Modena 19 maggio 2017

NEWS IN TERAPIA ANTIFUNGINA

Pierluigi Viale **Infectious Disease Unit** **Teaching Hospital S. Orsola – Malpighi Bologna**

About 1.2 billion people worldwide are estimated to suffer from a fungal disease. Most are infections of the skin or mucosa, which respond readily to therapy, but a substantial minority is invasive or chronic and difficult to diagnose and treat.

An estimated 1.5 to 2 million people die of a fungal infection each year, surpassing those killed by either malaria or tuberculosis.

Most of this mortality is caused by species belonging to four genera of fungi: *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis*.

Four areas that could refine the antifungal pipeline:

basic pursuits to identify fungal pathways, targets and mechanisms of action that could lead to new antifungal inhibitors

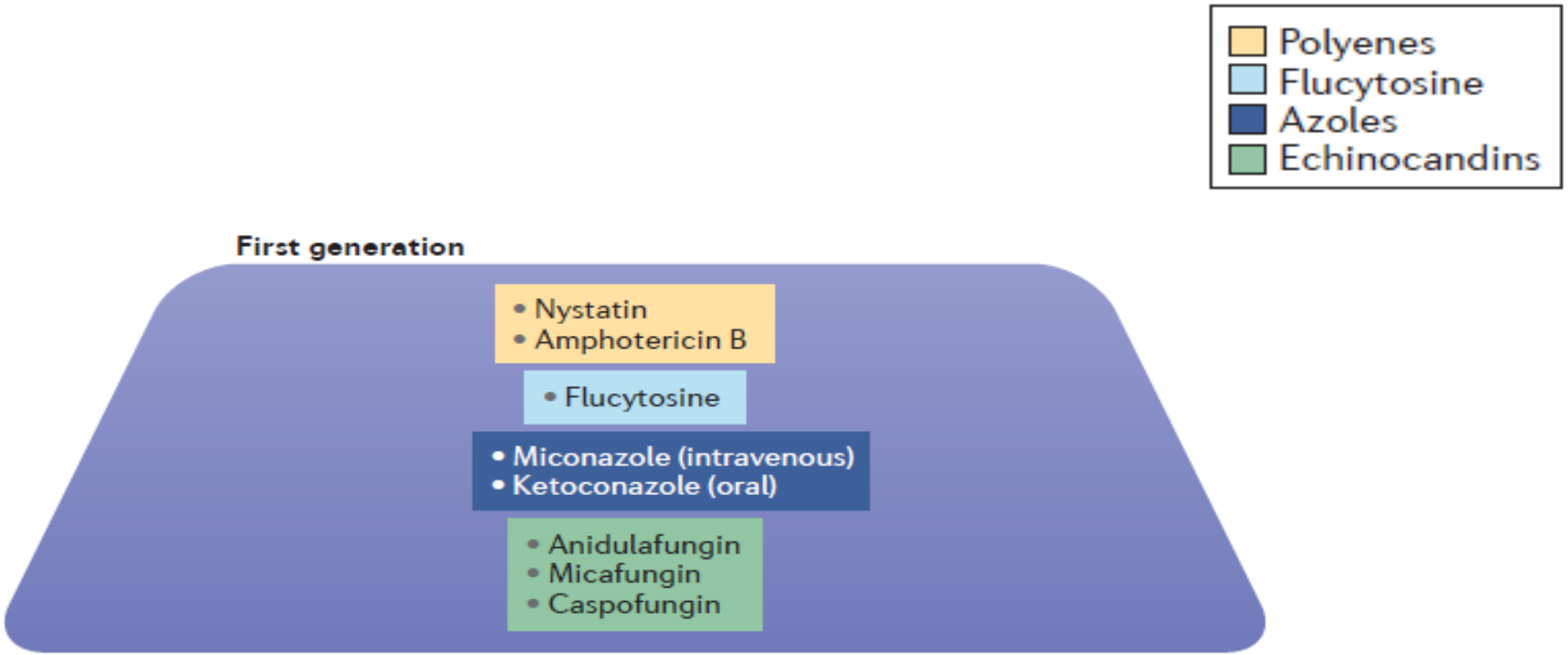
antifungal compounds and immune strategies currently in development that could become new antifungal therapies

improved formulations of existing compounds

the repurposing of drugs approved for other indications that have the potential to be antifungal agents.

The antifungal pipeline: a reality check

Perfect JR - Nature Rev Drug Discov. 2017 May 12



J Antimicrob Chemother 2016; **71**: 1786–1799
doi:10.1093/jac/dkw099 Advance Access publication 10 May 2016

Journal of Antimicrobial Chemotherapy

Utility of voriconazole therapeutic drug monitoring: a meta-analysis

Me-Linh Luong[1]*, Mona Al-Dabbagh[2,3], Andreas H. Groll[4], Zdenek Racil[5], Yasuhito Nannya[6], Dimitra Mitsani[7] and Shahid Husain[2]

Pooled analysis for efficacy endpoint demonstrated that patients with therapeutic voriconazole serum concentrations (1.0–2.2 mg/L) were more likely to have successful outcomes compared with those with subtherapeutic voriconazole serum concentrations (OR 2.30; 95% CI 1.39–3.81). A therapeutic threshold of 1.0 mg/L was most predictive of successful outcome (OR 1.94; 95% CI 1.04–3.62).

