06–4	0.06–4	0.06–4
Candida krusei	19	0.5–8	1–8	2–8	0.5–8	0.5–8	0.5–2
Candida lusitaniae	9	4–8	1–4	4–8	0.25–2	0.06–8	0.06–1
Candida tropicalis	10	0.5–4	0.3–2	0.5–8	0.25–>8	0.12–8	0.12–>8
Candida guilliermondii	4	2–4	1–4	2–>8	2–8	0.25–0.5	0.25–0.5
Others							
Saccharomyces cerevisiae	3	4–>8	2–4	4–8	4–>8	4–>8	4–>8
Cryptococcus neoformans var. *neoformans*	10	1–2	0.25–1	>8	0.5–2	0.06–0.5	0.125–0.5
Cryptococcus neoformans var. *gattii*	3	1–2	0.5–1	>8	0.5–1	0.125–0.5	0.125–1
Trichosporon inkin	3	1–2	0.125–0.5	>8	0.25–0.5	0.03–0.5	0.5–1
Trichosporon asahii	4	4–8	0.15–2	>8	4–>8	>8	>8
Geotrichum candidum	4	4–>8	>8	>8	>8	4–>8	>8

EU-CAST Yöntemine Göre In Vitro Duyarlılık

Lass-Flörl C et al. AAC 2008;52:3637

TABLE 2. MFC ranges for the various antifungal agents against molds

Species	No. of isolates	MFC range (μg/ml)					
		AMB	l-AMB	CPF	ITC	VRC	POS
Aspergillus species							
Aspergillus fumigatus	29	0.5–4	0.5–8	>8	2–4	0.5–8	0.5–8
Aspergillus terreus	34	4–>8	1–>8	>8	0.5–4	1–4	0.5–2
Aspergillus flavus	21	4–>8	4–>8	>8	0.5–2	1–4	0.5–1
Aspergillus niger	13	4–>8	1–>8	>8	4–>8	2–4	1–2
Zygomycetes							
Rhizomucor species	17	1–4	0.5–2	>8	2–>8	>8	2–>8
Absidia corymbifera	4	1–2	0.5–2	>8	2–>8	>8	2–4
Absidia species	17	1–8	0.5–>8	>8	2–>8	>8	0.5–4
Rhizopus microsporus var. *oligosporus*	3	4–8	1–2	>8	>8	>8	>8
Rhizopus oryzae	6	4–8	>8	>8	>8	>8	2–8
Rhizopus species	12	2–8	0.5–>8	>8	4–>8	>8	2–>8
Mucor hiemalis	3	1–2	0.5–2	>8	>8	>8	2–4
Mucor species	11	1–2	0.125–2	>8	4–>8	>8	2–8
Cunninghamella species	4	8–>8	0.5–>8	>8	4–8	>8	2–4
Others							
Scedosporium prolificans	2	>8	>8	>8	>8	>8	>8
Scedosporium apiospermum	3	>8	>8	>8	4–>8	>8	1–2
Penicillium marneffei	2	4–>8	0.125–0.5	>8	0.25–1	>8	0.25–0.5
Penicillium species	2	4–>8	0.5–2	>8	2–>8	>8	0.5–2
Fusarium solani	2	>8	>8	>8	>8	>8	>8
Fusarium oxysporum	2	1–2	0.15–0.5	>8	0.25–4	>8	0.25–1
Sporothrix schenckii	2	8–>8	>8	>8	0.5–4	>8	0.5–1
Curvularia lunata	2	1–2	0.5–1	>8	0.5–1	>8	0.5–1
Bipolaris australiensis	2	1–2	0.125–0.5	>8	0.5–2	>8	0.125–0.5
Rhinocladiella aquaspersa	2	1–2	0.5–1	>8	0.5–1	>8	0.125–0.5

Table 1 Susceptibility trends for *Exophiala* spp.

Isolate (N)	Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Exophiala attenuata (3)			
Amphotericin B	4–16	ND	ND
Itraconazole	≤0.015	ND	ND
Posaconazole	≤0.015	ND	ND
Voriconazole	0.03–0.06	ND	ND
E. bergeri (6)			
Amphotericin B	0.125–0.25	0.125	ND
Itraconazole	≤0.015–0.25	0.125	ND
Posaconazole	≤0.015–0.03	0.03	ND
Voriconazole	<0.015–2.0	1.0	ND
E. dermatitidis (27)			
Amphotericin B	0.125–1	0.5	1.0
Itraconazole	≤0.015–0.5	0.5	0.5
Posaconazole	≤0.015–0.25	0.03	0.06
Voriconazole	0.06–1.0	0.125	0.25
Exophiala spp. (3)			
Amphotericin B	0.25–0.5	ND	ND
Itraconazole	0.03	ND	ND
Posaconazole	≤0.015	ND	ND
Voriconazole	0.03–0.25	ND	ND
E. jeanselmei (8)			
Amphotericin B	0.25–1.0	0.5	ND
Itraconazole	≤0.015–0.125	0.03	ND
Posaconazole	≤0.015–0.03	≤0.015	ND
Voriconazole	0.06–0.5	0.125	ND
E. lecanii-corni (9)			
Amphotericin B	0.25–0.5	0.25	ND
Itraconazole	≤0.015–0.25	0.06	ND
Posaconazole	≤0.015–0.03	≤0.015	ND
Voriconazole	≤0.015–1.0	0.125	ND
E. mesophila (6)			
Amphotericin B	0.25–0.5	0.25	ND
Itraconazole	0.03–2.0	0.125	ND
Posaconazole	≤0.015–0.06	0.06	ND
Voriconazole	0.06–2.0	0.5	ND
E. oligosperma (40)			
Amphotericin B	0.125–1.0	0.25	0.5
Itraconazole	≤0.015–0.25	0.125	0.25
Posaconazole	≤0.015–0.06	0.03	0.03
Voriconazole	≤0.015–4.0	0.5	2.0
E. phaeomuriformis (11)			
Amphotericin B	0.25–2.0	0.5	1.0
Itraconazole	≤0.015–0.06	≤0.015	0.03
Posaconazole	≤0.015	≤0.015	≤0.015
Voriconazole	≤0.015–0.03	0.03	0.06
E. spinifera (8)			
Amphotericin B	0.25–1.0	0.5	ND
Itraconazole	≤0.015–0.125	0.03	ND
Posaconazole	≤0.015–0.03	≤0.015	ND
Voriconazole	0.06–0.5	0.25	ND
E. xenobiotica (39)			
Amphotericin B	0.125–1.0	0.25	0.5
Itraconazole	≤0.015–1.0	0.03	0.125
Posaconazole	≤0.015–0.06	≤0.015	0.03
Voriconazole	≤0.015–2.0	0.125	1.0

ND, not determined due to insufficient numbers of isolates tested.

