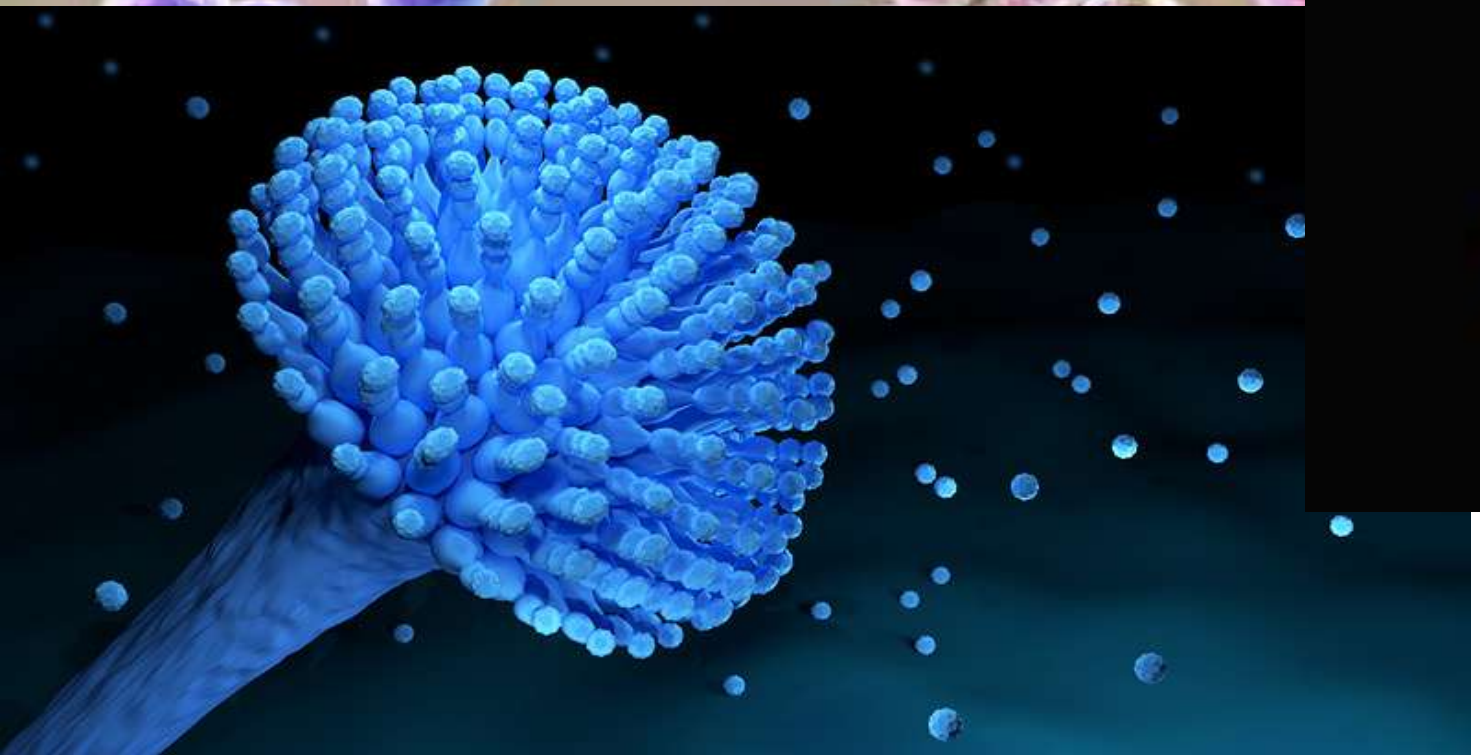
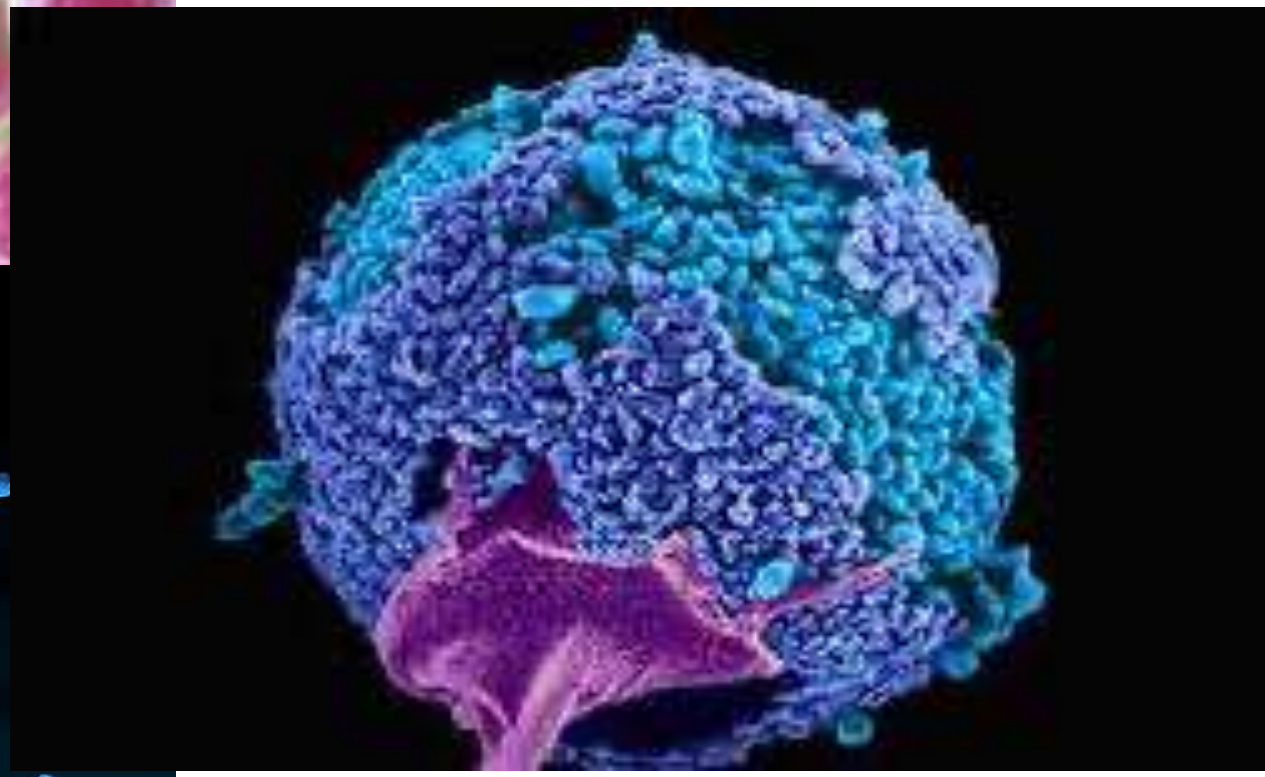
Posakonazol: İnvaziv fungal hastalık yönetimindeki yeri