Pooled analysis for toxicity endpoint demonstrated that patients with supra-therapeutic voriconazole serum concentrations (4.0–6.0 mg/L) were at increased risk of toxicity (OR 4.17; 95% CI 2.08–8.36). A supratherapeutic threshold of 6.0 mg/L was most predictive of toxicity (OR 4.60; 95% CI 1.49–14.16).

J Antimicrob Chemother 2016; **71**: 1772–1785
doi:10.1093/jac/dkw045 Advance Access publication 10 March 2016

Journal of Antimicrobial Chemotherapy

Trough concentration of voriconazole and its relationship with efficacy and safety: a systematic review and meta-analysis

Haiying Jin[1,2], Tiansheng Wang[1,3]*, Bonnie A. Falcione[4], Keith M. Olsen[5], Ken Chen[1,3], Huilin Tang[1], John Hui[6] and Suodi Zhai[1]

Results: A total of 21 studies involving 1158 patients were included. Compared with voriconazole trough concentrations of >0.5 mg/L, levels of <0.5 mg/L significantly decreased the rate of treatment success (risk ratio=0.46, 95% CI 0.29–0.74). The incidence of hepatotoxicity was significantly increased with trough concentrations >3.0, >4.0, >5.5 and >6.0 mg/L. The incidence of neurotoxicity was significantly increased with trough concentrations >4.0 and >5.5 mg/L.

Conclusions: A voriconazole level of 0.5 mg/L should be considered the lower threshold associated with efficacy. A trough concentration >3.0 mg/L is associated with increased hepatotoxicity, particularly for the Asian population, and >4.0 mg/L is associated with increased neurotoxicity.

Tissue Pharmacokinetics and Pharmacodynamics of L-AmB in Uninfected and Infected Animals and Their Effects on Dosing Regimens

Adler-Moore JP et al, J Liposome Res. 2017 May 7:1-53.

By selecting a unique combination of lipids and amph B, the liposome composition has been optimized resulting in a formulation that is minimally toxic, targets to fungal cell walls, and distributes into and remains for days to weeks in various host tissues at drug levels above the MIC for many fungi.

Tissue accumulation and clearance with single or multiple intravenous administration is similar in uninfected and infected animal species, with tissue accumulation being dose-dependent and the liver and spleen retaining the most drug. The efficacy in animals appears to be correlated with drug tissue levels although the amount needed in a given organ varies depending upon the type of infection.

The long-term tissue retention of bioactive L-AmBis in different organs suggests that for some indications, prophylactic and intermittent drug dosing would be efficacious reducing the cost and possible toxic side-effects.

In addition, preliminary preclinical studies using non-intravenous routes of delivery, such as aerosolized L-AmBis, catheter lock therapy, and intravitreal administration, suggest that alternative routes could possibly provide additional therapeutic applications for this antifungal drug.

J Antimicrob Chemother 2016; **71**: 2075–2078
doi:10.1093/jac/dkw036

40 Journal of Antimicrobial Chemotherapy
Celebrating 40 Years
1975-2015

New therapeutic strategies for invasive aspergillosis in the era of azole resistance: how should the prevalence of azole resistance be defined?

Alexandre Alanio[1–3], Blandine Denis[4], Samia Hamane[1], Emmanuel Raffoux[5], Régis Peffault de la Tour[2,6], Sophie Touratier[7], Anne Bergeron[2,8] and Stéphane Bretagne[1–3]*

Safety and efficacy of treatment with liposomal Amph B in elderly patients at least 65 years old with hematological diseases. ***Ueda S et al, J Infect Chemother 2016; 22: 287-291***