Exophialia türlerinin In Vitro Duyarlılığı

Fothergill AW, et al. Med Mycol 2008;47:41

160 izolat

Sadece ITR ve POS'de standart dozlarda elde edilebilen serum düzeyleri

ÖU 02/2009

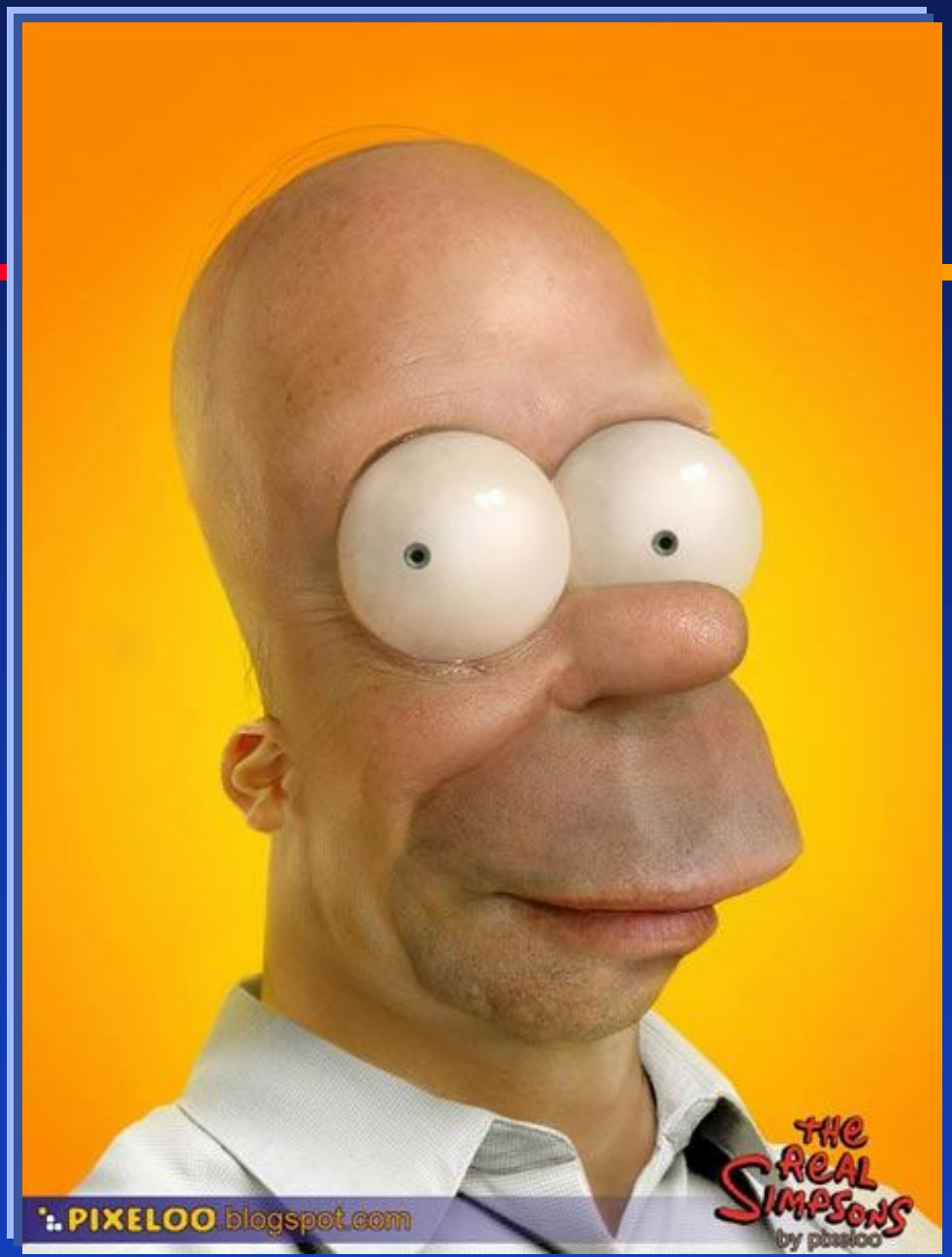
Küf Mantarlarında ITC - MCF Etkileşim

Ruiz-Cendoya M, et al. Int J Antimicrob Agents 2008;32:418

Table 1
In vitro interactions between itraconazole and micafungin against clinically important filamentous fungi

Species (no. of isolates)	MIC-2 (μg/mL)						Percentage of isolates showing the following interactions:		
	ITC		MFG		ITC/MFG				
	GM	Range	GM	Range	GM	Range	S	I	A
Pseudallescheria boydii (33)	0.64	0.125–8	44.7	1–64	0.31/3.57	0.06–2/0.06–64	21.2	78.8	0
Scedosporium prolificans (10)	8	8	64	64	5.65/51.9	1–8/16–64	10	90	0
Aspergillus flavus (10)	0.43	0.06–1	0.16	0.03–0.5	0.10/0.05	0.06–0.5/0.003–0.125	60	40	0
Aspergillus fumigatus (10)	0.37	0.25–1	0.09	0.06–0.25	0.08/0.02	0.06–0.25/0.007–0.03	80	20	0
Aspergillus niger (10)	0.61	0.5–1	0.14	0.06–0.25	0.30/0.08	0.06–1/0.07–0.25	20	80	0
Aspergillus terreus (10)	0.23	0.125–0.5	0.10	0.03–2	0.074/0.016	0.06–0.125/0.007–0.06	50	50	0
Fonsecaea spp. (10)	0.61	0.5–1	45.25	16–64	0.21/4.25	0.06–1/0.06–64	50	50	0
Paecilomyces lilacinus (10)	3.24	1–8	64	64	1.62/5.21	0.25–8/0.06–64	10	90	0
Sporothrix schenckii (10)	0.65	0.5–2	25.9	2–64	0.18/0.42	0.06–1/0.06–16	50	50	0
Fusarium solani (10)	8	8	64	64	8/64	8/64	0	100	0
Fusarium oxysporum (10)	8	8	64	64	8/64	8/64	0	100	0

MIC-2, the lowest drug concentration that produced 50% growth inhibition; ITC, itraconazole; MFG, micafungin; GM, geometric mean; S, synergism; I, indifference; A, antagonism.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THE REAL SIMPSONS
by pixeloo

Freeeman J, et al. 2007;60:907.

37 yaşında erkek hasta, lumbosakral vertebrada koksidiodomikozise bağlı osteomiyelit

Table 1. Plasma itraconazole and hydroxy-itraconazole levels

Formulation and dosage regimen	Day of regimen	Itraconazole level (μg/L)	Itraconazole and hydroxy-itraconazole level (μg/L)	CRP level (mg/L)
200 mg BD (capsules)	14	470	1340	—
	37	—	—	33
	473	75	220	—
	476	60	155	—
	486	78	174	—
	508	—	—	105
400 mg BD (capsules)	14	50	200	—
	16	—	—	109
	23	—	—	115
	26	27	47	—
	37	31	96	—
	39	52	177	—
200 mg BD (oral solution)	5	—	—	182
	23	830	2100	—
	36	1100	3150	12
	40	910	2870	—
	131	—	—	6
	161	970	2480	—
	265	1740	4290	—
	429	—	—	5.6

BD, twice daily.
Target serum concentrations: itraconazole, >250 μg/L; itraconazole and hydroxy-itraconazole, >1000 μg/L.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2004, p. 3151–3153 Vol. 48, No
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.8.3151–3153.2004

Pharmacokinetics of Intravenous Itraconazole in Stable Hemodialysis Patients

John F. Mohr,[1]* Kevin W. Finkel,[2] John H. Rex,[1]† Jose R. Rodriguez,[1]
Gerhard J. Leitz,[3] and Luis Ostrosky-Zeichner[1]

Division of Infectious Diseases and Center for the Study of Emerging and Re-emerging Pathogens[1]
and Department of Nephrology,[2] *University of Texas Health Science Center,*
Houston, Texas, and Ortho-Biotech Products L.P.,
Bridgewater, New Jersey[3]

Received 1 December 2003/Returned for modification 7 March 2004/Accepted 28 April 2004

The pharmacokinetics of intravenous itraconazole (ITC) was studied in dialysis patients. Dialysis had no effect on the half-life and clearance of ITC or OH-ITC. However, dialysis allowed the clearance of hydroxypropyl-β-cyclodextrin (HP-β-CD). The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) for HP-β-CD administered before dialysis was lower than the $AUC_{0-\infty}$ when it was administered after dialysis ($P < 0.01$). Administration of ITC intravenously just prior to hemodialysis appears to produce adequate systemic exposures of ITC and OH-ITC while allowing dialysis clearance of HP-β-CD. Studies of multiple administrations are warranted.

Greyfurt Suyu ile İTC Metabolizması Arasındaki Cinsiyete Bağlı Değişiklikler

Gubbins Po, Eur J Clin Pharmacol 2008;64:293.

Table 3 Summary of metabolite-to parent ratios for key pharmacokinetic variables in healthy females and males

OHITZ:ITZ ratio	Females (n=10)			Males (n=10)		
	Study Period[a]		p value (95% CI)	Study Period[a]		p value (95% CI)
	Water	GFJ		Water	GFJ	
C_{max} (ng/mL)						
Mean (±SD)	1.5 (0.27)	1.3 (0.26)	0.084 (−0.02–0.36)	1.3 (0.49)	1.2 (0.37)	0.41 (−0.12 to 0.27)
GM	1.5	1.3		1.2	1.2	
$AUC_{(0-48)}$ (mg·h/L)						
Mean (±SD)	2.8 (0.43)	2.6 (0.45)	0.048* (0.002–0.52)	2.5 (0.31)	2.4 (0.33)	0.14 (−0.07 to –0.44)
GM	2.8	2.5		2.5	2.3	
$AUC_{0-\infty}$ (mg·h/L)						
Mean (±SD)	2.5 (0.41)	2.2 (0.39)	0.047* (0.004–0.55)	2.2 (0.31)	2.0 (0.28)	0.15 (−0.08–0.47)
GM	2.4	2.1		2.2	2.0	

*GFJ vs. water is significant at $p \leq 0.05$

OHITZ, Hydroxyitraconazole; ITZ, itraconazole; GM, Geometric mean; 95% CI, 95% confidence interval

[a] All subjects were administered 200 mg itraconazole in an oral solution

Greyfurt Suyu ile İTC Metabolizması Arasındaki Cinsiyete Bağlı Değişiklikler

Gubbins Po, Eur J Clin Pharmacol 2008;64:293.