Dr. Ömrüm Uzun

Hacettepe Üniversitesi Tıp Fakültesi

Düşman

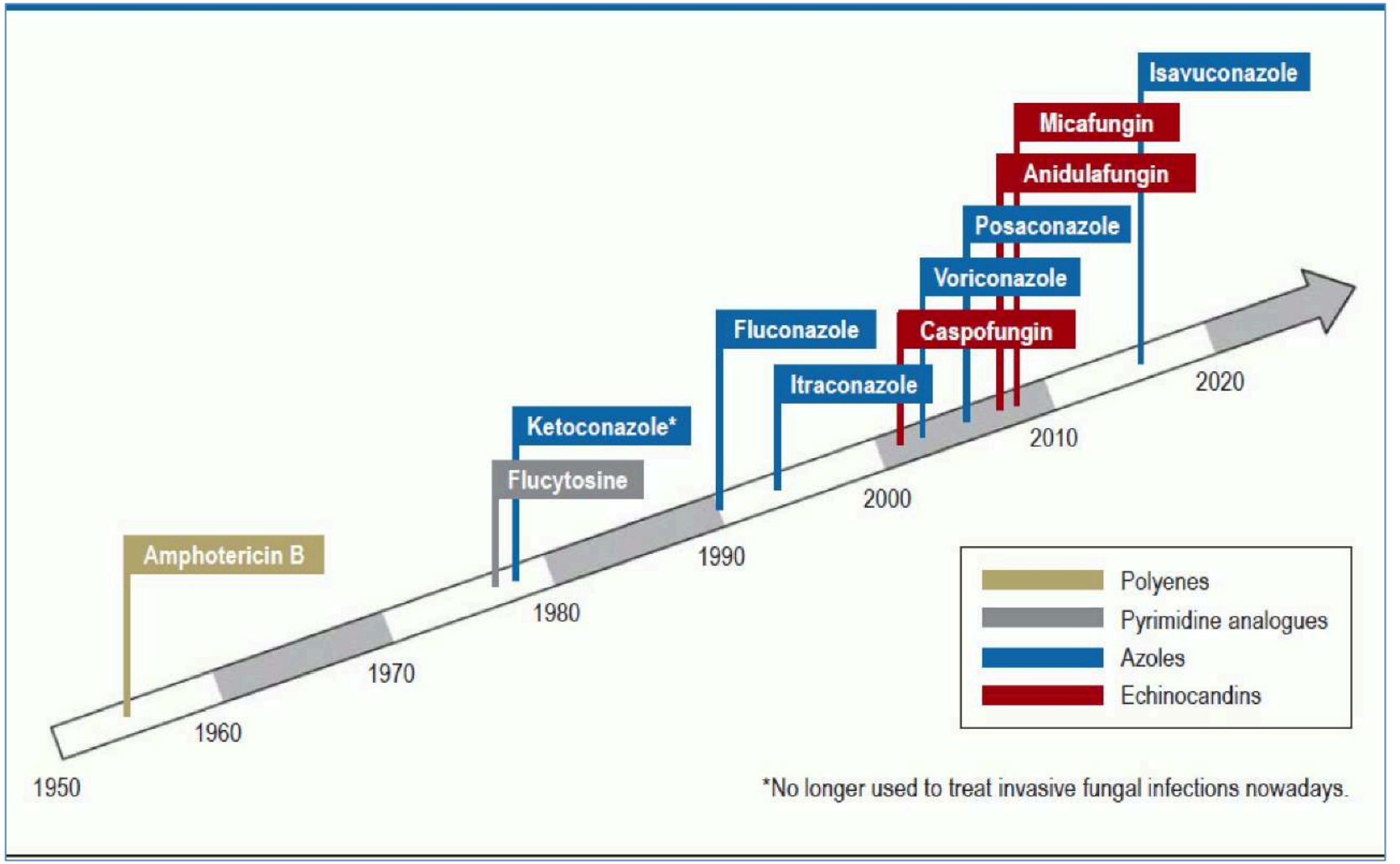




öu

Silahlar

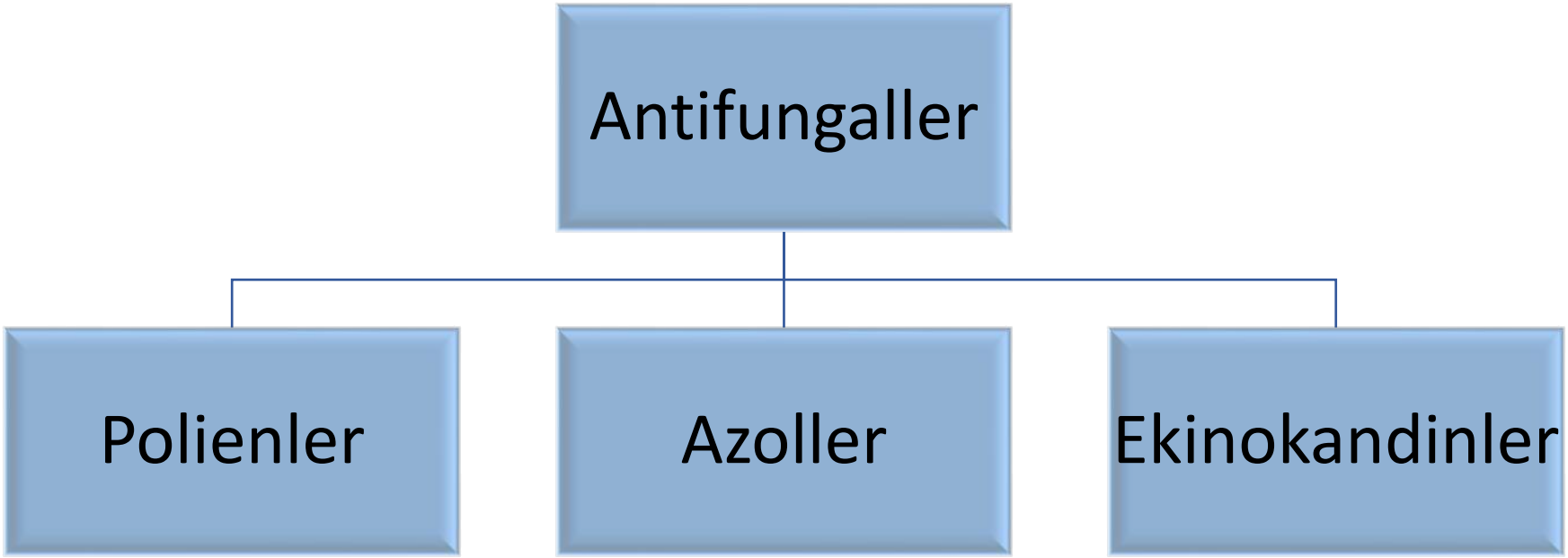
Antifungaller



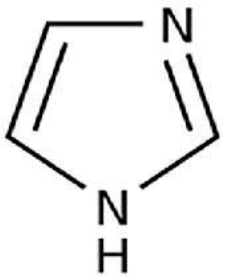
https://www.aerzteblatt.de/int/archive/article/206820

ÖU

Pratikte Genel Bakış

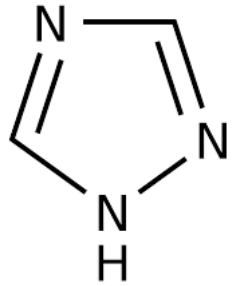


Azoller



İmidazol grubu

- Klotrimazol
- Mikonazol
- Ketokonazol



Triazol grubu

- Flukonazol
- İtrakonazol
- Vorikonazol
- Posakonazol
- İsavukonazol

İdeal Antifungal

- Etki spektrumu geniş
- İlgili hasta grubunda etkinliği kanıtlanmış (ör. nötropenik)
- İlgili İFH'a etkisi kanıtlanmış
- Güvenli
- Günde tek doz kullanımı mümkün
- İV ve oral formülasyonu mevcut
- Oral formunun biyoyararlanımı yüksek
- Dokulara dağılımı iyi
- İlaç etkileşimleri minimal
- Direnç gelişme potansiyeli minimal
- Maliyet-etkin

Sistemik Antifungallerin Etki Spektrumu

Spectrum of activity for systemic antifungal agents

	AMB	5FC	FLU	ITR	VOR	POS	ISA	CAS	MICA	ANI
Candida albicans	++	++	++	++	++	++	++	++	++	++
Candida glabrata	++	++	+	+	++	++	++	+	+	+
Candida parapsilosis	++	++	++	++	++	++	++	++	++	++
Candida tropicalis	++	++	++	++	++	++	++	++	++	++
Candida krusei	++	+	–	+	++	++	++	++	++	++
Candida lusitaniae	–	++	++	++	++	++	++	++	++	++
Aspergillus fumigatus	++	–	–	+	++	++	++	+	+	+
Cryptococcus neoformans	++	++	++	++	++	++	++	–	–	–
Mucorales	++	–	–	–	–	++	++	–	–	–
Fusarium spp	+	–	–	+	++	++	++	–	–	–
Scedosporium spp	+	–	–	+	+	+	+	–	–	–
Blastomyces dermatitidis	++	–	+	++	++	++	++	–	–	–
Coccidioides immitis	++	–	++	++	++	++	++	–	–	–
Histoplasma capsulatum	++	–	+	++	++	++	++	–	–	–

Abbreviations: 5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MICA, micafungin; POS, posaconazole; VOR, voriconazole.

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Candida tropicalis	++	++	++	++	++	++	++	++	++	++
Candida krusei	++	+	–	+	++	++	++	++	++	++
Candida lusitaniae	–	++	++	++	++	++	++	++	++	++
Aspergillus fumigatus	++	–	–	+	++	++	++	+	+	+
Cryptococcus neoformans	++	++	++	++	++	++	++	–	–	–
Mucorales	++	–	–	–	–	++	++	–	–	–
Fusarium spp	+	–	–	+	++	++	++	–	–	–
Scedosporium spp	+	–	–	+	+	+	+	–	–	–

Abbreviations: 5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MICA, micafungin; POS, posaconazole; VOR, voriconazole.

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Candida albicans	++	++	++	++	++	++	++	++	++	++
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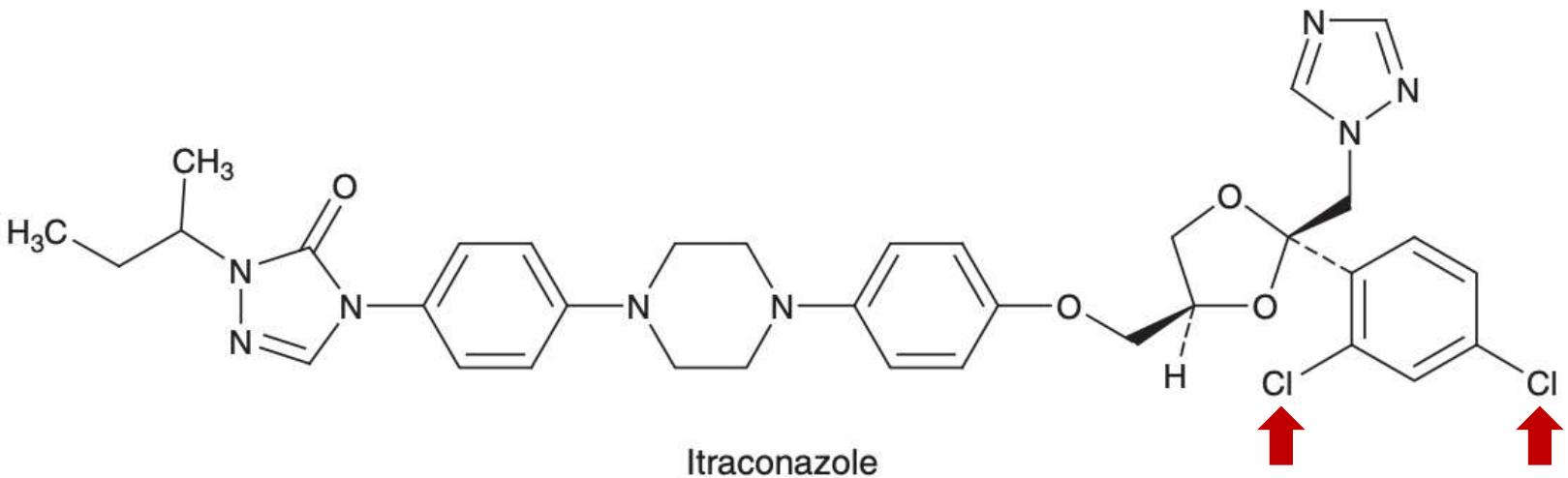
Candida parapsilosis	++	++	++	++	++	++	++	++	++	++
Candida tropicalis	++	++	++	++	++	++	++	++	++	++
Candida krusei	++	+	–	+	++	++	++	++	++	++
Candida lusitaniae	–	++	++	++	++	++	++	++	++	++
Aspergillus fumigatus	++	–	–	+	++	++	++	+	+	+
Cryptococcus neoformans	++	++	++	++	++	++	++	–	–	–
Mucorales	++	–	–	–	–	++	++	–	–	–
Fusarium spp	+	–	–	+	++	++	++	–	–	–
Scedosporium spp	+	–	–	+	+	+	+	–	–	–

Abbreviations: 5FC, flucytosine; AMB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; MICA, micafungin; POS, posaconazole; VOR, voriconazole.

ÖU

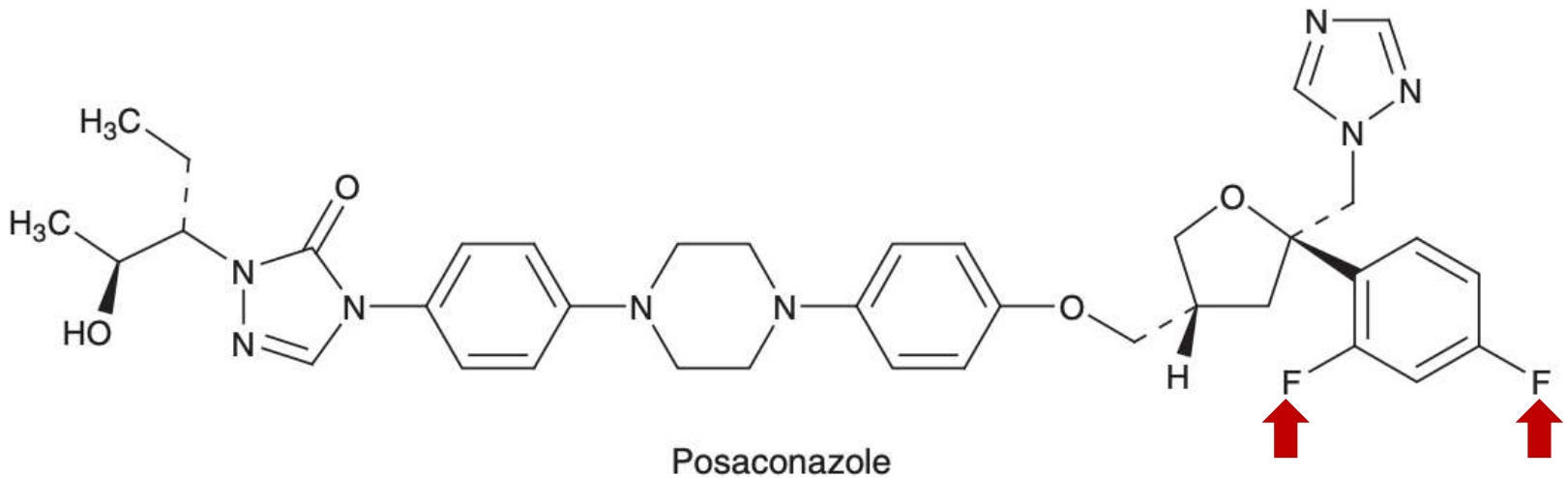
Posakonazol

a



Itraconazole

b



Posaconazole

öu

Farmakoloji

- Oral süspansiyondan hemen serbest kalır. Sulu ve asidik ortamda eriyebilirliği düşük olduğu için emilim doz-kısıtlıdır, bölünmüş dozlarda ve besinlerle birlikte alındığında artar.
- >%98 albumine bağlanır (FLU %11, VOR %58). Dağılım hacmi geniştir (5-25 L/kg).