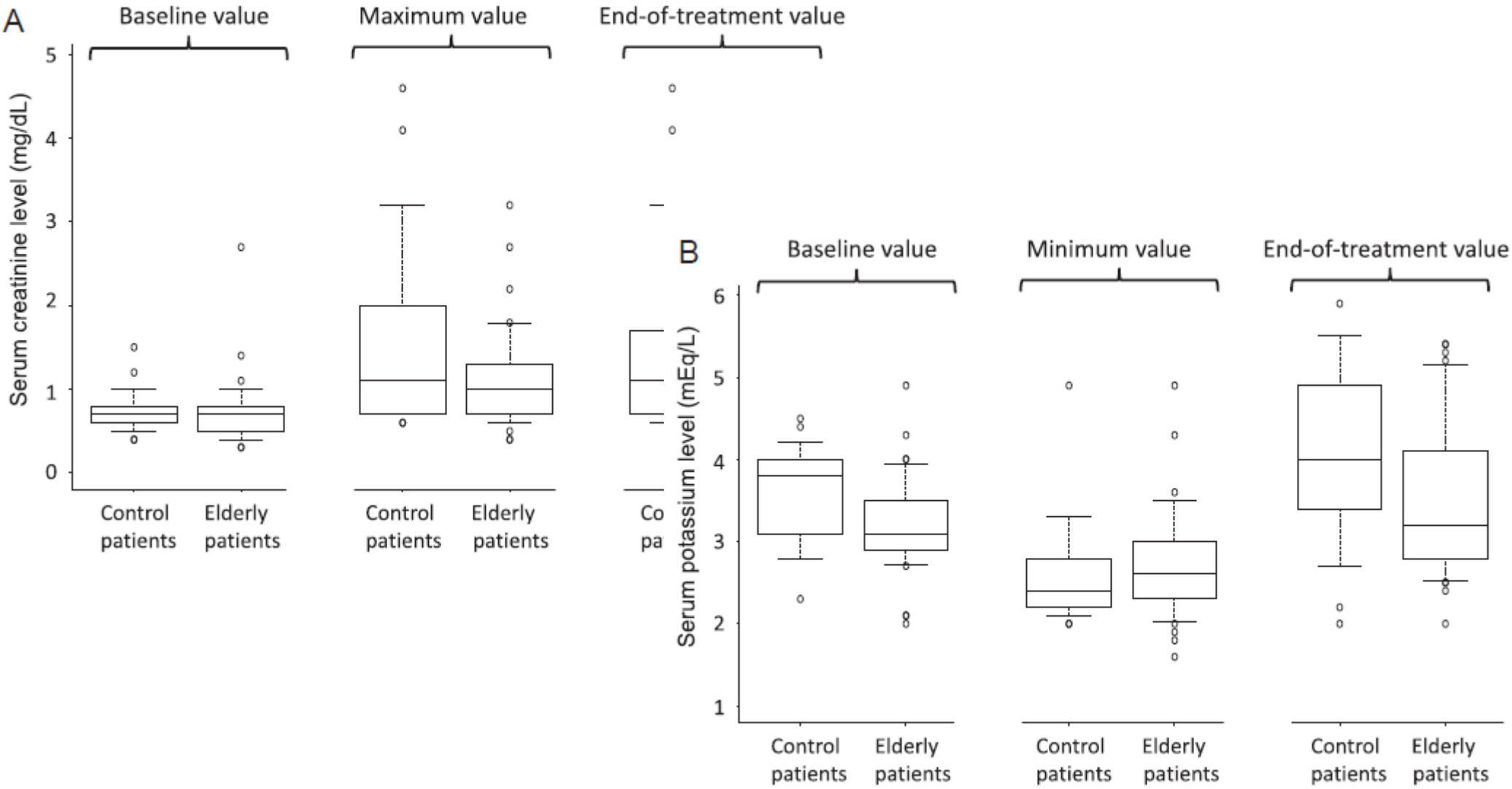
A retrospective analysis of 33 elderly patients with hematological diseases who received L-AMB. Their clinical outcomes were compared to those of 21 patients who were younger than 65 years.

		Elderly	Younger
Fungal infection	Aspergillosis	28	15
	Candidiasis	3	1
	Empirical therapy	2	5
Treatment type	Empirical therapy	2	5
	Possible infection	14	7
	Probable/proven infection	17	9
Dose of L-AMB	1.25 mg/kg/day	4	2
	2.5 mg/kg/day	25	18
	5.0 mg/kg/day	4	1
Combination with other antifungal agents	Fluconazole	4	0
	Itraconazole	4	1
	Voriconazole	1	1
	Micafungin	19	13
Use of other nephrotoxic agents	Calcineurin inhibitors	7	6
	Aminoglycoside/glycopeptide	13	9

Safety and efficacy of treatment with liposomal Amph B in elderly patients at least 65 years old with hematological diseases. *Ueda S et al, J Infect Chemother 2016; 22: 287-291*

	Elderly	Younger	*P* value
Alanine aminotransferase elevation			
Grade II–IV	4	7	0.085
Grade III–IV	1	5	0.028
2× baseline elevation	13	13	0.16
Aspartate aminotransferase elevation			
Grade II–IV	3	6	0.13
Grade III–IV	1	6	0.011
2× baseline elevation	15	11	0.78
Creatinine elevation			
Grade II–IV	5	6	0.31
Grade III–IV	0	2	0.15
2× baseline elevation	7	8	0.22
Hypokalemia			
Grade II–IV	26	20	0.13
Grade III–IV	24	16	1.00