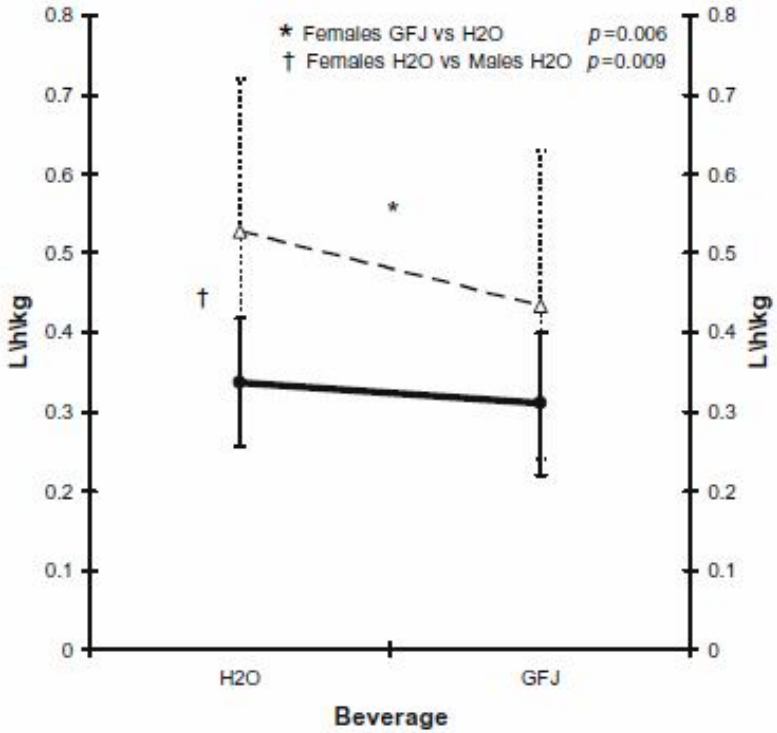
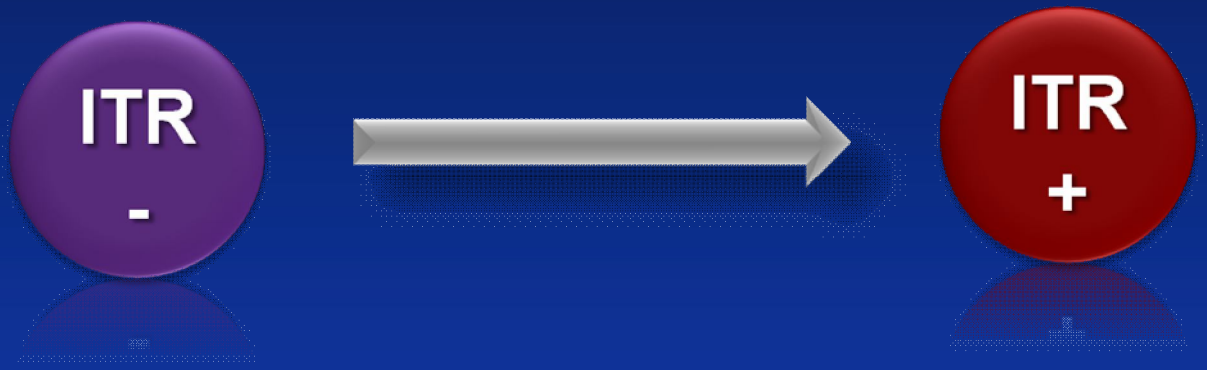


Fig. 1 Mean intra- and inter-sex changes in itraconazole weight-adjusted oral CL/F (apparent itraconazole oral clearance) following the administration of itraconazole with water or grapefruit juice. *Filled circles* Males, *open triangles* females, *error bars* standard deviation

Renal Transplant Alıcılarında Cyc-A ile ITR Arasındaki Farmakokinetik Etkileşim

Florea NR, et.al. Transpl Proc 2003;35:2873.



Siklosporin günlük dozunda %48 azalma

Günlük siklosporin maliyetinde yaklaşık 10 USD azalma

INTERNAL MEDICINE

□ CASE REPORT □

Itraconazole Oral Solution Enhanced Vincristine Neurotoxicity in Five Patients with Malignant Lymphoma

Naoto Takahashi[1], Yoshihiro Kameoka[1], Yasuo Yamanaka[1], Kumi Ubukawa[1], Kunie Saito[1], Masumi Fujishima[1], Naohito Fujishima[1], Hirofumi Saito[1], Makoto Hirokawa[1], Stuart A. Scott[2] and Kenichi Sawada[1]

Abstract

To prevent fungal infections in patients undergoing treatment for hematological malignancies, we investigated the use of oral itraconazole solution as opposed to itraconazole or fluconazole capsules. Herein, we report five lymphoma patients with severe vincristine neurotoxicity in strong association with oral itraconazole solution. Four patients suffered from severe myalgia with or without arthralgia which clinically resembled polymyalgia rheumatica. Two patients suffered from constipation due to subileus and one patient had a severe paralytic ileus. Appropriate management of the above symptoms, which included discontinuation of oral itraconazole solution, resulted in rapid recovery from neurotoxicity. Given the more consistent plasma concentrations of oral itraconazole solution when compared to itraconazole capsules and the ability of itraconazole to interfere with hepatic vincristine metabolism, we strongly recommend avoiding the combined administration of oral itraconazole solution and vincristine.

Key words: itoraconazol oral solution, vincristine, neurotoxicity, polymyalgia rheumatica

(Inter Med 47: 651-653, 2008)

Korunma

Hematolojik Maligniteli Nötropenik Hastalarda ITR Profilaksisi: Meta-Analiz

Glasmacher A, et al. J Clin Oncol 2003;21.4615.

13 çalışma

3597 hasta

Table 3. Characteristics of Included Studies: Antifungal Prophylaxis in Intervention and Control Arm

Study	Incidence* n/N	Incidence* %	Intervention Arm: Itraconazole	Control Arm
Vreugdenhil et al[12]	11/167	6.6	Capsules 400 mg/day PO plus amphotericin B 4,000 mg/day PO	Amphotericin B 4,000 mg/day PO
Nucci et al[17]	13/210	6.2	Capsules 200 mg/day PO	Placebo only
Annaloro et al[25]	5/59	8.5	Capsules 400 mg/day PO plus nystatin 4.5 MU/day	Fluconazole 300 mg/day PO plus nystatin 4.5 MU/day PO
Huijgens et al[18]	8/213	3.8	Capsules 200 mg/day PO plus intranasal amphotericin B 6 mg/day	Fluconazole capsules 100 mg/day PO plus intranasal amphotericin B 6 mg/day
Harousseau et al[13]	21/557	3.8	Oral solution 5 mg/kg body weight/day PO	Amphotericin B 2,000 mg/day PO
Menichetti et al[16]	12/405	3.0	Oral solution 5 mg/kg body weight/day PO plus nystatin 2.0 MU/day PO	Nystatin 2.0 MU/day PO
Morgenstern et al[14]	7/581	1.2	Oral solution 5 mg/kg body weight/day PO	Fluconazole 100 mg/day PO
Boogaerts et al[15]	14/277	5.1	Oral solution 200 mg/day PO	Amphotericin B 1,500 mg/day PO plus nystatin 8.0 MU/day PO
Winston et al[9]	23/138	16.7	Intravenous solution 400 mg day 1-2, 200 mg day 3-14, oral solution 400 mg day 15-100 (back to IV if necessary)	Fluconazole IV solution 400 mg day 1-14, oral 400 mg day 15-100 (back to IV if necessary)
Lass-Flörl et al[8]	4/115	3.5	Oral solution 10 mg/kg body weight/day PO	Amphotericin B 3,000 mg/day PO
Marr et al[10]	19/295	6.4	Oral solution 7.5 mg/kg body weight/day PO or 200 mg/day IV	Fluconazole 400 mg/day PO or IV
ITR-GER-23	9/494	1.8	Oral solution 5 mg/kg body weight/day PO	Fluconazole 400 mg/day PO
Kaptan et al[26]	4/97	4.1	Capsules 400 mg/day PO	No treatment

Abbreviations: n, number of events; N, number of patients or episodes; PO, orally; IV, intravenous.
*Incidence of proven invasive fungal infections in the complete study population.