	Posakonazol	Vorikonazol
Metabolizma	UDP-glukuronoziltransferaz (UGT)	*CYP2C19, CYP3A4, CYP2C9 ve flavin içeren monooksijenazlar
Enzim inhibisyonu	CYP3A4	CYP2B6, CYP2C19, CYP2C9,CYP3A4
Enzim indüksiyonu	-	CYP2C9, CYP2C19, CYP3A4

Li Y, et al. Clin Pharmacother 2010;49:379

ÖU

öu

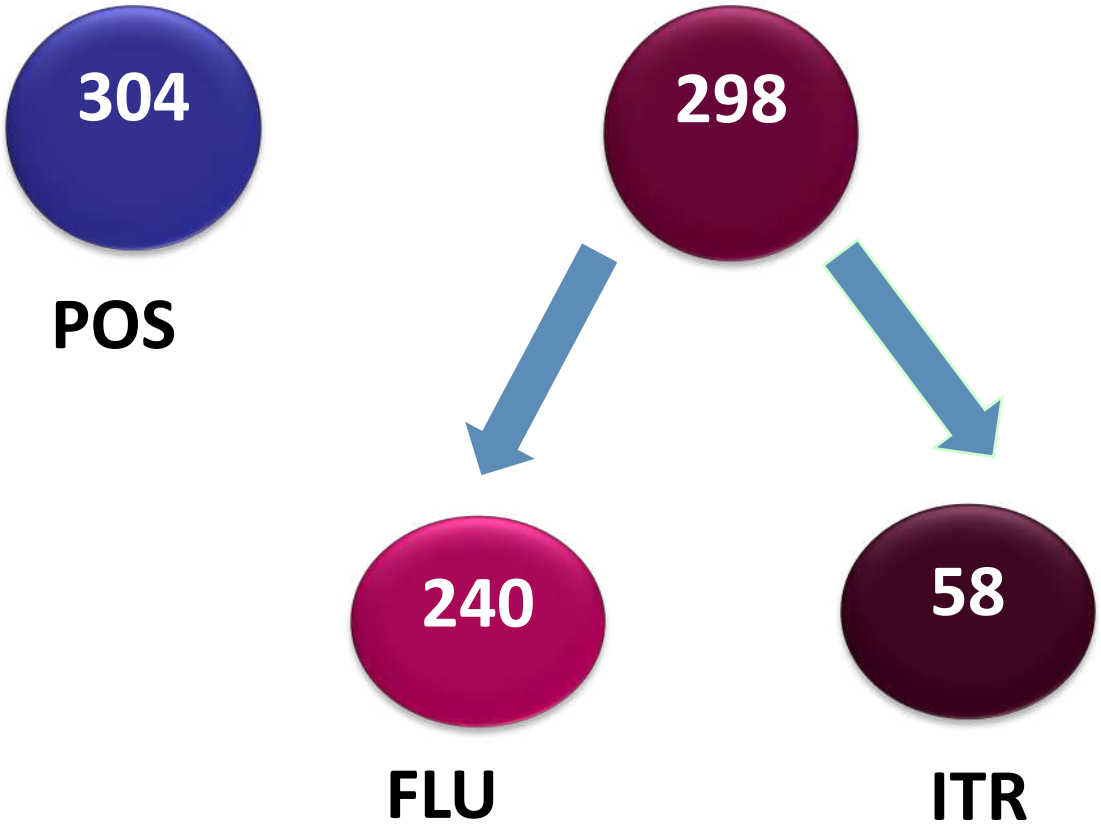
Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

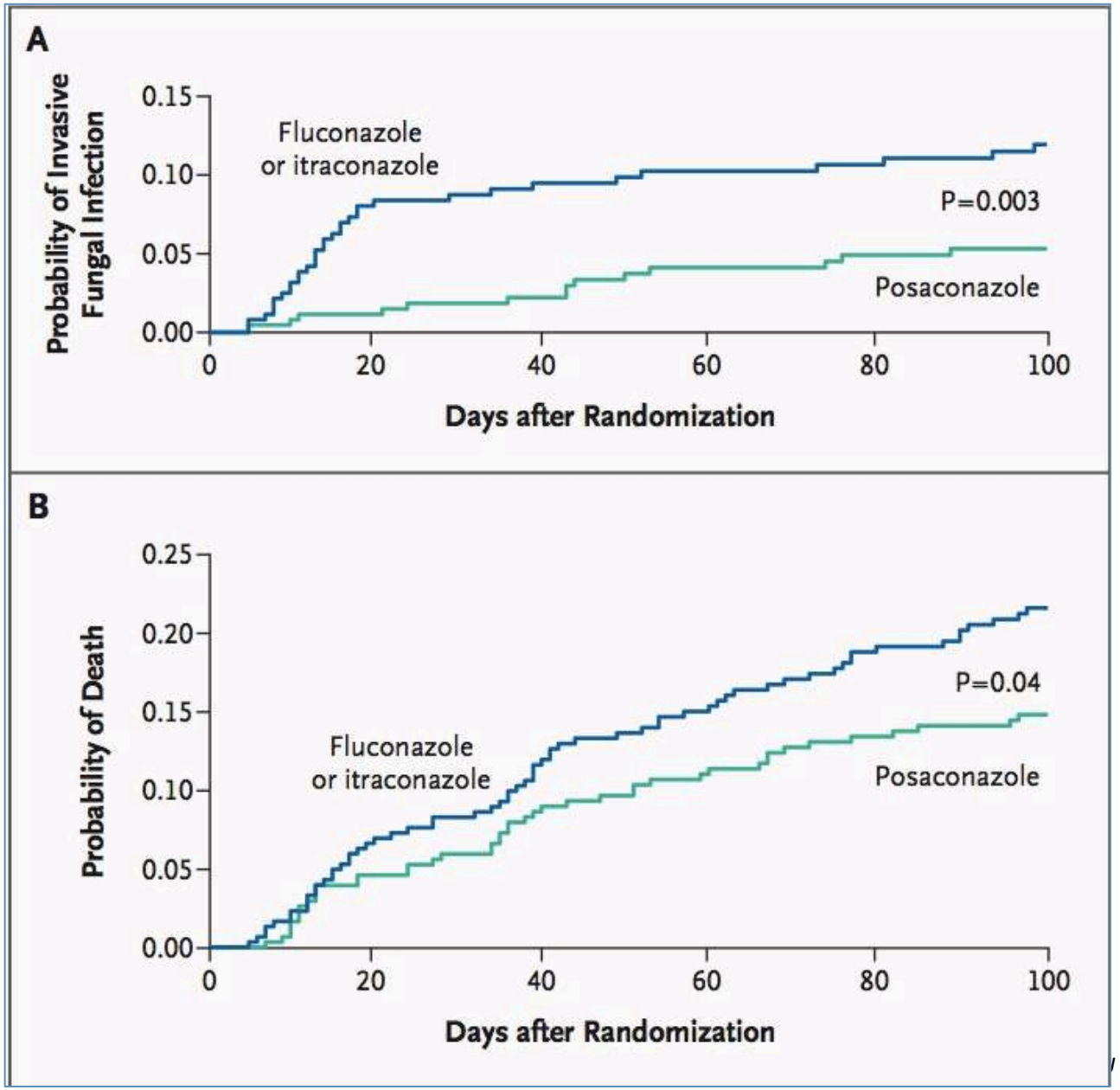
N Engl J Med 2007;356:348-59.

Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

öU

AML İndüksiyonda Posakonazol Profilaksisi





Cornely OA, 2007

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Andrew J. Ullmann, M.D., Jeffrey H. Lipton, M.D., David H. Vesole, M.D., Ph.D., Pranatharthi Chandrasekar, M.D., Amelia Langston, M.D., Stefano R. Tarantolo, M.D., Hildegard Greinix, M.D., Wellington Morais de Azevedo, M.D., Ph.D., Vijay Reddy, M.D., Navdeep Boparai, M.S., Lisa Pedicone, Ph.D., Hernando Patino, M.D., and Simon Durrant, M.D.*

öu

Table 2. Proven or Probable Invasive Fungal Infections during the Fixed Treatment Period and the Exposure Period, According to Pathogen, among Patients Assigned to a Study Drug.

Pathogen or Pathogen Group	Posaconazole Group (N=301)	Fluconazole Group (N=299)	Odds Ratio (95% CI)	P Value
	no. (%)			
Fixed treatment period				
All proven and probable invasive fungal infections*	16 (5.3)	27 (9.0)	0.56 (0.30–1.07)	0.07
All invasive aspergillosis	7 (2.3)	21 (7.0)	0.31 (0.13–0.75)	0.006
Aspergillus (not otherwise specified)	0	5		
Aspergillus galactomannan antigen index	5	6		
A. fumigatus	2	5		
A. flavus	0	3		
A. niger	0	1		
A. terreus	0	1		
All candida species	4	4		
C. krusei	1	1		
C. albicans	0	1		
C. glabrata	2	1		
C. parapsilosis	0	1		
Candida (not otherwise specified)	1	0		
Other fungi	5	2		
Pseudallescheria boydii	1	0		
Rhizomucor miehei	0	1		
Trichosporon beigelii	1	0		
Scedosporium prolificans	1	0		
Mold (not otherwise specified)	2	1		

Ullman AJ, et al, 2007.

öu

Başarısızlık Nedenleri

- Sekestre alanda enfeksiyon
- Ağır immunsupresyon
- İlaç uyumsuzluğu
- Kaynak kontrol sorunu

- Biyoyararlanım
  - emilim
  - metabolizma
  - ilaç etkileşimi

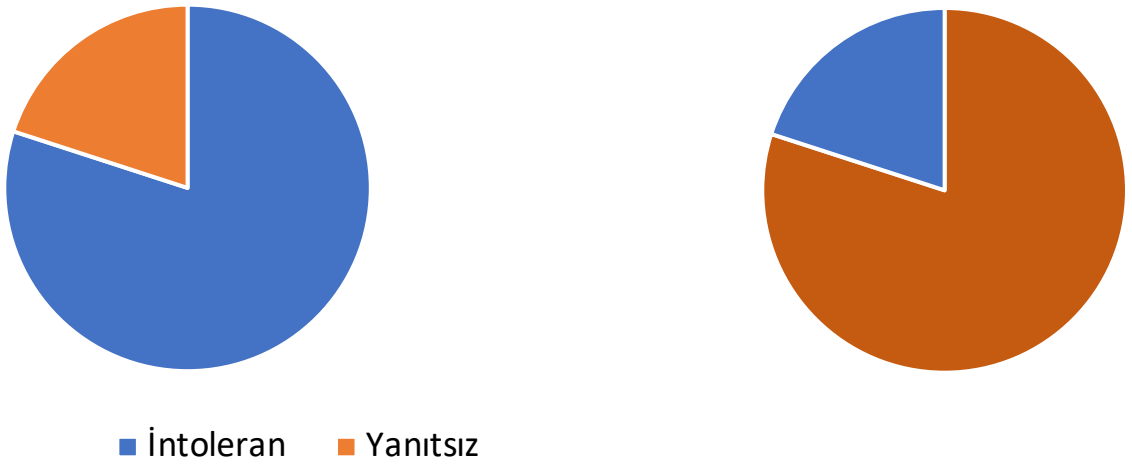
- Direnç
  - edinsel
  - kazanılmış
- Süperenfeksiyon

BAŞARISIZLIK

Kurtarma (“Salvage”)