Safety and efficacy of treatment with liposomal Amph B in elderly patients at least 65 years old with hematological diseases. ***Ueda S et al, J Infect Chemother 2016; 22: 287-291***



Safety and efficacy of treatment with liposomal Amph B in elderly patients at least 65 years old with hematological diseases. *Ueda S et al, J Infect Chemother 2016; 22: 287-291*

	Elderly	Younger	*P* value
Failure	2	1	0.88
Stable disease	12	5	
Partial or complete response	17	10	

REVIEWS OF ANTI-INFECTIVE AGENTS INVITED ARTICLE

Louis D. Saravolatz, Section Editor

Clinical Infectious Diseases® 2015;61(10):1558–65

Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent

Marisa H. Miceli[1] and Carol A. Kauffman[1,2]

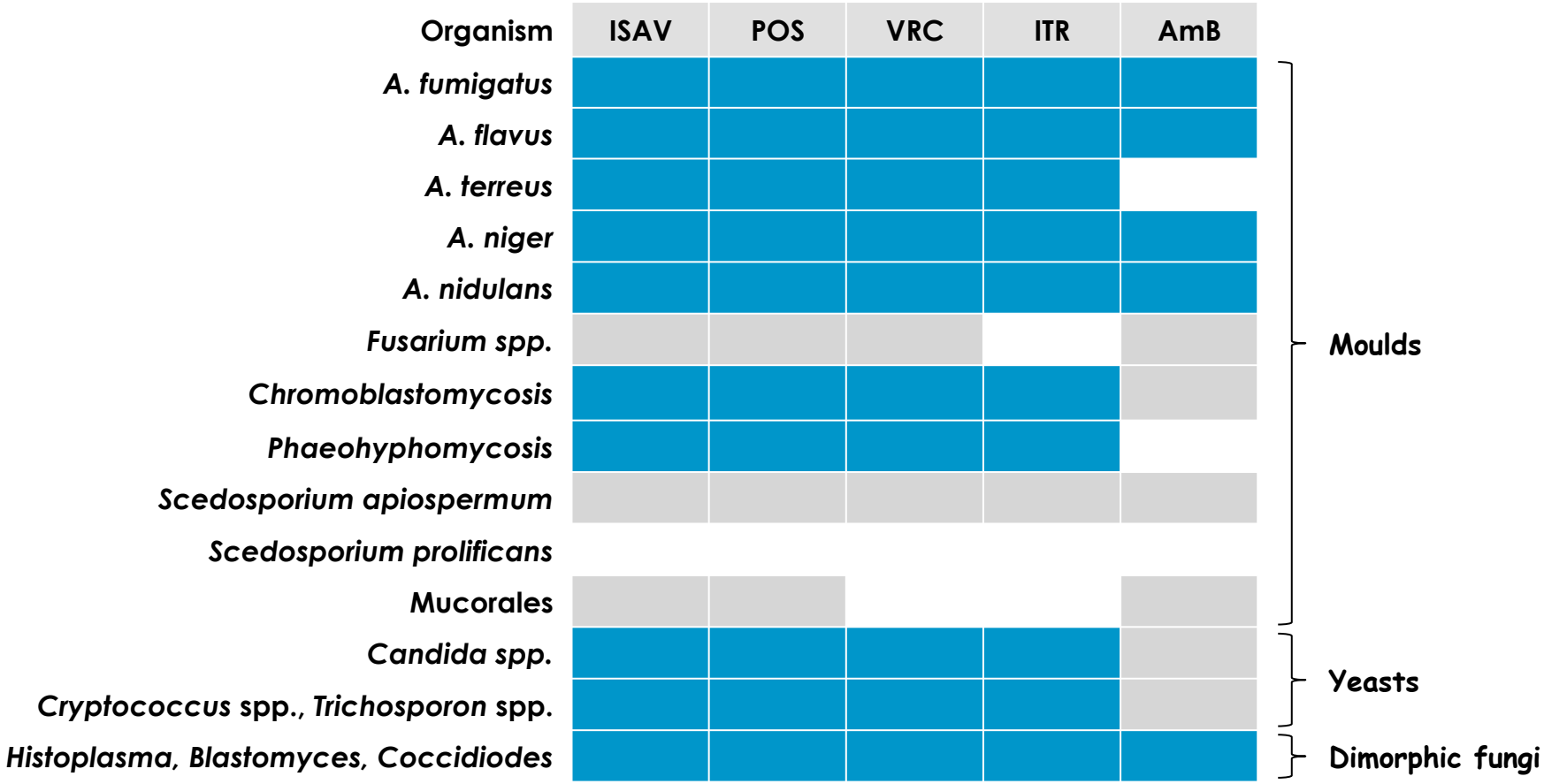
Isavuconazole is a new extended-spectrum triazole with activity against yeasts, molds, and dimorphic fungi. It is approved for the treatment of invasive aspergillosis and mucormycosis. Advantages of this triazole include the availability of a water-soluble intravenous formulation, excellent bioavailability of the oral formulation, and predictable pharmacokinetics in adults. A randomized, double-blind comparison clinical trial for treatment of invasive aspergillosis found that the efficacy of isavuconazole was noninferior to that of voriconazole. An open-label trial that studied primary as well as salvage therapy of invasive mucormycosis showed efficacy with isavuconazole that was similar to that reported for amphotericin B and posaconazole. In patients in these studies, as well as in normal volunteers, isavuconazole was well tolerated, appeared to have few serious adverse effects, and had fewer drug–drug interactions than those noted with voriconazole. As clinical experience increases, the role of this new triazole in the treatment of invasive fungal infections will be better defined.