Glasmacher, 2003

Kanıtlanmış Fungal İnfeksiyonlar

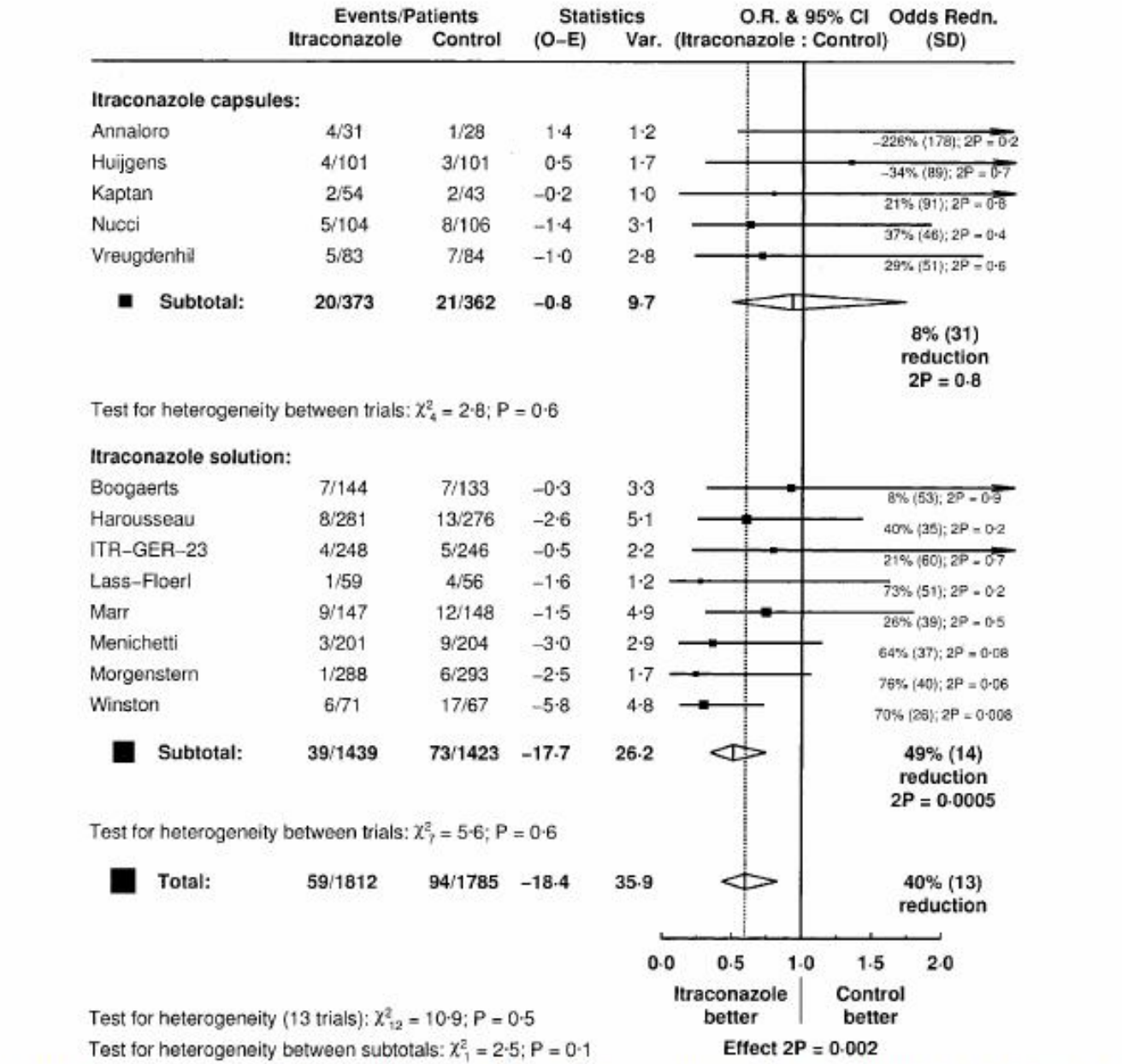
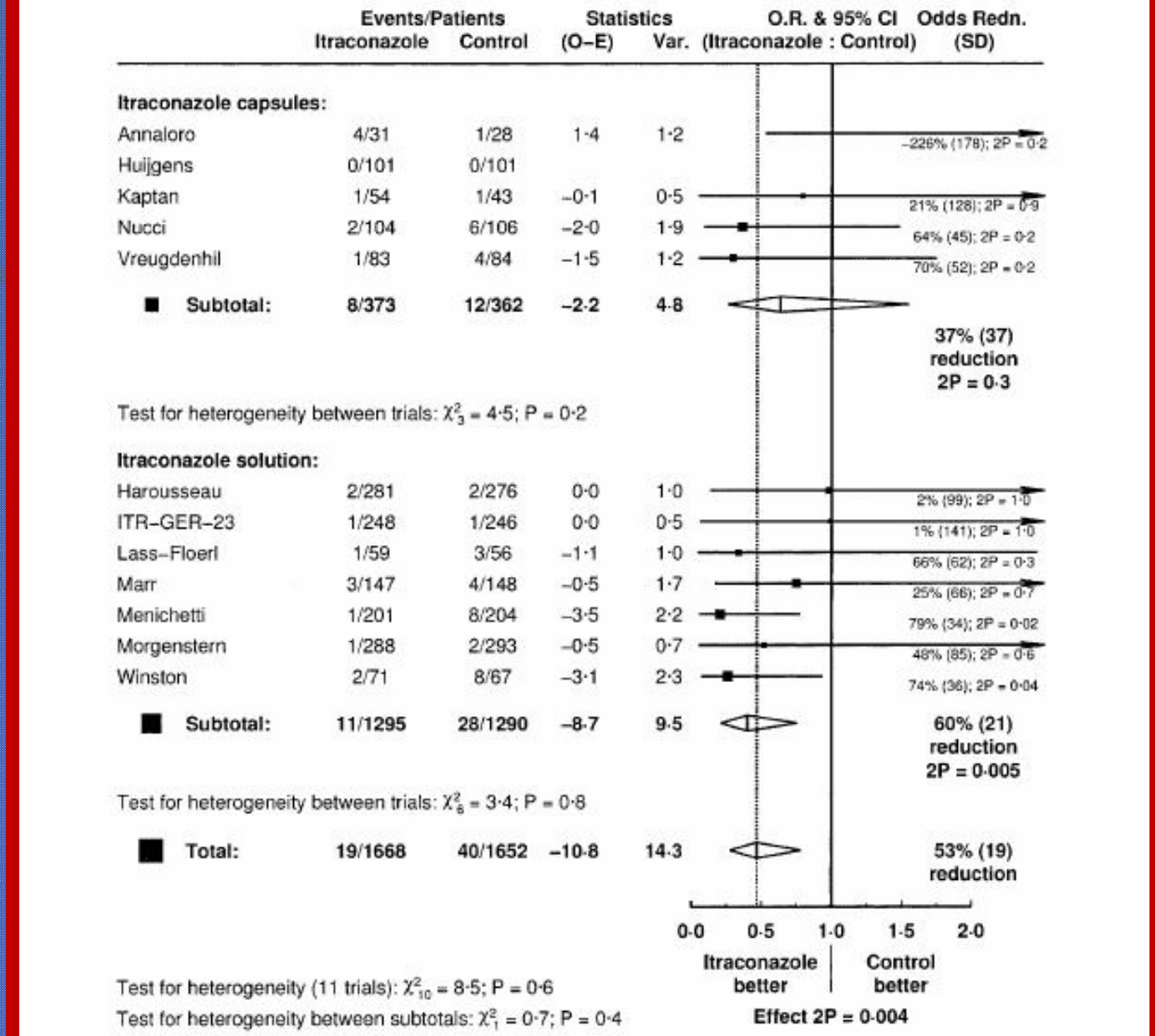


Fig 1. Incidence of proven invasive fungal infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

Glasmacher, 2003

Kanıtlanmış İnvaziv Maya İnfeksiyonları



	Events/Patients Itraconazole	Control	Statistics (O–E)	Var.	O.R. & 95% CI (Itraconazole : Control)	Odds Redn. (SD)
Itraconazole capsules:						
Annaloro	4/31	1/28	1·4	1·2		–226% (178); 2P = 0·2
Huijgens	0/101	0/101				
Kaptan	1/54	1/43	–0·1	0·5		21% (128); 2P = 0·9
Nucci	2/104	6/106	–2·0	1·9		64% (45); 2P = 0·2
Vreugdenhil	1/83	4/84	–1·5	1·2		70% (52); 2P = 0·2
Subtotal:	**8/373**	**12/362**	**–2·2**	**4·8**		**37% (37) reduction 2P = 0·3**
Test for heterogeneity between trials: $\chi^2_3 = 4{\cdot}5$; P = 0·2						
Itraconazole solution:						
Harousseau	2/281	2/276	0·0	1·0		2% (99); 2P = 1·0
ITR–GER–23	1/248	1/246	0·0	0·5		1% (141); 2P = 1·0
Lass–Floerl	1/59	3/56	–1·1	1·0		66% (62); 2P = 0·3
Marr	3/147	4/148	–0·5	1·7		25% (66); 2P = 0·7
Menichetti	1/201	8/204	–3·5	2·2		79% (34); 2P = 0·02
Morgenstern	1/288	2/293	–0·5	0·7		48% (85); 2P = 0·6
Winston	2/71	8/67	–3·1	2·3		74% (36); 2P = 0·04
Subtotal:	**11/1295**	**28/1290**	**–8·7**	**9·5**		**60% (21) reduction 2P = 0·005**
Test for heterogeneity between trials: $\chi^2_6 = 3{\cdot}4$; P = 0·8						
Total:	**19/1668**	**40/1652**	**–10·8**	**14·3**		**53% (19) reduction**
Test for heterogeneity (11 trials): $\chi^2_{10} = 8{\cdot}5$; P = 0·6						
Test for heterogeneity between subtotals: $\chi^2_1 = 0{\cdot}7$; P = 0·4						

0·0 0·5 1·0 1·5 2·0

Itraconazole better | Control better

Effect 2P = 0·004

Fig 2. Incidence of proven invasive yeast infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