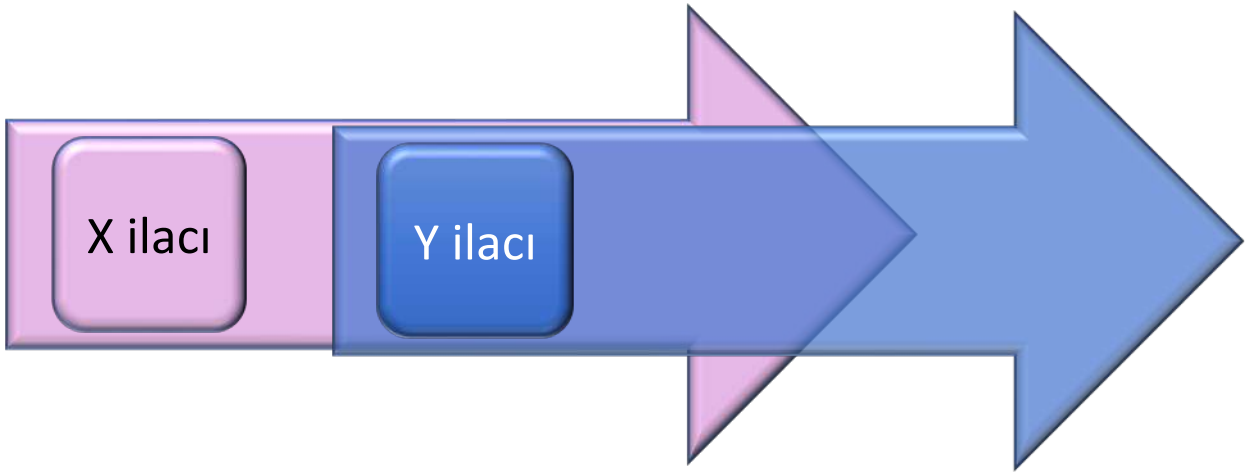
İNTOLERANS

‘’Kurtarma’’ Tedavisi Çalışmaları



Hangisinde daha iyi yanıt beklersiniz?

Primer Antifungal İlacın Etkisi



Treatment of Invasive Aspergillosis with Posaconazole in Patients Who Are Refractory to or Intolerant of Conventional Therapy: An Externally Controlled Trial

CID 2007;44:2.

Thomas J. Walsh,[1] Issam Raad,[3] Thomas F. Patterson,[4] Pranatharthi Chandrasekar,[5] Gerald R. Donowitz,[6] Richard Graybill,[4] Reginald E. Greene,[7] Ray Hachem,[3] Susan Hadley,[8] Raoul Herbrecht,[16] Amelia Langston,[9] Arnold Louie,[10a] Patricia Ribaud,[17,a] Brahm H. Segal,[11] David A. Stevens,[12] Jo-Anne H. van Burik,[13] Charles S. White,[2] Gavin Corcoran,[14,a] Jagadish Gogate,[14,a] Gopal Krishna,[14] Lisa Pedicone,[14] Catherine Hardalo,[14] and John R. Perfect[15]

[1]National Cancer Institute, Bethesda, and [2]University of Maryland, Baltimore, Maryland; [3]The MD Anderson Cancer Center, Houston, and [4]The University of Texas Health Science Center, San Antonio, Texas; [5]Wayne State University, Detroit, Michigan; [6]University of Virginia, Charlottesville; [7]Massachusetts General Hospital and [8]New England Medical Center, Boston, Massachusetts; [9]Emory University Hospital, Atlanta, Georgia; [10]Albany Medical Center, Albany, and [11]Roswell Park Memorial Cancer Center, Buffalo, New York; [12]Santa Clara Valley Medical Center, San Jose, California; [13]University of Minnesota School of Medicine, Minneapolis; [14]Schering-Plough Research Institute, Kenilworth, New Jersey; [15]Duke University, Durham, North Carolina; and [16]Hôpital de Hautepierre, Strasbourg, and [17]Hospital Saint Louis, Paris, France

Bazal Demografik Özellikler

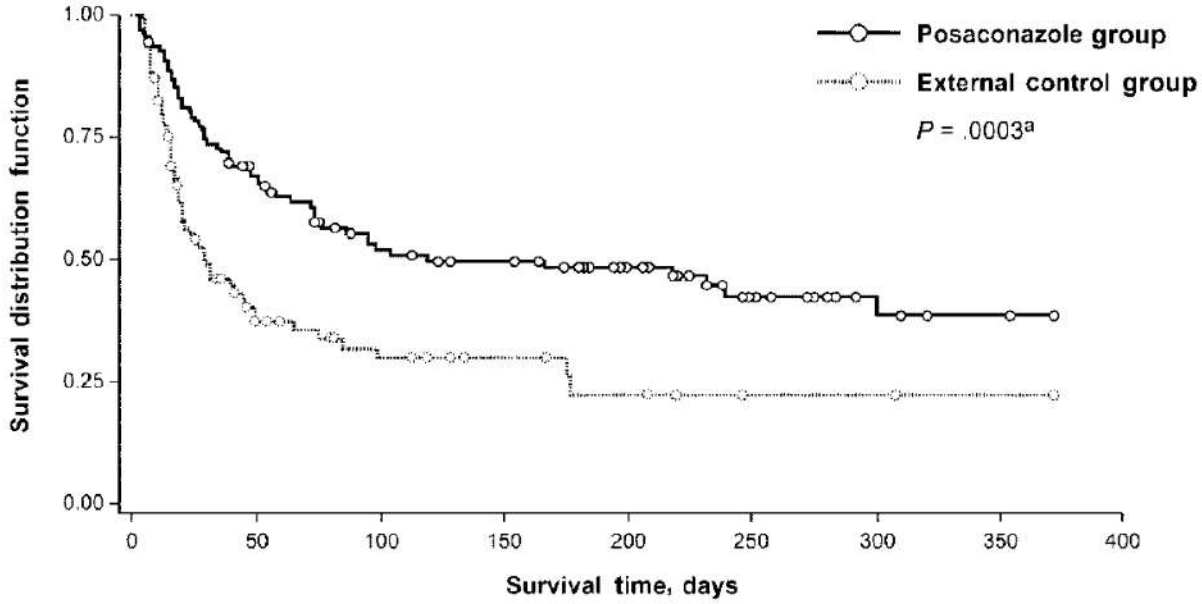
	POS, n=107 (%)	Kontrol, n=86 (%)
Hematolojik malignite	79 (74)	70 (81)
Allo-HSCT	48 (45)	34 (40)
PNL <500/mm^3	21 (20)	26 (30)
Refrakter	55 (51)	48 (56)
Refrakter + İntoleran	39 (36)	20 (23)
İntoleran	12 (12)	18 (21)

Walsh TJ, CID 2007;44:2.

ÖU

Table 6. Global response by salvage therapy (the modified intent-to-treat subset).

Therapy	No. of subjects	No. (%) of responders
Posaconazole group	107	45 (42)
Control group: all therapies	86	22 (26)
Amphotericin B[a]	80	16 (20)
Itraconazole[b]	49	14 (29)
Amphotericin B and itraconazole	45	10 (22)
Other therapies[c]	36	11 (31)



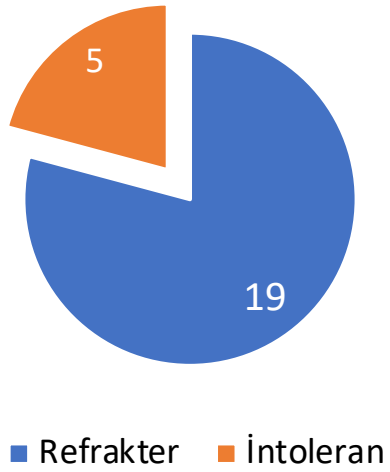
Walsh TJ, CID 2007;44:2

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2006, p. 126–133 Vol. 50, No. 1
0066-4804/06/$08.00+0 doi:10.1128/AAC.50.1.126–133.2006

Posaconazole as Salvage Therapy for Zygomycosis

R. N. Greenberg,[1,2*] K. Mullane,[3] J.-A. H. van Burik,[4] I. Raad,[5] M. J. Abzug,[6] G. Anstead,[7] R. Herbrecht,[8] A. Langston,[9] K. A. Marr,[10] G. Schiller,[11] M. Schuster,[12] J. R. Wingard,[13] C. E. Gonzalez,[14] S. G. Revankar,[15] G. Corcoran,[16] R. J. Kryscio,[17] and R. Hare[18]

24 hasta



Önceki AF İlaç	Sayı
AmB formülasyonları	19
ABLC + CAS	1
L-AmB + CAS + ITC	1
VRC	1

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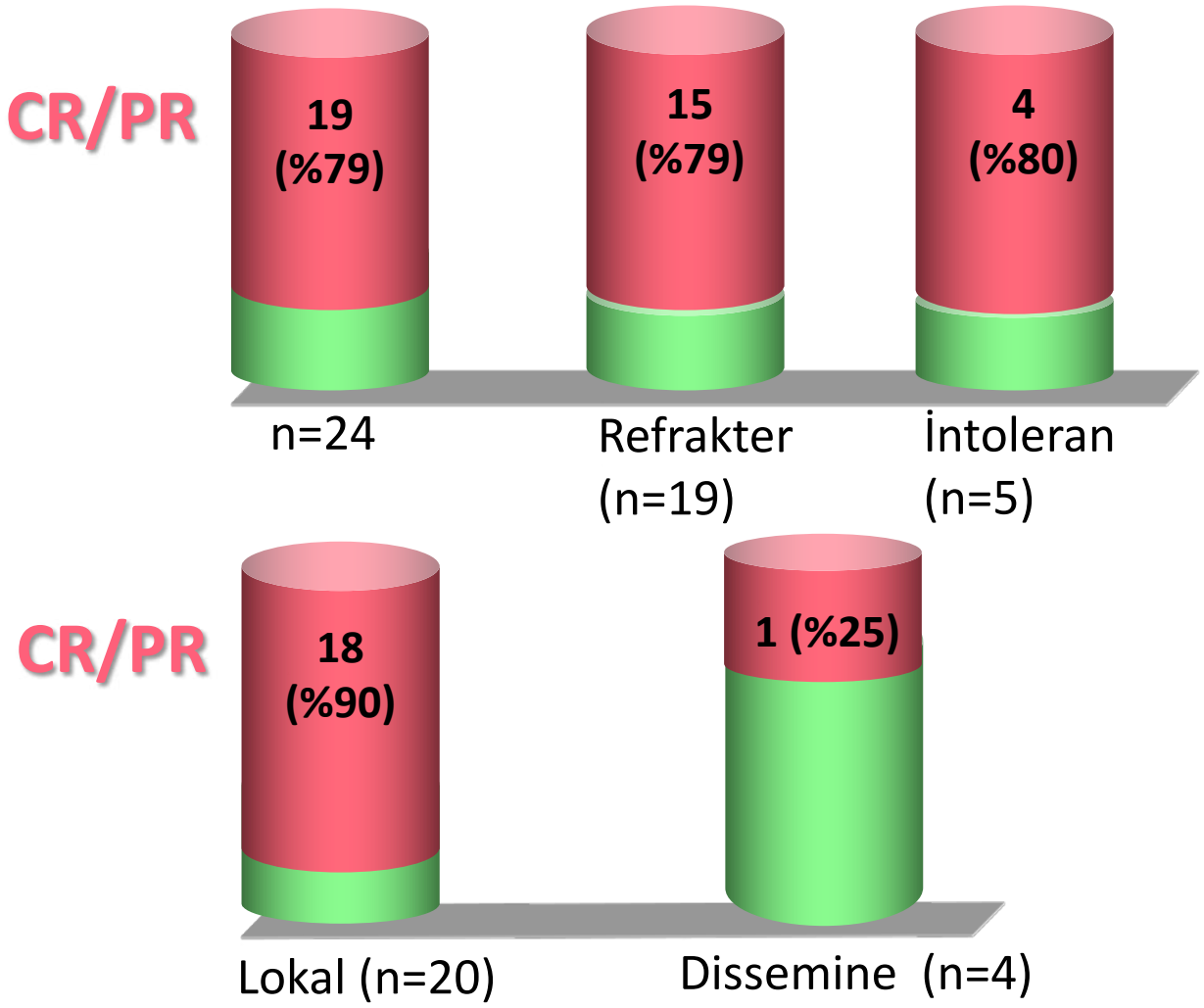
Yanıt



Mortalite: 9/24 (%37.5)

Greenberg RN, et al. AAC 2006;50:126

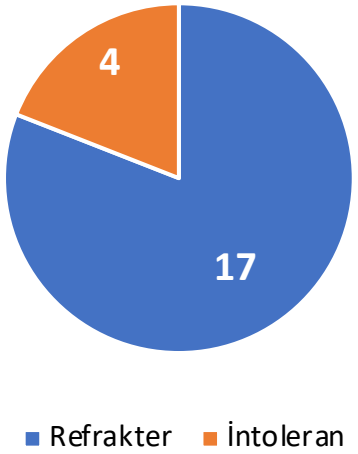
Posaconazole as Salvage Treatment for Invasive Fusariosis in Patients with Underlying Hematologic Malignancy and Other Conditions

CID 2006;42:1398.