KEY FACTS ON ISAVUCONAZOLE CLINICAL PHARMACOLOGY

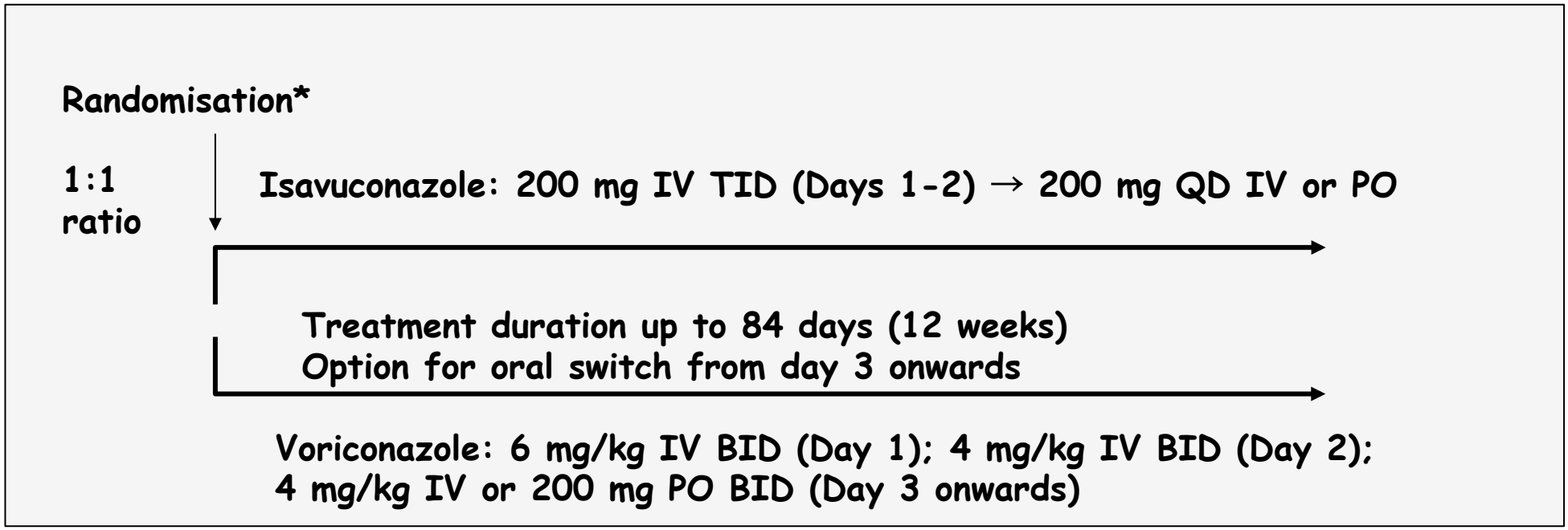
- Rapidly absorbed with 98% oral bioavailability
- No food effect, no pH effect
- Dose proportional increases in exposure up to 600 mg
- Large volume of distribution (450 L)
- Strong protein binding (>99%)
- Main route of elimination is via CYP3A4/5 metabolism
- <1% of unchanged drug excreted by kidneys
- Long terminal elimination half-life (~130 hours) requires a loading dose regimen to rapidly achieve steady-state
- No clinically relevant or significant exposure differences in elderly, Black, Caucasian, female, male, renally impaired including ESRD subjects