Glasmacher, 2003

Kanıtlanmış IA İnfeksiyonları

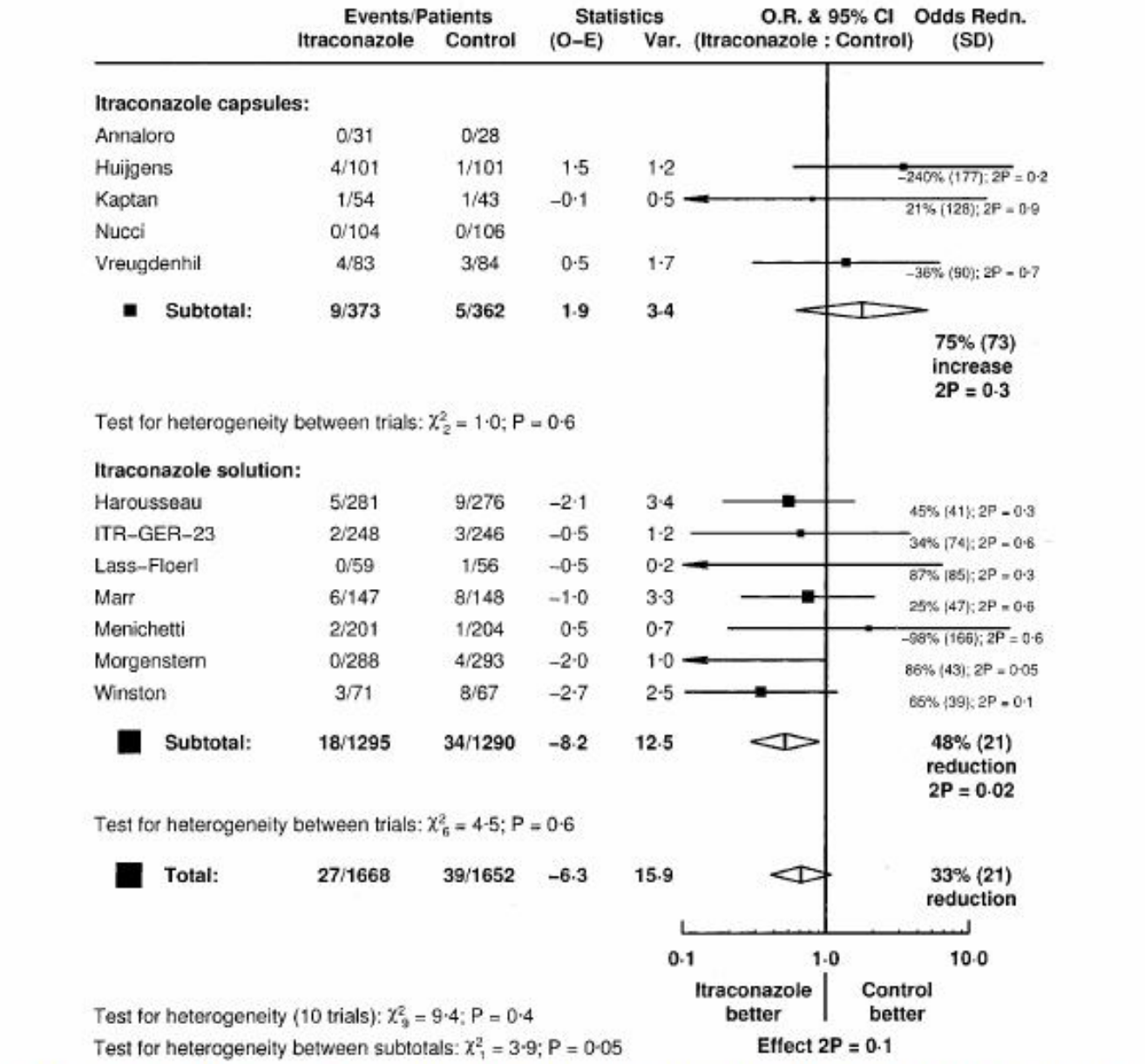


Fig 3. Incidence of proven invasive *Aspergillus* infections. OR, odds ratio; O-E, observed minus expected events; Var., variance of O-E; Odds Redn., odds reduction; SD, standard deviation.

Hematolojik Maligniteli Nötropenik Hastalarda ITR Profilaksisi: Meta-Analiz

Glasmacher A, et al. J Clin Oncol 2003;21.4615.

		Risk Azalması	P değeri
IFI riski		%40 ± %13	.002
İnvaziv maya infeksiyonu		%53 ± %19	.004
IFI mortalitesi		%35 ± %17	.04
IA infeksiyonu	Sol.	%48 ± %21	.02
	Kap.	%75 ± %73↑	.3

Hematolojik Maligniteli Hastalarda IV ITR vs. CSP Profilaksisi

Mattiuzzi GN, et al. AAC 2006;50:143

	ITR	CSP
	2 x 200 mg 2 gün 200 mg/gün iv	50 mg/gün iv
Randomize edilen	92	108
MITT	90	107

ÖU 02/2009

Hematolojik Maligniteli Hastalarda IV ITR vs. CSP Profilaksisi

Mattiuzzi GN, et al. AAC 2006;50:143

	ITR	CSP
Candida sp.	3 (1 CK, 2 CG)	1 (CP)
Trichosporon sp.		2
Aspergillus sp.	1 (AV)	2 (AF)
Fusarium		1
Mikst	1	1
TOPLAM	5	7

ÖU 02/2009

Hematolojik Maligniteli Hastalarda IV ITR vs. CSP Profilaksisi

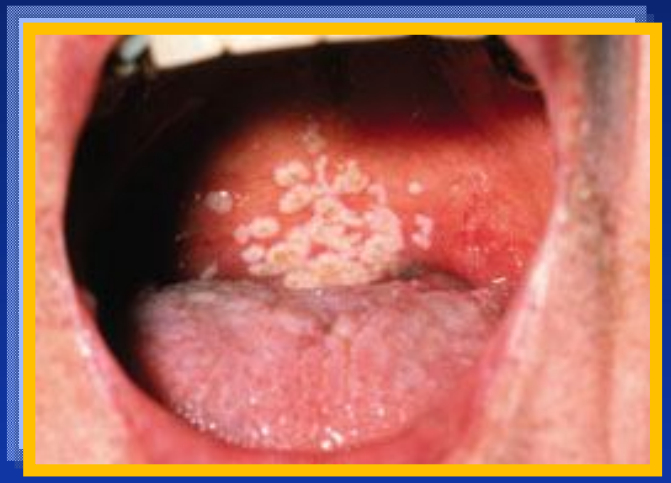
Mattiuzzi GN, et al. AAC 2006;50:143

MORTALİTE	ITR	CSP
İnfeksiyon-dışı	4	2
Sepsis	1	1
Dissemine Trichosporon+VRE		1
Aspergillus pnömonisi	1	2
Asper. Pnömonisi + kandidemi	1	
Curvularia pnömonisi		1