Issam I. Raad,[1] Ray Y. Hachem,[1] Raoul Herbrecht,[5] John R. Graybill,[2] Roberta Hare,[3] Gavin Corcoran,[4] and Dimitrios P. Kontoyiannis[1]

[1]The M. D. Anderson Cancer Center, Houston, and [2]The University of Texas Health Science Center at San Antonio, San Antonio, Texas; [3]Schering-Plough Research Institute, Kenilworth, New Jersey; [4]Steifel Laboratories, Coral Gables, Florida; and [5]Hôpitaux Universitaires de Strasbourg, Strasbourg, France

21 hasta



Hematolojik malignite	%76.2
Allo-HSCT	%28.6
DM	%28.6

Önceki tedavi: Lipid AmB 20/21

Süre (ortalama, sınır): 8 gün (2-38)

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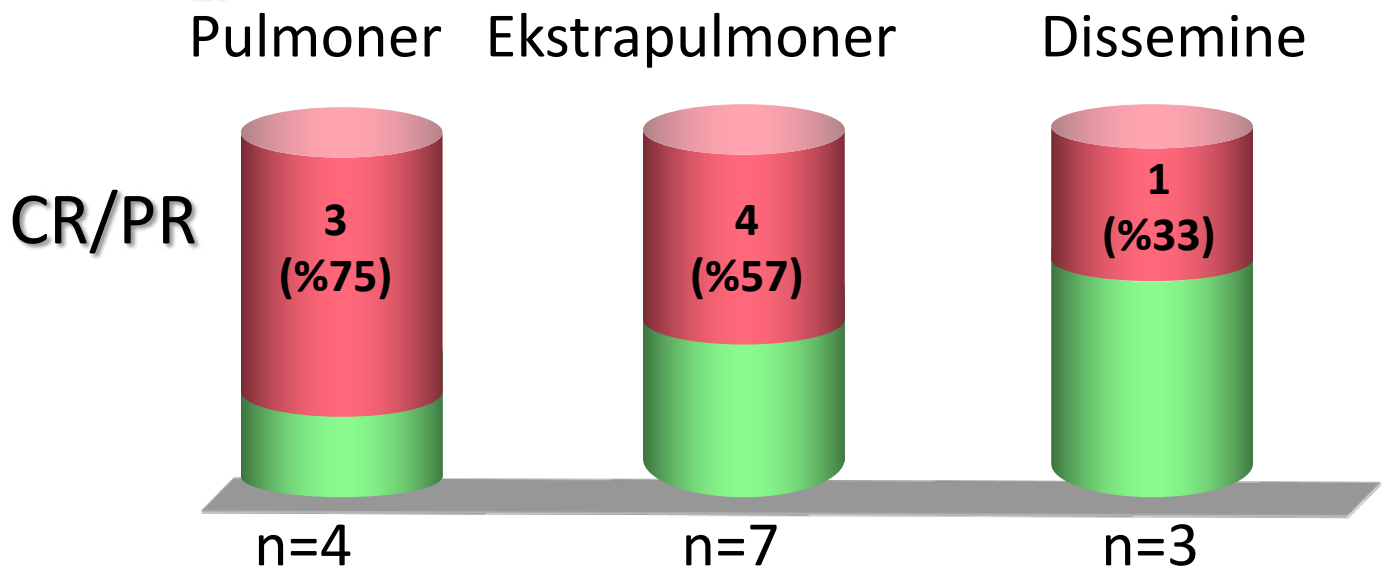

Nötropenisi düzelen:	%67
Nötropenik:	%20

Raad II, et al. CID 2006;42:1398

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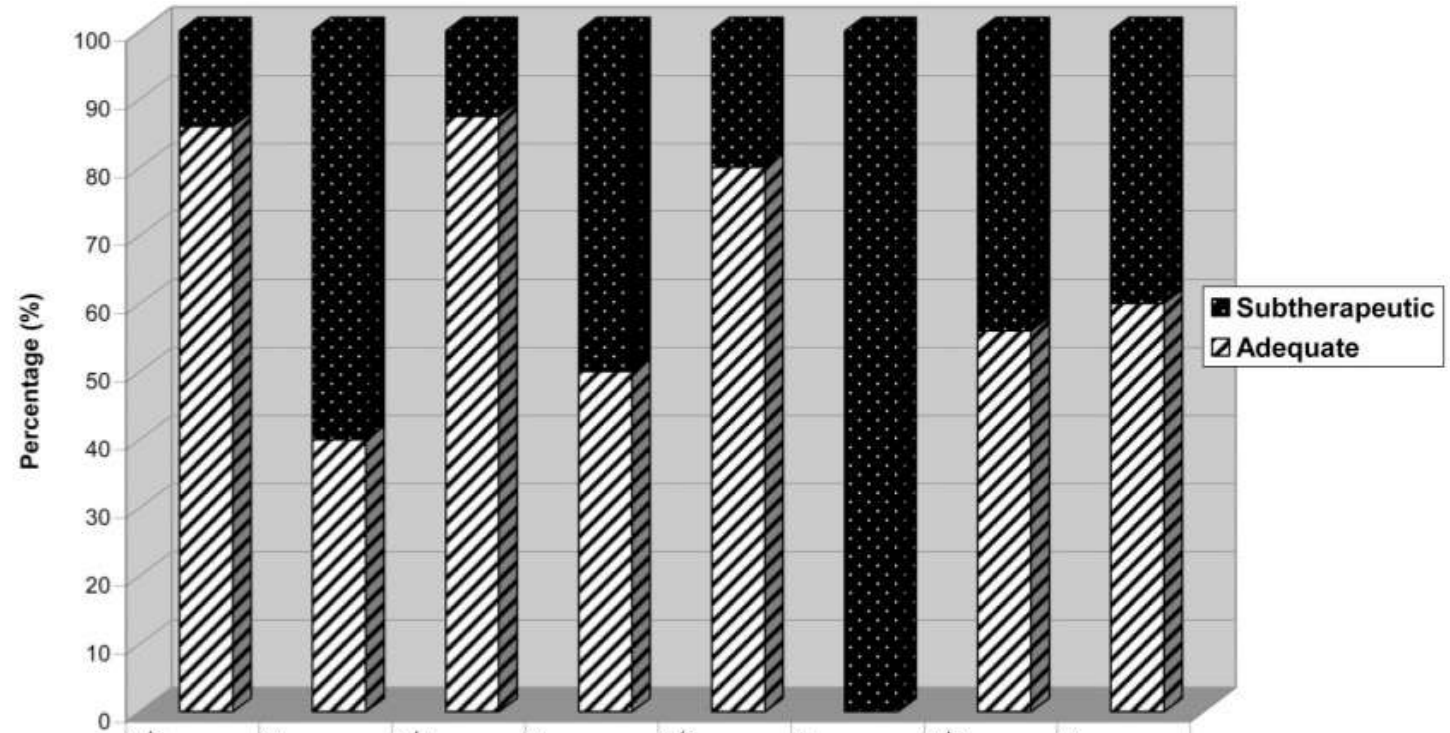
Posakonazol Serum Düzeyleri



	w/o	w	w/o	w	w/o	w	w/o	w
	PPI usage		GvHD		Diarrhoea		Neutropenia	
Subtherapeutic	14	60	12,5	50	20	100	44	40
Adequate	86	40	87,5	50	80	0	56	60
Total (*n*)	7	20	8	24	15	7	25	5

Crombag MR, Ther Drug Monit 2012

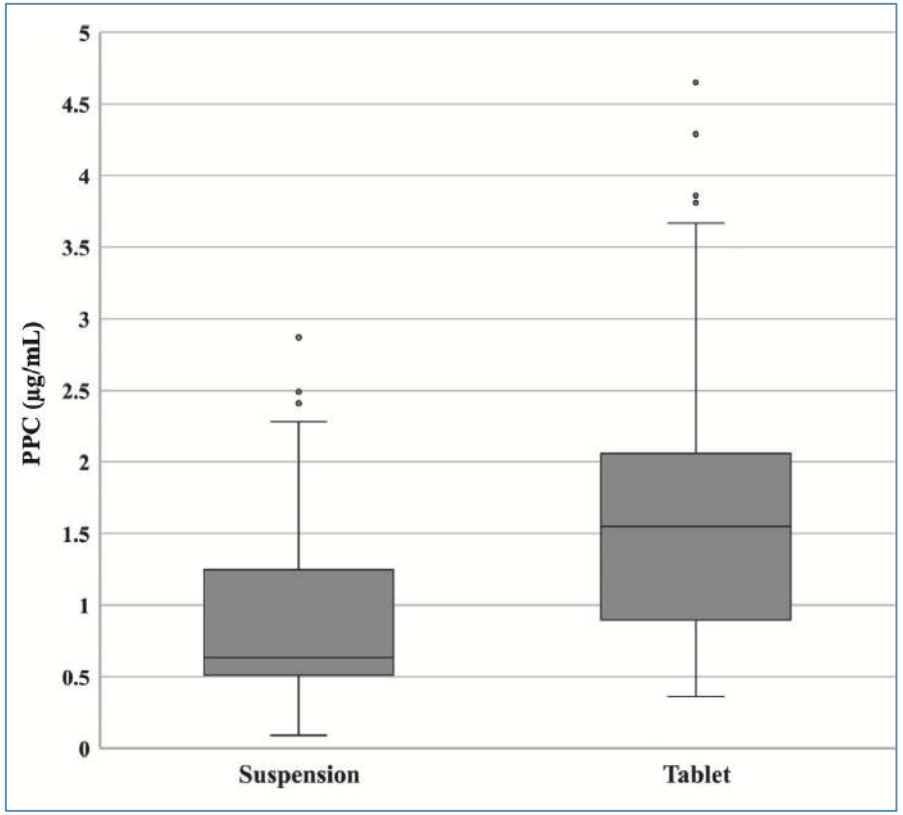
FDA onayı: Kasım 2013

Hematolojik maligniteli hastalarda AF profilakside posakonazol ”delayed-release” tablet

TABLE 2 Serum posaconazole trough level

	Suspension (n = 88)	Tablet (n = 154)	*P*
PPC			
<0.7 μg/mL, n (%)	47 (53.4)	17 (11.0)	<.001
≥0.7 μg/mL, n (%)	41 (46.6)	137 (89.0)	
Day of blood sampling for TDM			
Median (range)	8.0 (7.0-21.0)	8.0 (7.0-28.0)	.533

Abbreviations: PPC, plasma posaconazole concentration; TDM, therapeutic drug monitoring.