Isavuconazole: Overview of spectrum of activity

Activity
Variable activity
Little or no activity



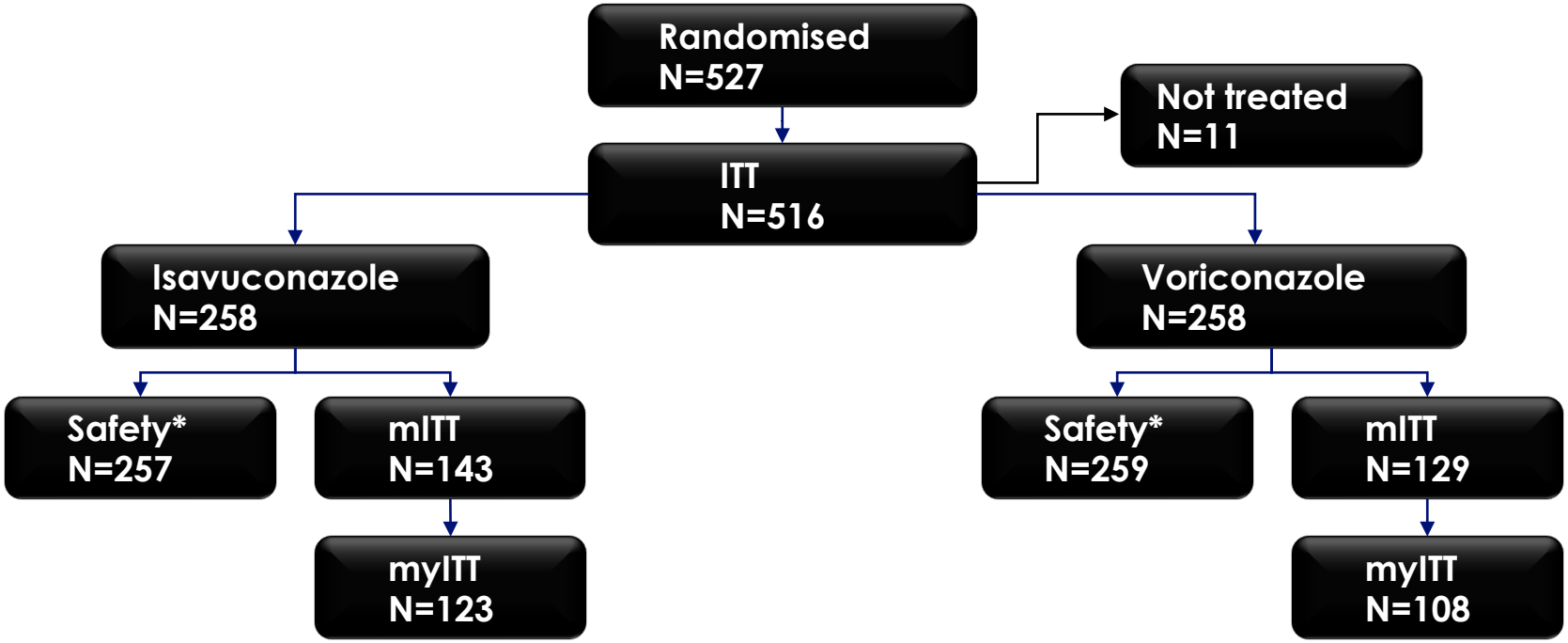
Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised - controlled, non-inferiority trial. *Maertens JA et al, Lancet 2016;387:760-9.*



Efficacy and safety assessments: Days 1, 2, 3, 7, 14, 28, 42, 63, 84;

Post-treatment Follow-up: 28 (±7) days after EOT

Patient disposition



Intent-to-treat (ITT): Received at least one dose of study medication

Modified ITT (mITT): Proven/probable IFD (DRC-assessed)

Mycological ITT (myITT): Microbiologically-confirmed invasive aspergillosis

Primary end point

All-cause mortality (ACM) through Day 42 (ITT population)

	Isavuconazole N=258	Voriconazole N=258
All-cause mortality, n (%)	48 (18.6)	52 (20.2)
Adjusted treatment difference, % (95% CI)	-1.0 (-7.8, 5.7)	
Deaths, n (%)	45 (17.4)	50 (19.4)
Unknown survival status, n (%)[b]	3 (1.2)	2 (0.8)

[a] Isavuconazole–voriconazole calculated by a stratified Cochran–Mantel–Haenszel method (strata: Geographic region, Allogeneic BMT/HSCT, and uncontrolled malignancy status)
[b] Patients with unknown survival status were counted as deaths

Overall response at end of treatment

Overall response, assessed by Data Review Committee, was similar for isavuconazole and voriconazole in modified intent-to-treat population

Overall response at EOT	Isavuconazole N=143 %	Voriconazole N=129 %
Success	35.0	36.4
Adjusted treatment difference* (95% CI)	1.6 (-9.3, 12.6#)	
Complete	11.9	10.1
Partial	23.1	26.4
Failure	65.0	63.6
Stable	29.4	25.6
Progression	35.7	38.0

Treatment-emergent adverse events

Patients with Treatment-emergent Adverse Events (TEAEs)	Isavuconazole N=257 %	Voriconazole N=259 %	p-value
Patients with any TEAE	96.1	98.5	NS
Study drug-related TEAEs	42.4	59.8	<0.05
Serious TEAEs	52.1	57.5	NS
Study drug-related serious TEAEs	10.9	11.2	NS
TEAEs leading to study drug discontinuation	14.4	22.8	<0.05
Study drug-related TEAEs leading to discontinuation	8.2	13.5	NS
Death	31.5	33.6	NS