Tedavi

HIV(+) Hastalarda Orofaringeal Kandidiyaziste ITR Oral Solüsyon

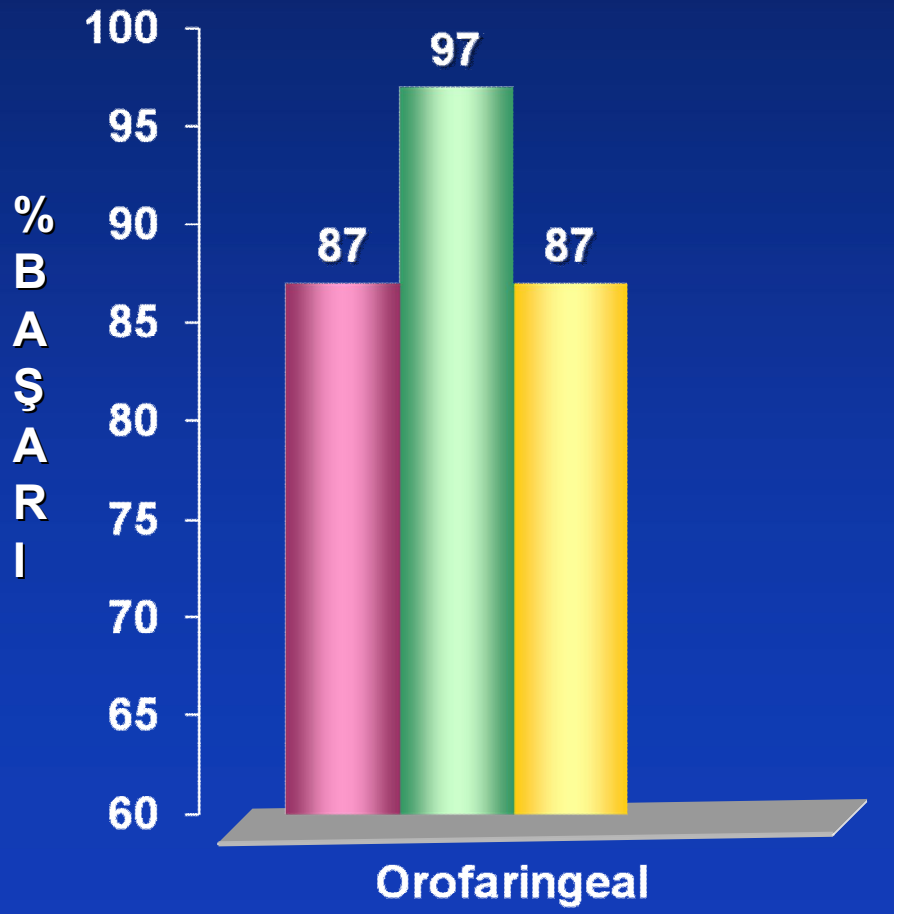
Graybill JR et al. Am J Med 1998;104:33



ITR, 200 mg/gün, 7 gün ,n=60

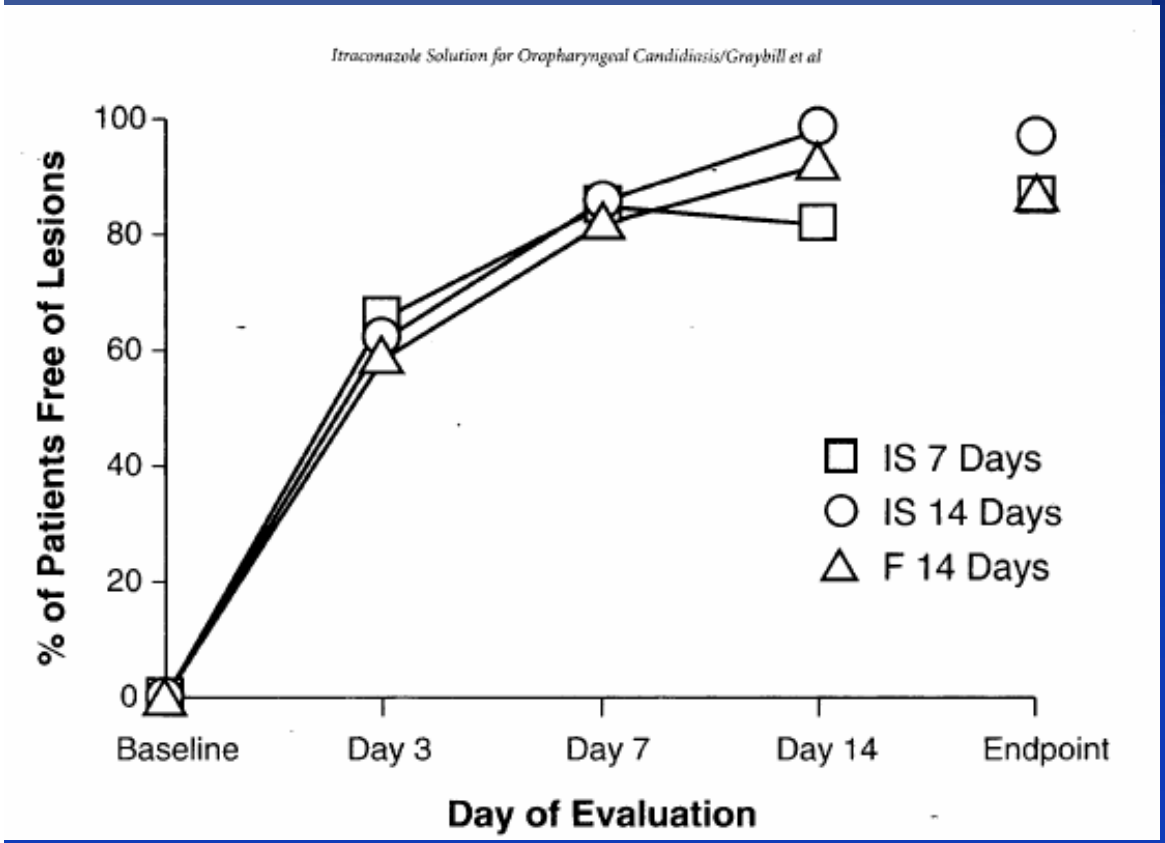
ITR, 200 mg/gün 14 gün, n=59

FLC 100 mg/gün, 14 gün n=60



HIV(+) Hastalarda Orofaringeal Kandidiyaziste ITR Oral Solüsyon

Graybill JR et al. Am J Med 1998;104:33



İstenmeyen Etkiler

Gastro-intestinal: %25 (3 kol)
Solunum :%14 (ITR), %21 (FLC)
Lab. değişikliği :yok

Empirik Tedavide ITR vs AmB-d

Booagerts M et al. Ann Intern Med 2001;135:412

ITR	AMB-d
192	192
2 x 200 mg 2 gün (iv) 200 mg/gün (iv/oral)	0.7-1.0 mg/kg/gün

Empirik Tedavide ITR vs AmB-d

Booagerts M et al. Ann Intern Med 2001;135:412

	ITR	AMB-d
yaş	46.5	50
AML	%56	%56
Relaps/refrakter	65	64
Oto-SCT	%35	%39
Çalışma öncesi np, med.gün	7	7
Çalışma sırası np, med.gün	10	8

Empirik Tedavide ITR vs AmB-d

Booagerts M et al. Ann Intern Med 2001;135:412

BAŞARISIZLIK:

- Tedavi sırasında İFİ
- 3 gün Rx sonrası herhangi bir nedene bağlı ölüm
- Nötropeniden çıkınca / 28. günde ateşin düşmemesi
- Araştırıcının empirik tedaviyi değiştirmesi
- İntolerans nedeniyle ilacın değiştirilmesi
- <10 gün tedavi alan ve tedavi kesildikten sonra en az 3 gün ateşsiz olmayan hastalar

DEĞERLENDİRME-DIŞI:

- <3 gün tedavi
- Ateş nedeni olan klinik / mikrobiyolojik dökümente bakteriyel infeksiyon

YANIT:

- ilk 2 gruba girmeyen hastalar
- 10 gün tedavi almış ve en az 2 gün ateşsiz kalmış hastalar

Empirik Tedavide ITR vs AmB-d

Booagerts M et al. Ann Intern Med 2001;135:412

Table 2. **Response to Empirical Antifungal Therapy**

Response	Itraconazole Group (*n* = 179)*	Amphotericin B Group (*n* = 181)*	Difference (95% CI)†
Overall, *n/n* (%)	84/179 (47)	68/181 (38)	9.0 (−0.8 to 19.5)
By sign/transplantation status, *n/n* (%)‡			
No signs, no transplantation	51/103 (49)	34/105 (32)	17.0 (−4.0 to 30.3)
No signs, transplantation	24/52 (46)	22/48 (46)	0 (−19.2 to 19.9)
Signs, no transplantation	4/14 (29)	6/18 (33)	−4.0 (−36.9 to 27.4)
Signs and transplantation	5/10 (50)	6/10 (60)	−10.0 (−53.4 to 33.4)
Defervescence, *n/n* (%)	131/179 (73)	127/181 (70)	3.0 (−6.3 to 12.3)
Median time to defervescence (range), *d*	7 (1–26)	6 (1–22)	
By previous antifungal prophylaxis, *n/n* (%)			
Yes	63/132 (48)	48/139 (35)	13.0 (1.6 to 24.8)
No	21/47 (45)	20/42 (48)	−3.0 (−23.7 to 17.8)
By duration of fever that did not respond to antibiotic therapy, *n/n* (%)			
<5 d	32/70 (46)	34/70 (49)	−3.0 (−19.4 to 13.7)
≥5 d	52/109 (45)	34/110 (31)	6.0 (4.0 to 29.5)
By duration of neutropenia, *n/n* (%)			
<7 d	27/60 (45)	23/58 (40)	5.0 (−12.5 to 23.1)
≥7 d	56/107 (52)	44/108 (41)	11.0 (−1.6 to 24.8)
Breakthrough fungal infections, *n*	5	5	
Candidemia	2§	2‖	
Filamentous fungal pneumonia	3¶	3**	

* Four patients (3 in the itraconazole group and 1 in the amphotericin B group) had no global evaluation.
† Differences are expressed as percentage points.
‡ Signs or symptoms of invasive fungal infection were cough, dyspnea, chest pain, increased respiratory rate, headaches, or confusion. Transplantation was hematopoietic stem-cell transplantation.
§ *Candida krusei* in 1 patient and *C. guillermondii* in 1 patient.
‖ *Candida albicans.*
¶ *Aspergillus fumigatus* in 1 patient, *A. sydowi* in 1 patient, and *Geotrichum capitatum* in 1 patient.
** *Aspergillus fumigatus.*

Empirik Tedavide ITR vs AmB-d

Booagerts M et al. Ann Intern Med 2001;135:412

Klinik İstenmeyen Etki	ITC,%	AmB-d,%
Ateş	6	10
Kusma	24	23
Titreme	10	40
Nefes darlığı	9	11
Hipotansiyon	7	11

Empirik Tedavide ITR vs AmB-d

Booagerts M et al. Ann Intern Med 2001;135:412

Laboratuvar değerleri	ITC,%	AmB-d,%
Nefrotoksisite	5	24*
Hipokalemi	18	31*
Hipomagnezemi	7	9
Bilirubinemi	10*	5
ALT ↑	3	2
AST	2	1
GGT ↑	2	2

ÖU 02/2009

ONKOLOGIE

Original Article · Originalarbeit

Onkologie 2007;30:185–191
DOI: 10.1159/000100055

Published online: March 19, 2007

Safety and Efficacy of Itraconazole Compared to Amphotericin B as Empirical Antifungal Therapy for Neutropenic Fever in Patients with Haematological Malignancy*

Ulrich Schuler[a] Susanne Bammer[b] Walter E. Aulitzky[c] Claudia Binder[d] Angelika Böhme[e]
Gerlinde Egerer[f] Michael Sandherr[g] Rainer Schwerdtfeger[h] Gerda Silling[i] Hannes Wandt[j]
Axel Glasmacher[k] Gerhard Ehninger[a]

Empirik Tedavide ITR vs AmB-d

Schuler U et al. Onkologie 2007;30:185

ITR	AMB-d
81	81
2 x 200 mg 2 gün (iv) 200 mg/gün (iv/oral)	0.7-1.0 mg/kg/gün

Empirik Tedavide ITR vs AmB-d

Schuler U et al. Onkologie 2007;30:185

	ITR	AMB-d
yaş	55	50
AML	52	53
KT	30	28
Allo-SCT	15	16
Oto-SCT	2.5	2.5
PBSCT	23.5	23.5
Akciğerde infiltrat	27	41

Empirik Tedavide ITR vs AmB-d: Değerlendirme Kriterleri

Schuler U et al. Onkologie 2007;30:185

BAŞARISIZLIK:

- İFİ ile uyumlu CT
- İFİ sonucu ölüm
- 28. gün ateş devam
- İFİ'a bağlı olduğu düşünülen belirti ve bulgularda kötüleşme
- Araştırıcının empirik tedaviyi değiştirmesi
- İntolerans nedeniyle ilacın değiştirilmesi

DEĞERLENDİRME-DIŞI:

- İntolerans dışı nedenlerle <3 gün tedavi
- İFİye bağlı olmayan ölüm
- Ateş nedeni olan klinik / mikrobiyolojik dökümente bakteriyel infeksiyon

YANIT:

- ilk 2 gruba girmeyen hastalar
- 10 gün tedavi almış ve en az 2 gün ateşsiz kalmış hastalar

Empirik Tedavide ITR vs AmB-d: Sonuçlar

Schuler U et al. Onkologie 2007;30:185

	Itracona-zole	Amphoteri-cin B	P value
Discontinued treatment due to any adverse event, %	22.2	56.8	< 0.0001
Average treatment period, days	14.5	9.3	< 0.0001
Response rate, %	61.7	42	< 0.0001
Success rate, %	70.4	49.3	< 0.0001
Composite endpoint (according to Walsh [5]), %	55.1	26.6	0.0002
Fungal infections			
Baseline	4	2	n.s.
Breakthrough[a]	6	6	n.s.

[a]1 in each group based on CT scans only.
n.s. = Not significant.