Oh J, et al. Mycoses 2020;63:89.

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Posakonazol için TDM Önerileri

Recommendation: prophylaxis target: > 0.7 mg/L (BII)

- Pending further data, TDM is still recommended in patients receiving posaconazole tablets or IV formulation for prophylaxis **(CIII)**
- TDM is recommended in patients receiving posaconazole tablets or IV formulation receiving treatment for suspected or documented fungal infection **(CIII)**
- TDM is indicated for patients receiving tablets or IV formulation in the setting of breakthrough or progressing infection unresponsive to treatment, treatment of pathogens with reduced susceptibility, or drug interactions **(CIII)**

additional data are needed

https://www.ecil-leukaemia.com/en/resources/resources-ecil

ÖU

Posakonazol tablet kullanımı (Aralık 2021 öncesi)

	FDA	EMA	TR
Endikasyon			
Profilaksi	• KT'ye bağlı uzun süren nötropenisi olan hematolojik maligniteli hastalar • GvHH olan HSCT alıcıları	• AML veya uzun süreli nötropeni beklenen MDS hastalarında • GVHH için yüksek doz immunsupresif tedavi alan HSCT alıcıları	EMA ile aynı
Tedavi	Orofaringeal kandidiyazis (FLU ve/veya ITR refrakter dahil)	• AmB veya ITR'e refrakter / intoleran hastada İA • AMB'ye refrakter / intoleran hastada fusairosis • ITR'e refrakter / intoleran hastada kromoblastomikozis ve miçetoma • Amb, ITR veya FLU' refrakter/itoleran hastada koksidiodomikozis	EMA ile aynı
Doz	300 mg 12 saat arayla 2 doz yükleme, 300 mg/gün idame	Aynı	Aynı

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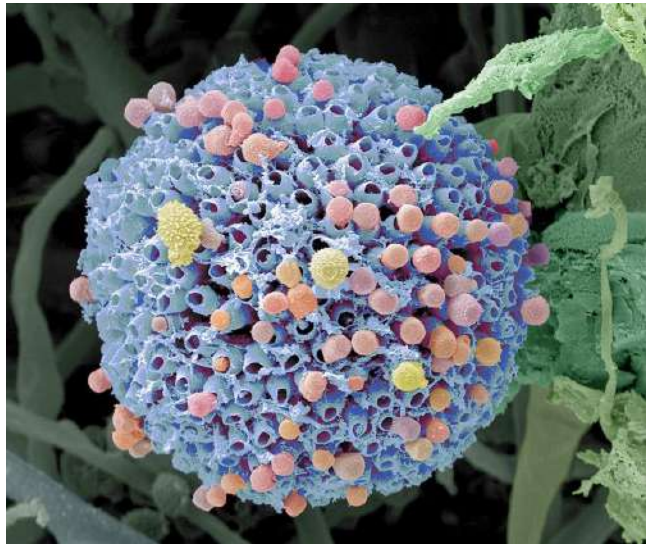
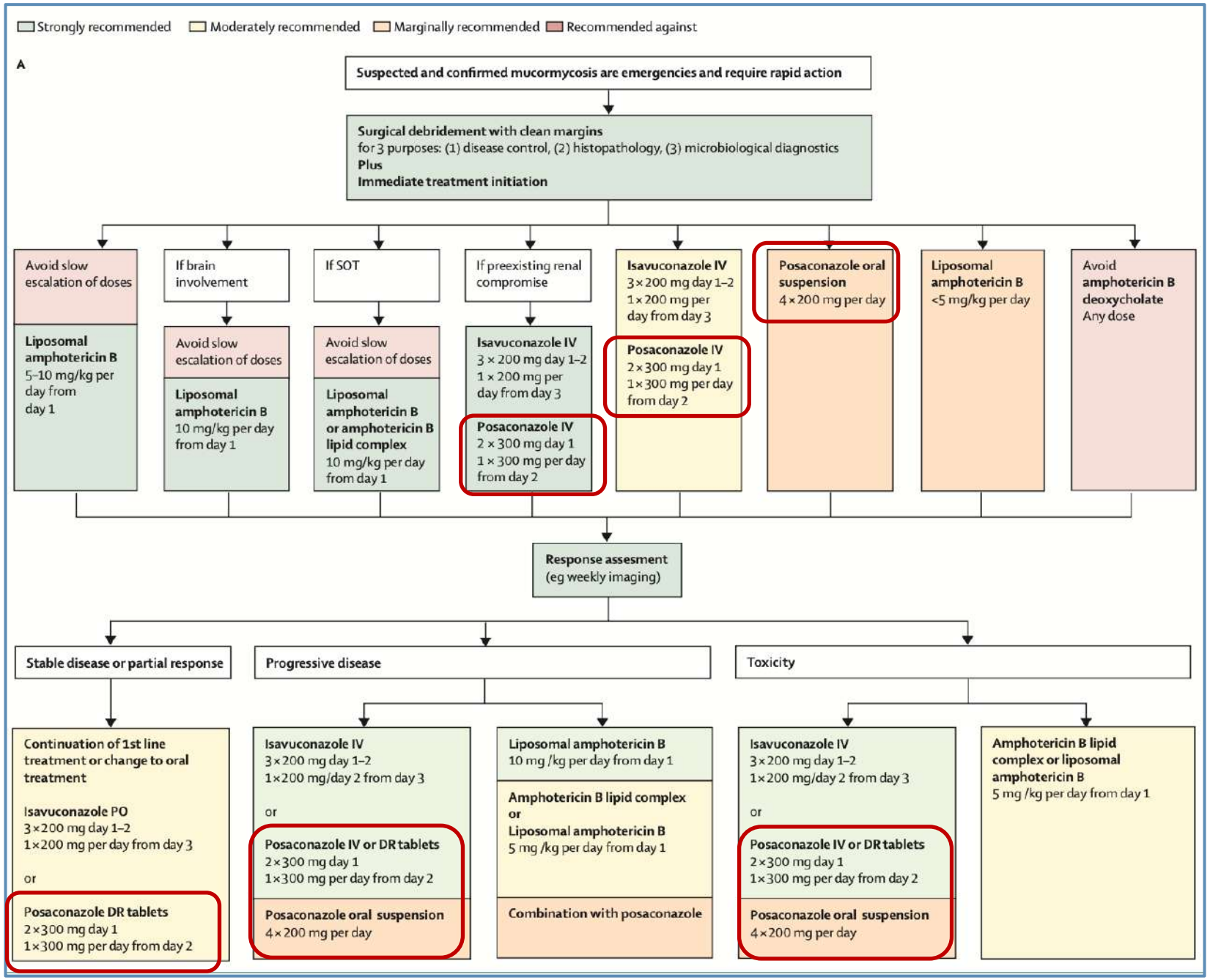


Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium

Oliver A Cornely, Ana Alastruey-Izquierdo, Dorothee Arenz, Sharon C A Chen, Eric Dannaoui, Bruno Hochhegger, Martin Hoenigl, Henrik E Jensen, Katrien Lagrou, Russell E Lewis, Sibylle C Mellinghoff, Mervyn Mer, Zoi D Pana, Danila Seidel, Donald C Sheppard, Roger Wahba, Murat Akova, Alexandre Alanio, Abdullah M S Al-Hatmi, Sevtap Arikan-Akdagli, Hamid Badali, Ronen Ben-Ami, Alexandro Bonifaz, Stéphane Bretagne, Elio Castagnola, Methee Chayakulkeeree, Arnaldo L Colombo, Dora E Corzo-León, Lubos Drgona, Andreas H Groll, Jesus Guinea, Claus-Peter Heussel, Ashraf S Ibrahim, Souha S Kanj, Nikolay Klimko, Michaela Lackner, Frederic Lamoth, Fanny Lanternier, Cornelia Lass-Floerl, Dong-Gun Lee, Thomas Lehrnbecher, Badre E Lmimouni, Mihai Mares, Georg Maschmeyer, Jacques F Meis, Joseph Meletiadis, C Orla Morrissey, Marcio Nucci, Rita Oladele, Livio Pagano, Alessandro Pasqualotto, Atul Patel, Zdenek Racil, Malcolm Richardson, Emmanuel Roilides, Markus Ruhnke, Seyedmojtaba Seyedmousavi, Neeraj Sidharthan, Nina Singh, János Sinko, Anna Skiada, Monica Slavin, Rajeev Soman, Brad Spellberg, William Steinbach, Ban Hock Tan, Andrew J Ullmann, Jörg J Vehreschild, Maria J G T Vehreschild, Thomas J Walsh, P Lewis White, Nathan P Wiederhold, Theoklis Zaoutis, Arunaloke Chakrabarti, for the Mucormycosis ECMM MSG Global Guideline Writing Group

Lancet Infect Dis 2019;19:e405



Lancet Infect Dis 2019;19:e405

ÖU

öu

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial

*Johan A Maertens, Galia Rahav, Dong-Gun Lee, Alfredo Ponce-de-León, Isabel Cristina Ramírez Sánchez, Nikolay Klimko, Anne Sonet, Shariq Haider, Juan Diego Vélez, Issam Raad, Liang-Piu Koh, Meinolf Karthaus, Jianying Zhou, Ronen Ben-Ami, Mary R Motyl, Seongah Han, Anjana Grandhi, Hetty Waskin, on behalf of the study investigators**

Lancet 2021; 397: 499–509

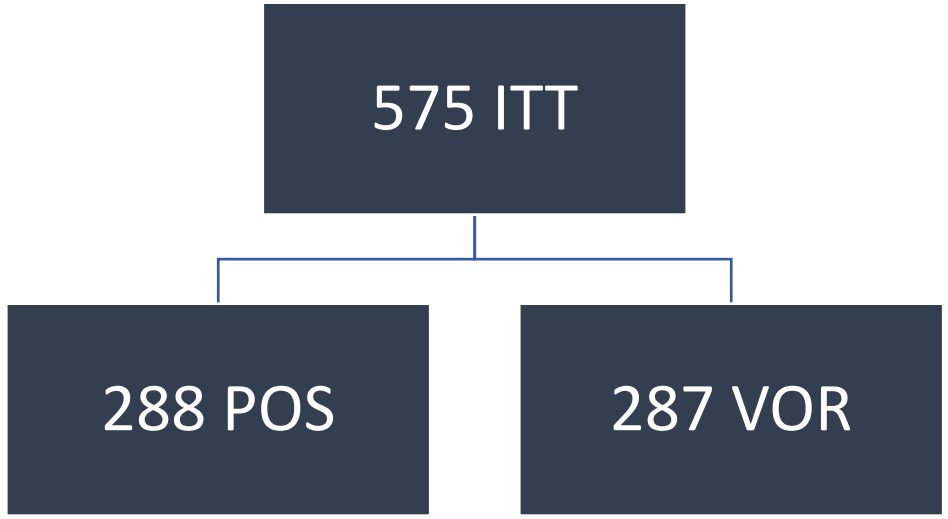
öU

Çalışma tasarımı

25 Ekim 2013-
10 Eylül 2019

663 hasta
değerlendirildi

≤ 12 hafta
(2-84 gün)