Most frequent AEs (≥10%*) by System Organ Class

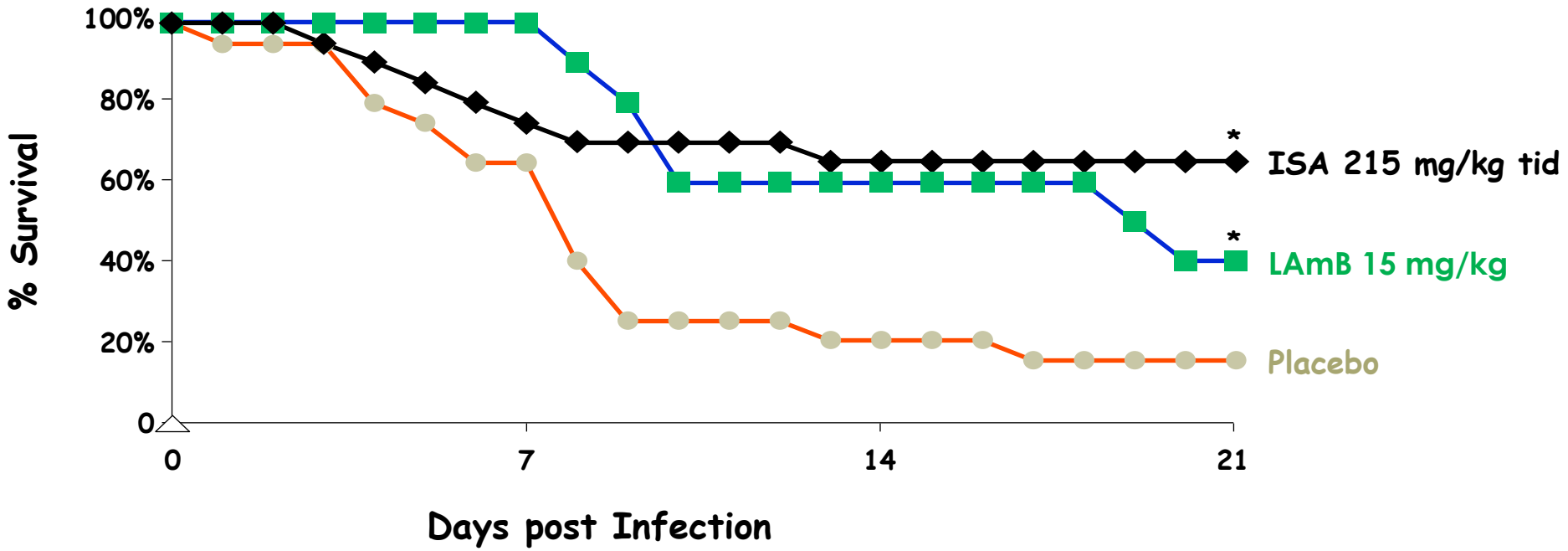
System Organ Class (%)	Isavuconazole (N=257)	Voriconazole (N=259)
Patients with any AE	96.1	98.5
Gastrointestinal disorders	67.7	69.5
Infections and infestations	59.1	61.0
General disorders and administration site conditions	57.6	55.6
Respiratory, thoracic and mediastinal disorders	55.6	56.8
Metabolism and nutrition disorders	42.0	46.7
Nervous system disorders	37.0	34.4
Skin and subcutaneous tissue disorders	33.5#	42.5
Investigations	33.1	37.1
Blood and lymphatic system disorders	30.0	31.7
Psychiatric disorders	27.2	33.2
Musculoskeletal and connective tissue disorders	26.8	29.7
Vascular disorders	26.1	29.7
Renal and urinary disorders	21.4	22.4
Cardiac disorders	16.7	22.0
Eye disorders	15.2#	26.6
Injury, poisoning and procedural complications	12.8	15.1
Hepatobiliary disorders	8.9#	16.2
Neoplasms benign, malignant and unspecified	7.4	12.0

Most frequent drug-related AEs (≥ 2%) by System Organ Class

System Organ Class (%)	Isavuconazole (N=257)	Voriconazole (N=259)
Gastrointestinal disorders	15.2	15.1
General disorders and administration site conditions	9.7	8.1
Investigations	9.7#	18.1
Nervous system disorders	7.4	6.9
Respiratory, thoracic and mediastinal disorders	6.2#	1.9
Skin and subcutaneous tissue disorders	5.4	7.7
Cardiac disorders	4.3	3.9
Metabolism and nutrition disorders	4.3	4.2
Vascular disorders	3.5	3.5
Eye disorders	3.1#	10.8
Infections and infestations	2.7	1.2
Psychiatric disorders	2.3#	11.2
Hepatobiliary disorders	1.9#	10.0
Blood and lymphatic system disorders	1.2	3.1

Isavuconazole efficacy in a neutropenic mouse model of mucormycosis

Isavuconazole enhanced survival of neutropenic mice with mucormycosis pneumonia to a similar extent as LAmB