Empirik Tedavide ITR vs AmB-d

Schuler U et al. Onkologie 2007;30:185

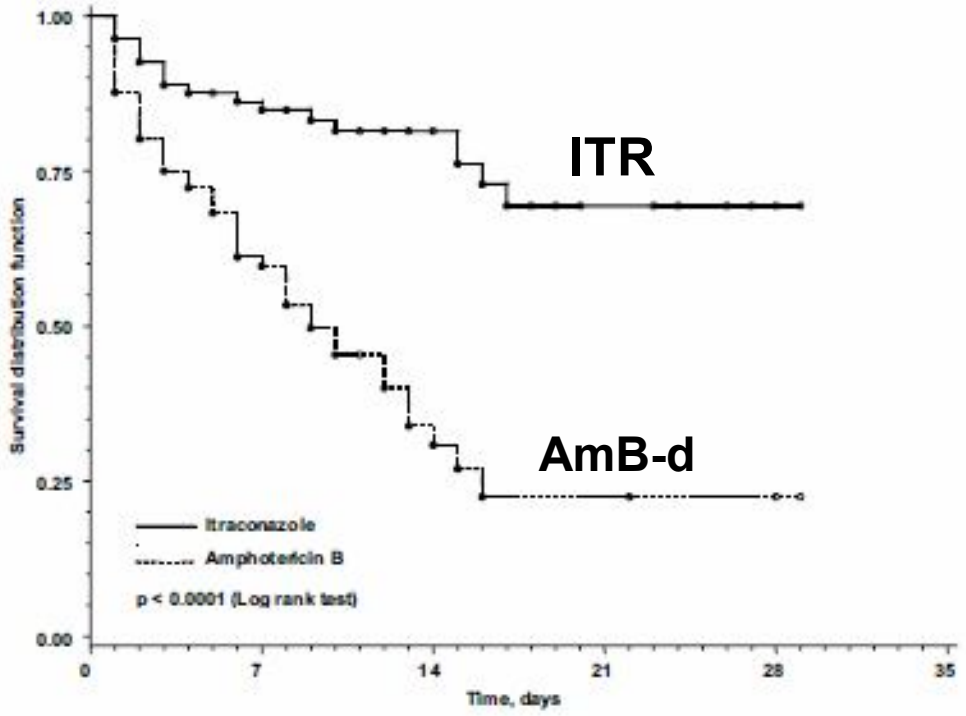


Fig. 1. Time to permanent discontinuation of itraconazole or amphotericin B treatment due to any adverse event for the safety population (n = 162). For patients whose treatment did not discontinue due to adverse events, time until discontinuation was censored at their last time point (ρ At least 1 discontinuation; φ censored only).

Empirik Tedavide ITR vs AmB-d

Schuler U et al. Onkologie 2007;30:185

Klinik İstenmeyen Etki	ITC,%	AmB-d,%
Ateş	8.6	16
Kusma	14.8	8.6
Titreme	1.2	19.8
Diyare	13.6	6.2
Deri Dökünütüsü	4.9	9.9
Nefes darlığı	9.9	4.9
Ajitasyon	6.2	6.2

Empirik Tedavide ITR vs AmB-d

Schuler U et al. Onkologie 2007;30:185

Laboratuvar değerleri	ITC,%	AmB-d,%
Serum kreatinin ↑	1.2	35.8
Hipokalemi	6.2	34.0
Bilirubinemi	8.6	21.1
LDH ↑	8.6	17.8
GGT ↑	3.7	16.2
BUN ↑	2.5	14.6

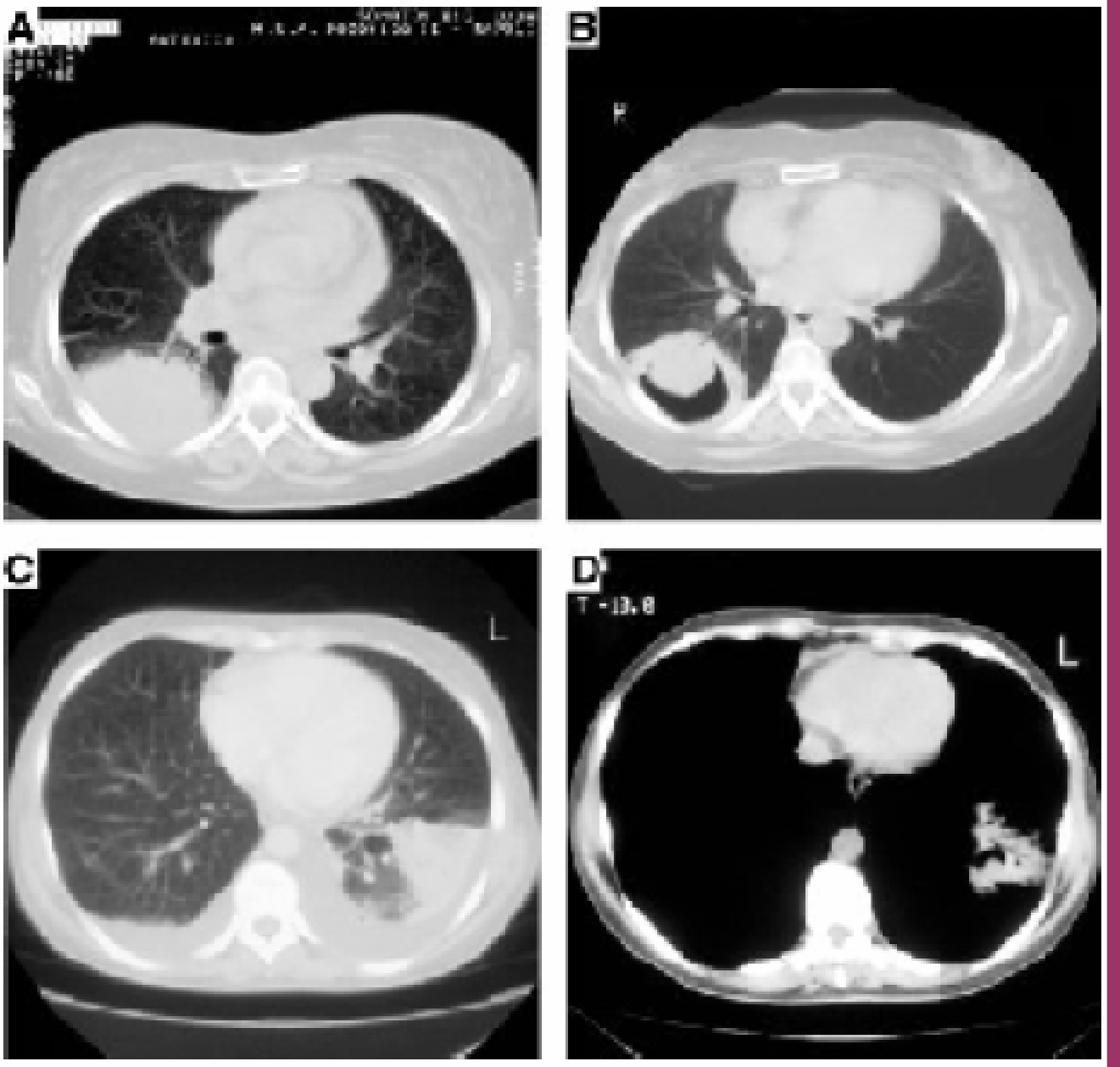
M. Picardi et al.

Intravenous itraconazole for treating invasive pulmonary aspergillosis in neutropenic patients with acute lymphoblastic leukemia

Aspergillus infection is associated with a high mortality rate in immunocompromised hosts; more effective drugs for this infection are needed. Oral itraconazole has been studied in neutropenic fungus-infected patients. Using a novel formulation (intravenous) of itraconazole, we successfully treated severe necrotizing pneumonias due to Aspergillus species occurring during a post-chemotherapy prolonged aplastic phase in two patients with acute lymphoblastic leukemia.

Haematologica 2007; 88:(1)e8-e9

Picardi et al, 2007



Improvement with long-term itraconazole therapy for *Fonsecaea pedrosoi*-related mediastinal phaeohyphomycosis

To the Editors:

In the September 2006 issue of the *European Respiratory Journal*, we reported the first culture-proven case of mediastinal mass due to *Fonsecaea pedrosoi* that had been successfully managed medically [1]. Maintenance therapy with oral itraconazole 100 mg *b.i.d.* was continued for a total of 3 yrs. This decision was taken in view of the rarity of the disease, paucity of data on the management of such cases and good clinico-radiological response to 6 months of therapy with this antifungal agent.

During this time period, the patient continued to experience clinical improvement, in the form of complete resolution of the dyspnoea and dysphagia that had mandated tracheostomy and feeding jejunostomy, respectively, at the time of initial presentation. Hoarseness of voice had also improved significantly with speech therapy. The patient is now able to carry out all activities of daily living and has restarted his professional work. The patient was assessed with repeat computed tomography (CT) scans of the thorax at 1-yr intervals. A significant regression in the size of the mediastinal mass was also observed on CT (fig. 1). In view of the patient's clinical and radiological stability, itraconazole treatment has now been stopped and a close follow-up planned.

The authors' aim behind this communication is only to stress the fact that long-term itraconazole therapy may help to achieve sustained improvement followed by stability in both clinical symptoms and radiological lesions of patients with this rare entity.