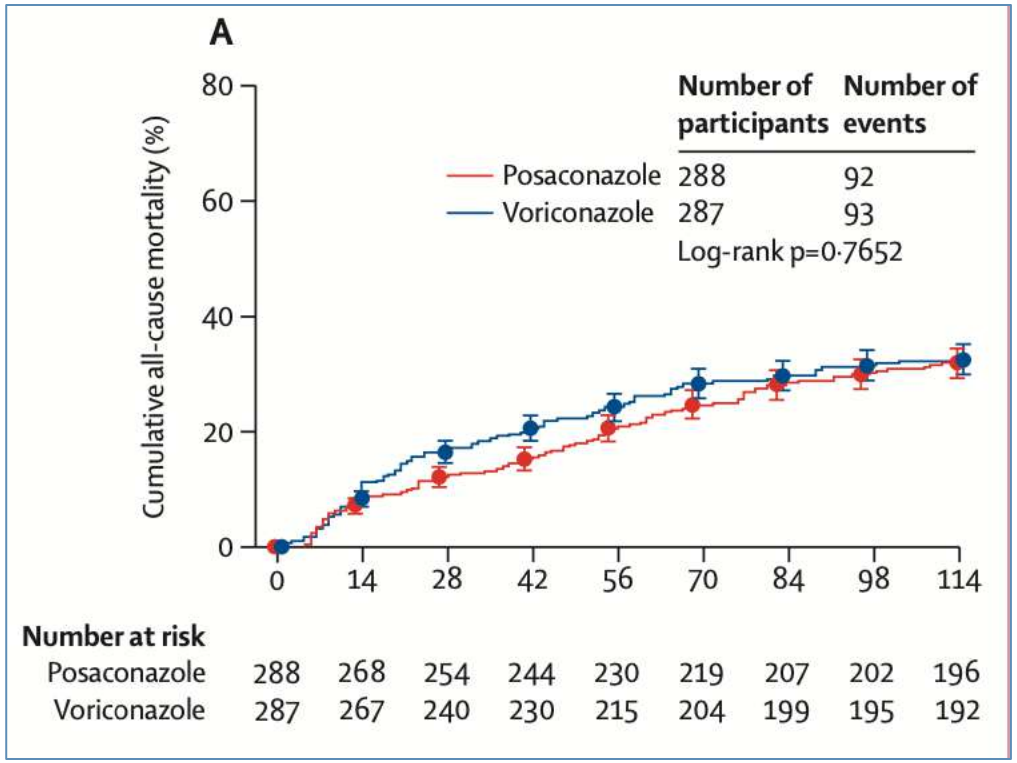
Maertens JA, et al. Lancet 2021;397:499

ÖU

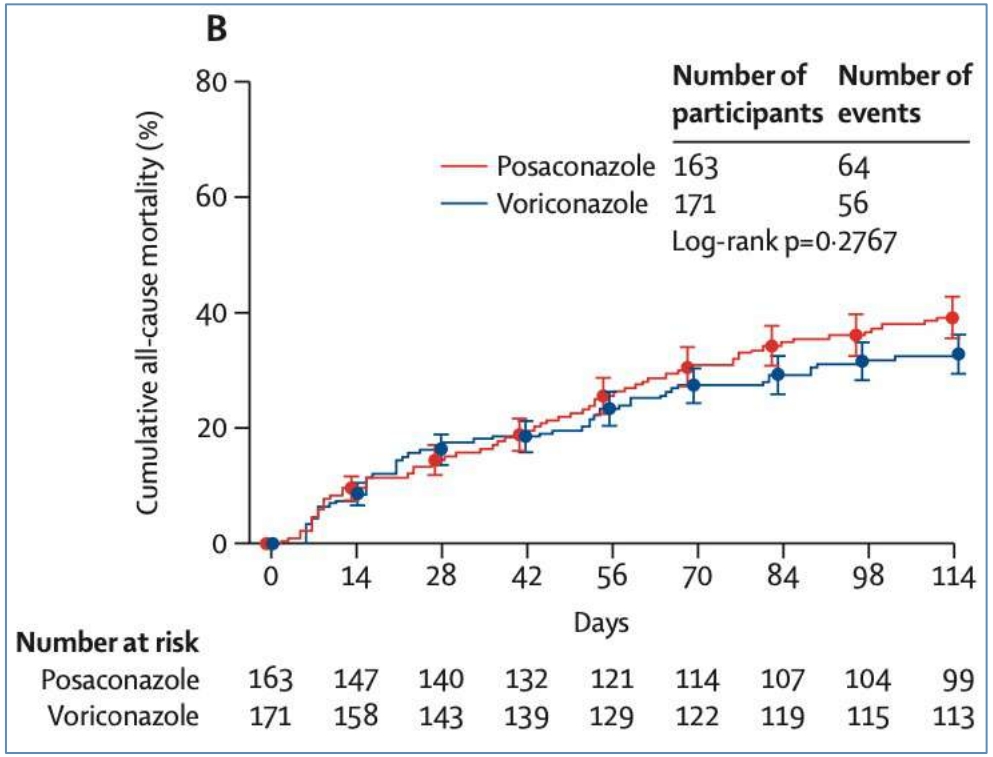
MORTALİTE VE TEDAVİYE YANIT

	Posaconazole group	Voriconazole group	Treatment difference (95% CI)*	p value
All-cause mortality				
ITT population				
Day 42 all-cause mortality†	44/288 (15%)	59/287 (21%)	−5·3% (−11·6 to 1·0)‡	<0·0001§
Day 84 all-cause mortality	81/288 (28%)	88/287 (31%)	−2·5% (−9·9 to 4·9)	NA
FAS population				
Day 42 all-cause mortality†	31/163 (19%)	32/171 (19%)	0·3% (−8·2 to 8·8)	NA
Day 84 all-cause mortality	56/163 (34%)	53/171 (31%)	3·1% (−6·9 to 13·1)	NA
Global clinical response in the FAS population				
Success at week 6	73/163 (45%)	78/171 (46%)	0·6% (−11·2 to 10·1)	NA
Complete response¶	11/163 (7%)	9/171 (5%)	..	..
Partial response||	62/163 (38%)	68/171 (40%)	..	..
Stable response, progression of fungal disease, death, or unable to assess at week 6	90/163 (55%)	93/171 (54%)	..	..
Stable response**	12/163 (7%)	22/171 (13%)	..	..
Progression††	27/163 (17%)	21/171 (12%)	..	..
Death	34/163 (21%)	33/171 (19%)	..	..
Unable to assess	17/163 (10%)	17/171 (10%)	..	..
Success at week 12	69/163 (42%)	79/171 (46%)	−3·4% (−13·9 to 7·1)	NA
Complete response¶	20/163 (12%)	19/171 (11%)	..	..
Partial response||	49/163 (30%)	60/171 (35%)	..	..
Stable response, progression of fungal disease, death, or unable to assess at week 12	94/163 (58%)	92/171 (54%)	..	..
Stable response**	9/163 (6%)	7/171 (4%)	..	..
Progression††	13/163 (8%)	19/171 (11%)	..	..
Death	56/163 (34%)	51/171 (30%)	..	..
Unable to assess	16/163 (10%)	15/171 (9%)	..	..

Maertens JA, et al. Lancet 2021;397:499



ITT (all patients who received ≥ 1 dose)



ITT with proven or probable IA

Maertens JA, et al. Lancet 2021;397:499

ÖU

42. Gün Mortalite

	Posaconazole group	Voriconazole group	Treatment difference* (95% CI)
Age, years			
<18	1/3 (33%)	0/2	33·3% (−51·9 to 82·0)
18–57	14/151 (9%)	27/151 (18%)	−8·6% (−16·6 to −0·9)
>57	29/134 (22%)	32/134 (24%)	−2·2% (−12·3 to 7·9)
Sex			
Male	21/172 (12%)	38/172 (22%)	−9·9% (−17·9 to −1·9)
Female	23/116 (20%)	21/115 (18%)	1·6% (−8·7 to 11·8)
Risk status			
High risk	20/113 (18%)	23/113 (20%)	−2·7% (−13·0 to 7·7)
Not high risk	24/175 (14%)	36/174 (21%)	−7·0% (−15·0 to 1·0)
Type of invasive aspergillosis per adjudicator assessment			
Proven	7/26 (27%)	4/15 (27%)	0·3% (−29·6 to 26·5)
Probable	24/137 (18%)	28/156 (18%)	−0·4% (−9·2 to 8·5)
Possible	7/81 (9%)	18/79 (23%)	−14·1% (−25·7 to −3·0)
Cannot be determined	6/44 (14%)	9/37 (24%)	−10·7% (−28·7 to 6·5)
Site of invasive aspergillosis			
Lung	31/230 (13%)	39/230 (17%)	−3·5% (−10·1 to 3·1)
Multiple sites	12/48 (25%)	17/45 (38%)	−12·8% (−31·1 to 6·2)
Sinus	1/3 (33%)	2/7 (29%)	4·8% (−47·5 to 62·1)
Other	0/2	1/2 (50)	−50·0% (−92·4 to 46·8)
Neutropenia status at baseline, cells per L			
$<0·5 \times 10^9$	23/132 (17%)	34/137 (25%)	−7·4% (−17·1 to 2·4)
$\geq 0·5 \times 10^9$	20/142 (14%)	21/138 (15%)	−1·1% (−9·6 to 7·3)
Unknown	1/14 (7%)	4/12 (33%)	−26·2% (−56·2 to 5·4)

Maertens JA, et al. Lancet 2021;397:499

İstenmeyen etkiler

	Posaconazole group (n=288)	Voriconazole group (n=287)	Treatment difference (95% CI)*
Participants with treatment-emergent adverse events	281 (98%)	280 (98%)	0·0% (−2·8 to 2·8)
Serious	178 (62%)	172 (60%)	1·9% (−6·1 to 9·8)
Deaths	86 (30%)	87 (30%)	−0·5% (−7·9 to 7·0)
Leading to discontinuation of study drug	93 (32%)	102 (36%)	−3·2% (−11·0 to 4·5)
Participants with treatment-related adverse events	86 (30%)	115 (40%)	−10·2% (−17·9 to −2·4)
Serious	16 (6%)	20 (7%)	−1·4% (−5·6 to 2·7)
Deaths	0	3 (1%)	−1·0% (−3·0 to 0·3)
Leading to discontinuation of study drug	18 (6%)	28 (10%)	−3·5% (−8·1 to 1·0)

*Based on Miettinen and Nurminen's method.[11]

***Table 3*: Adverse events in the intention-to-treat population**

Maertens JA, et al. Lancet 2021;397:499

ÖU

Posakonazol tablet kullanımı

	FDA	EMA	TR
Endikasyon			
Profilaksi	• KT'ye bağlı uzun süren nötropenisi olan hematolojik maligniteli hastalar • GvHH olan HSCT alıcıları	• AML veya uzun süreli nötropeni beklenen MDS hastalarında • GVHH için yüksek doz immunsupresif tedavi alan HSCT alıcıları	• EMA ile aynı
Tedavi	Orofaringeal kandidiyazis (FLU ve/veya ITR refrakter dahil)	• AmB veya ITR'e refrakter / intoleran hastada İA • AMB'ye refrakter / intoleran hastada fusairosis • ITR'e refrakter / intoleran hastada kromoblastomikozis ve miçetoma • Amb, ITR veya FLU' refrakter/itoleran hastada koksidiodomikozis	• EMA ile aynı
		İnvaziv aspergillosis primer tedavisi (Aralık 2021)	**İnvaziv aspergillosis primer tedavisi (Mayıs 2023)**
Doz	300 mg 12 saat arayla 2 doz yükleme, 300 mg/gün idame	Aynı	Aynı


24 Tablet
POSAGiL 100 mg
GASTRO-REZİSTAN TABLET
POSAKONAZOL
ABDIIBRAHIM

öu

ORIGINAL ARTICLE

Infect Dis Clin Microbiol 2023; 5(4): 341-52

Single-Dose Crossover Comparative Bioavailability Study of Two Different Posaconazole 100 mg Gastro-Resistant Tablets Under Fasted and Fed Conditions in Healthy Volunteers

Nilden Dayan[1], Elif Oğralı[1], Cihan Kirişçioğlu[1], Udaya Kumar Dude[1], Recep Erşahin[1]

[1] Abdi İbrahim Pharmaceuticals Inc., İstanbul, Türkiye

Posagil® biyoeşdeğerlilik çalışması

T: test ilacı (Posagil®) 100 mg tb
R: referans ilaç (Noxafil®) 100 mg tb

Table 2. Crossover design for consecutive treatment periods.