ITC'de Dikkate Alınması Gereken Noktalar

- İlaç etkileşimleri
  - maligniteler (vinkristin, siklofosfamid)
  - transplant alıcıları (siklosporin, takrolimus)
  - HIV(+) hastalar (ritonavir, indinavir)
- Etki spektrumu
  - *Fusarium*, *Zygomycetes*, *Scedosporium* sp.
- Diğer azollerle çapraz direnç (Erg 11 gen mutasyonu)

Tedavi Maliyeti

Renilt Van Gool, Drugs 2001;61(suppl.1):49.

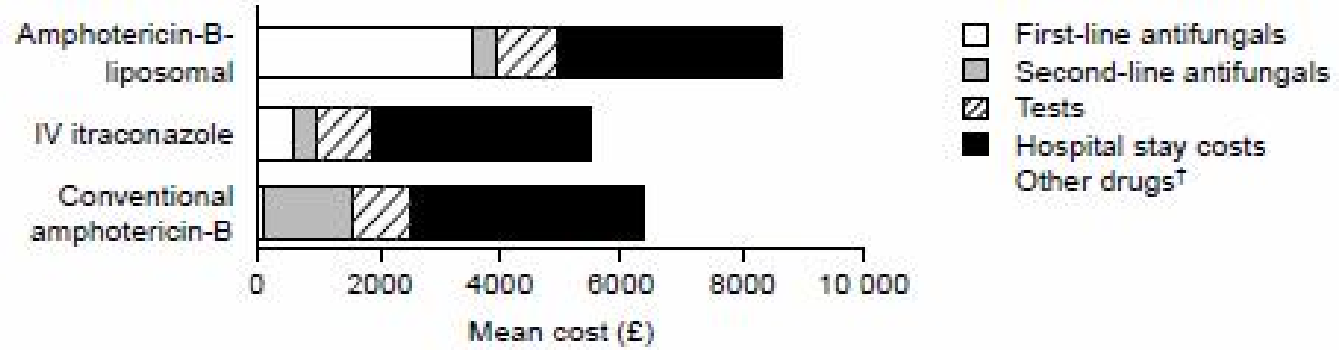


Fig. 1. Average costs per patient (neutropenic patients and bone marrow transplant recipients) of empirical treatment with conventional amphotericin-B, amphotericin-B-liposomal and intravenous (IV) itraconazole. Although not obvious from the figure, length of stay and test costs with conventional amphotericin-B are increased.

† Costs for 'Other drugs' associated with these treatments were as follows: £17 (conventional amphotericin-B); £13 (IV itraconazole); and £14 (amphotericin-B-liposomal).

PIN19

Pharmacoeconomic Evaluation of Parenteral Itraconazole Use in the Empirical Antifungal Treatment of Febrile Neutropenia in Turkey

Kanbur B, Sarioz F, Tatar F

Janssen-Cilag, Istanbul, Turkey

Table 1. *Probabilities of discontinuation of and response to treatment*

	Itraconazole	Amphotericin-B
Probability of stopping the treatment	19%	38%
Probability of continuing the treatment	81%	62%
Continue - ; response +	57%	57%
Continue - ; response -	43%	43%
Continue + ; response +	59%	63%
Continue + ; response -	41%	37%

Table 2. *Resource utilization*

Question	Daily dose
Itraconazole	400 mg/day for first 2 days, 200 mg/day for maintenance
Amphotericin-B	0.7 mg/kg/day
Amphotericin-B (liposomal)	3 mg/kg/day
N-Acetylcysteine (IV)	1200 mg/day
Teophilin (IV)	6 mg/kg/day
Proven treatment duration	20 days
Unproven treatment duration	10 days
Treatment duration in nonresponding cases	10 days

PIN19

Pharmacoeconomic Evaluation of Parenteral Itraconazole Use in the Empirical Antifungal Treatment of Febrile Neutropenia in Turkey

Kanbur B, Sarioz F, Tatar F

Janssen-Cilag, Istanbul, Turkey

Table 3. *Unit costs*

Cost item	Unit	Cost (€)
Itraconazole	1 mg	0.44
Amphotericin-B	1 mg	0.16
Amphotericin-B (liposomal)	1 mg	3.14
N-Acetylcysteine (IV)	1 mg	0.0018
Teophilin (IV)	1 mg	0.0056

Table 4. *Results-Cost-effectiveness analysis*

Treatment	Cost (€)	IC (€)	Effectiveness (clinical response)	IE (clinical response)	ICER (€/clinical response)
Itraconazole	2.460		0.59		
Amphotericin B	2.773	313	0.61	0.02	14.898

PIN18

Analysis of Cost-Effectiveness of Itraconazole in the Treatment of Invasive Aspergillusis in Turkey

Kanbur B, Sarioz F, Tatar F
Janssen-Cilag, Istanbul, Turkey

Table 1. *Discontinuation and response rates to treatment*

Reference	Parameter	Itraconazole	Voriconazole	Amphotericin B
(7, 15)	Response rate*	42.9%	52.8%	19.0%
(7, 10, 16)	Rate of discontinuation of treatment at day 3	2.8%	2.8%	19.5%
	Rate of discontinuation of treatment at day 16	25.4%	26.4%	67.3%
	Discontinuation due to toxicity at day 16	5.1%	0%	38.3%
	Discontinuation due to other causes at day 16	20.3%	26.4%	29.0%

*Since the response rates were evaluated at week 14 treatment period in the study by Caillot et al. (15), this rate was adjusted to week 12 with the assumption that the response rates were exponentially distributed.

Table 2. *Resource utilization and unit costs*

Medication	Daily dosage*	Price (per mg)	Daily cost
Itraconazole	400 mg/day IV for 2 days 200 mg/day IV for 14 days 400 mg/day PO for 50 days	€0.44 (IV) €0.01 (PO)	€88.23 €4.17
Voriconazole	12 mg/kg on the first day 8 mg/kg IV for 14 days 400 mg/day PO for 50 days	€0.71 (IV) €0.20 (PO)	€398.31 €78.01
Amphotericin B	1 mg/kg/day for 21 days	€0.16	€11.55
Liposomal amphotericin B	3 mg/kg/day	€3.14	€671.91
N-Acetylcysteine (IV)	1200 mg/day	€0.0018	2.25
Teophilin (IV)	6 mg/kg/day	€0.0056	2.25

*Calculation of dosages is based on the assumption that the average body weight is 70 kg. IV: intravenous; PO: per oral

PIN18

Analysis of Cost-Effectiveness of Itraconazole in the Treatment of Invasive Aspergillusis in Turkey

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Table 3. *Results - Cost-effectiveness analysis*

	Itraconazole	Voriconazole	Amphotericin B
Response rate	40.0%	47.0%	32.0%
Incremental response rate	Reference*	7.0%	-8.0%
Total cost	€2,555	€8,903	€3,786
Incremental cost	Reference*	€6,348	€1,230
ICER (Δ€/Δresponse rate)	Reference*	€91,042	Dominated
NNT	2.50	2.13	3.13
Cost per one responder	€6,388	€18,964	€11,850

* Itraconazole is the reference category for incremental figures, ICER: incremental cost-effectiveness ratio

Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America

Thomas J. Walsh,[1,a] Elias J. Anaissie,[2] David W. Denning,[13] Raoul Herbrecht,[14] Dimitrios P. Kontoyiannis,[3] Kieren A. Marr,[5] Vicki A. Morrison,[6,7] Brahm H Segal,[8] William J. Steinbach,[9] David A. Stevens,[10,11] Jo-Anne van Burik,[7] John R. Wingard,[12] and Thomas F. Patterson[4,a]

[1]Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland; [2]University of Arkansas for Medical Sciences, Little Rock; [3]The University of Texas M. D. Anderson Cancer Center, Houston, and [4]The University of Texas Health Science Center at San Antonio, San Antonio; [5]Oregon Health and Sciences University, Portland; [6]Veterans Affairs Medical Center and [7]University of Minnesota, Minneapolis, Minnesota; [8]Roswell Park Cancer Institute, Buffalo, New York; [9]Duke University Medical Center, Durham, North Carolina; [10]Santa Clara Valley Medical Center, San Jose, and [11]Stanford University, Palo Alto, California; [12]University of Florida, College of Medicine, Gainesville, Florida; [13]University of Manchester, Manchester, United Kingdom; and [14]University Hospital of Strasbourg, Strasbourg, France

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Condition	Therapy[a]		Comments
	Primary	Alternative[b]	
Invasive pulmonary aspergillosis	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), caspofungin (70 mg day 1 IV and 50 mg/day IV thereafter), micafungin (IV 100–150 mg/day; dose not established[c]), posaconazole (200 mg QID initially, then 400 mg BID PO after stabilization of disease[d]), itraconazole (dosage depends upon formulation)[e]	Primary combination therapy is not routinely recommended based on lack of clinical data; addition of another agent or switch to another drug class for salvage therapy may be considered in individual patients; dosage in pediatric patients for voriconazole is 5–7 mg/kg IV every 12 h and for caspofungin is 50 mg/m^2/day; limited clinical experience is reported with anidulafungin; dosage of posaconazole in pediatric patients has not been defined; indi-

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- Bir çok hastada IA primer tedavisinde Vorikonazol önerilir (A-I).
- Bazı hastalarda alternatif primer tedavi olarak lipozomal AmB düşünülebilir (A-I).
- Kurtarma tedavisinde AMB lipid formülasyonları (A-II), posakonazol (B-II), itrakonazol (B-II), kaspofungin (B-II) veya mikafungin (B-II) kullanılabilir.
- Bir ilaca refrakter ise başka sınıf ilaca geçilmesi veya kombinasyon tedavisi düşünülebilir.