	Treatment period I (Day 1)	WOP (Days 1-14)	Treatment period II (Day 15)	WOP (Days 15-28)	Treatment period III (Day 29)	WOP (Days 29-42)	Treatment period IV (Day 43)	EOS (Day 49)
Sequence I (n= 9)	T-fasted		R-fasted		R-fed		T-fed	
Sequence II (n= 9)	R-fasted		T-fed		T-fasted		R-fed	
Sequence III (n= 9)	T-fed		R-fed		R-fasted		T-fasted	
Sequence IV (n= 9)	R-fed		T-fasted		T-fed		R-fasted	

WOP: Wash-out period, **EOS:** End of study, **T-fasted:** Posagil® 100 mg gastro-resistant tablet [test] under fasted conditions, **R-fasted:** Noxafil® 100 mg gastro-resistant tablet [reference] under fasted conditions, **T-fed:** Posagil® 100 mg gastro-resistant tablet [test] under fed conditions, **R-fed:** Noxafil® 100 mg gastro-resistant tablet [reference] under fed conditions.

Dayan N, et al. IDCM 2023;5:341

ÖU

Biyoeşdeğerlilik kriteri

- “Least-squares mean” (LSMeans): Lineer modeldeki diğer terimler (“covariate” gibi) düzeltilmiştir, kayıp veriye duyarlılık azdır. Aritmetik ortalamaya göre gerçek popülasyon ortalamasını daha iyi yansıtır ve analiz modelinden (ör. varyans analizi, kovaryans analizi) hesaplandığı için klinik araştırmalarda daha sık kullanılır.
- ”Geometric least-squares mean ratio”: İki LSMeans arasındaki fark ve %90 güvenlik aralığı (CI). Biyoeşdeğerlilik çalışmalarında kullanılır.
- Biyoeşdeğerlilik için incelenen parametrelerde (C_{max}, AUC_{0-T}, $AUC_{0-\infty}$) %90 CI %80 ile %125 arasında olmalı.

http://onbiostatistics.blogspot.com/2021/01/arithmetic-mean-geometric-mean-harmonic.html

Posagil® biyoeşdeğerlilik çalışması

Table 4. Bioequivalence assessment for test and reference products under fasted (T-fasted vs. R-fasted) and fed (T-fed vs. R-fed) conditions.

	Bioequivalence of test vs. reference product under fasted conditions					
	Intra-subject CV (%)	Geometric LSMeans		Ratio (%)	90% Confidence limits (%)	
		T-fasted (n=33)	R-fasted (n=33)		Lower	Upper
C_{max} (ng/mL)	15.1	445.68	275.99	161.49	151.61	172
AUC_{0-T} (ng·h/mL)	11.5	11,444.3	8246.08	138.78	132.28	145.61
$AUC_{0-\infty}$ (ng·h/mL)	11.7	11,684.54	8487.3	137.67	131.11	144.56
	Bioequivalence of test vs. reference product under fed conditions					
	Intra-subject CV (%)	Geometric LSMeans		Ratio (%)	90% Confidence limits (%)	
		T-fed (n=33)	R-fed (n=33)		Lower	Upper
C_{max} (ng/mL)	13.6	380.61	390.74	97.41	91.95	103.19
AUC_{0-T} (ng·h/mL)	7.5	11,279.27	11,574.23	97.45	94.41	100.6
$AUC_{0-\infty}$ (ng·h/mL)	7.7	11,544.87	11,892.18	97.08	93.97	100.29

CV: Coefficient of variation, **LSMeans:** Least squares means, **T-fasted:** Posagil® 100 mg gastro-resistant tablet [test] under fasted conditions, **R-fasted:** Noxafil® 100 mg gastro-resistant tablet [reference] under fasted conditions, **T-fed:** Posagil® 100 mg gastro-resistant tablet [test] under fed conditions, **R-fed:** Noxafil® 100 mg gastro-resistant tablet [reference] under fed conditions.

Dayan N, et al. IDCM 2023;5:341

ÖU

Posagil® biyoeşdeğerlilik çalışması

Table 5. Food effect on test (T-fed vs. T-fasted) and reference (R-fed vs. R-fasted) products.

	Food effect on test product					
	Intra-subject CV (%)	Geometric LSMeans		Ratio (%)	90% Confidence limits (%)	
		T-fed (n=32)	T-fasted (n=32)		Lower	Upper
C_{max} (ng/mL)	18.9	386.28	443.55	87.09	80.38	94.35
AUC_{0-T} (ng·h/mL)	9.4	11,424.35	11,715.35	97.52	93.71	101.48
$AUC_{0-\infty}$ (ng·h/mL)	9.4	11,693.41	11,976.76	97.63	93.79	101.63
	Food effect on reference product					
	Intra-subject CV (%)	Geometric LSMeans		Ratio (%)	90% Confidence limits (%)	
		R-fed (n=33)	R-fasted (n=33)		Lower	Upper
C_{max} (ng/mL)	24.9	394.54	271.5	145.32	131.14	161.03
AUC_{0-T} (ng·h/mL)	14	11,371.42	8190.37	138.84	130.98	147.17
$AUC_{0-\infty}$ (ng·h/mL)	14.1	11,669.96	8428.32	138.46	130.58	146.82

CV: Coefficient of variation, **LSMeans:** Least squares means, **T-fasted:** Posagil® 100 mg gastro-resistant tablet [test] under fasted conditions, **R-fasted:** Noxafil® 100 mg gastro-resistant tablet [reference] under fasted conditions, **T-fed:** Posagil® 100 mg gastro-resistant tablet [test] under fed conditions, **R-fed:** Noxafil® 100 mg gastro-resistant tablet [reference] under fed conditions.

Dayan N, et al. IDCM 2023;5:341

ÖU

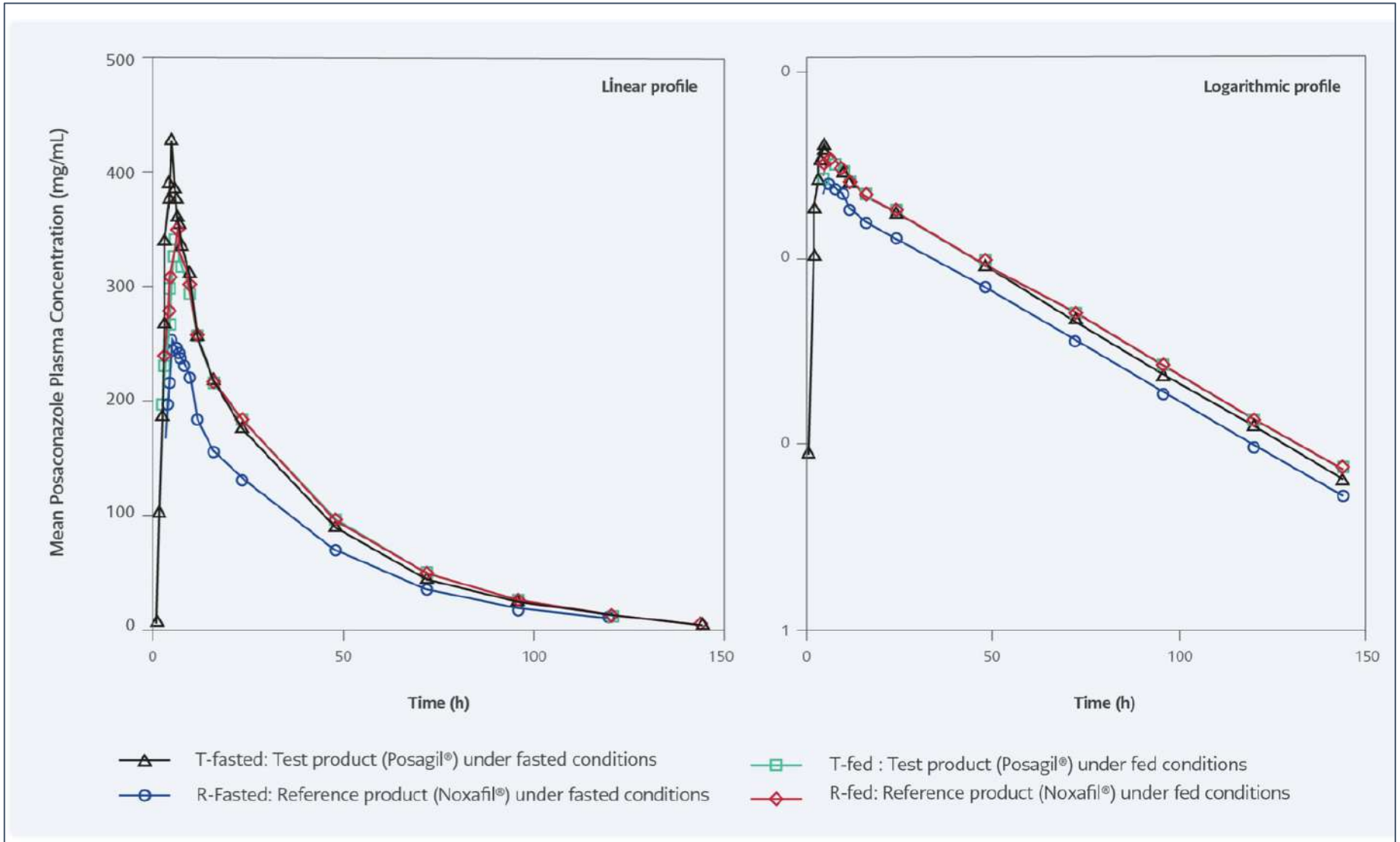


Figure 1. Linear and logarithmic mean posaconazole plasma concentration-time profiles following a single oral dose of 100 mg of posaconazole (test and reference product) administered to healthy subjects under fasted and fed conditions.

Dayan N, et al. IDCM 2023;5:341

ÖU

İdeal Antifungal

- Etki spektrumu geniş
- İlgili hasta grubunda etkinliği kanıtlanmış (ör. nötropenik)
- İlgili İFH'a etkisi kanıtlanmış
- Güvenli
- Günde tek doz kullanımı mümkün
- İV ve oral formülasyonu mevcut
- Oral formunun biyoyararlanımı yüksek
- Dokulara dağılımı iyi
- İlaç etkileşimleri minimal
- Direnç gelişme potansiyeli minimal
- Maliyet-etkin


Teşekkürler