N = 20 mice/group for placebo/ISA
N = 10 mice/group for LAmB

* p=0.025/0.04 for LAmB/ISA, respectively vs placebo; logrank test

Luo, Ibrahim et al., AAC 2014;58:2450-3

Isavuconazole vs Amphotericin B

Case-matched Analysis

Study population

21 patients from VITAL study receiving isavuconazole as primary treatment for proven/ probable Mucormycosis were matched with 33 FungiScope controls treated with various amphotericin formulations

Case matching criteria

- **Severe disease (CNS involvement or disseminated disease)**
- **Hematologic malignancy**
- **Surgery (resection or debridement)**

Primary efficacy end point

All-cause mortality through Day 42

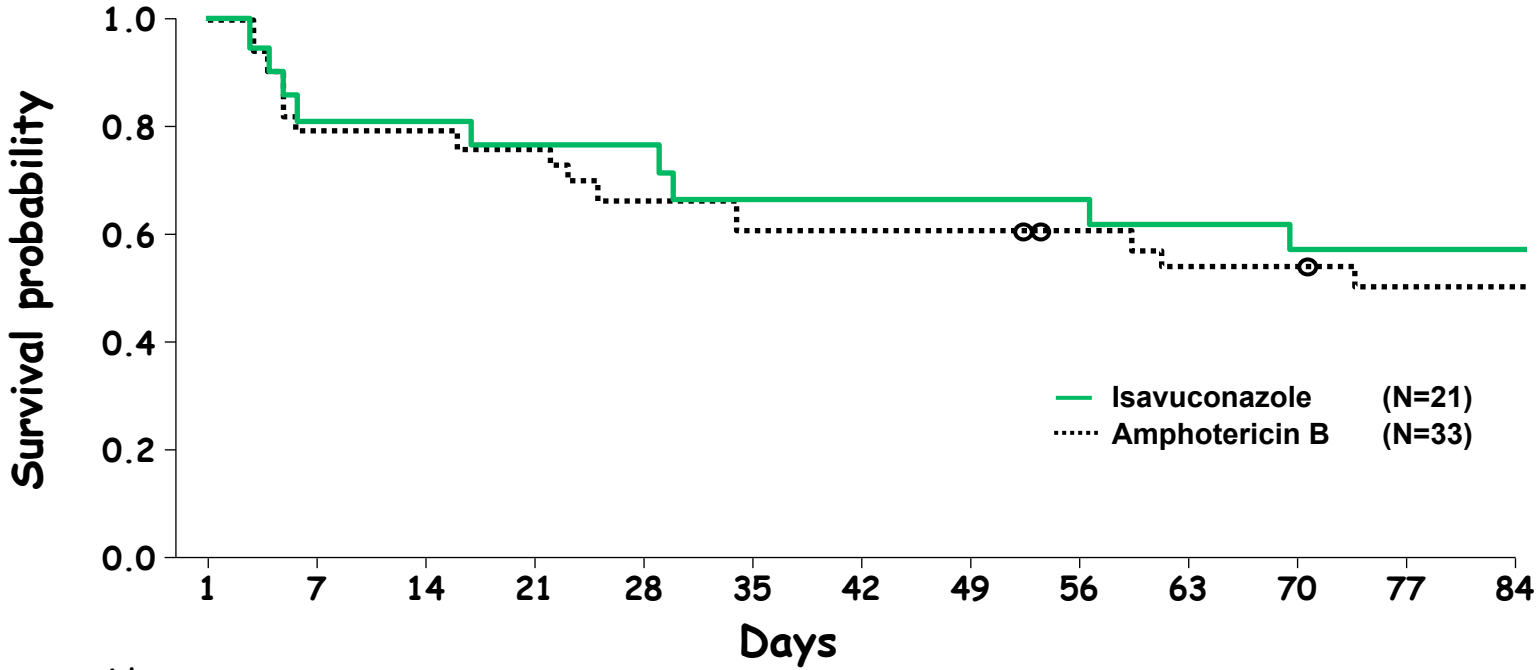
All-cause mortality through Day 42

ACM (crude and weighted rates) was similar between isavuconazole (33.3%) and amphotericin B (crude 39.4%, weighted 41.3%) for the primary treatment of Mucormycosis.

	All-cause mortality n/N (%)	95% CI
Study 0103 *Mucorales* primary therapy cases	7/21 (33.3)	(14.588, 56.968)†
Amphotericin-treated matched-controls (crude mortality)	13/33 (39.4)	(22.907, 57.861)†
Amphotericin-treated matched-controls (weighted mortality)	(41.3)	(20.213, 62.326)‡

Kaplan–Meier analysis through Days 42 and 84

Survival through Day 84 was similar between isavuconazole- and amph B-treated patients



Number of subjects at risk

The antifungal pipeline: a reality check

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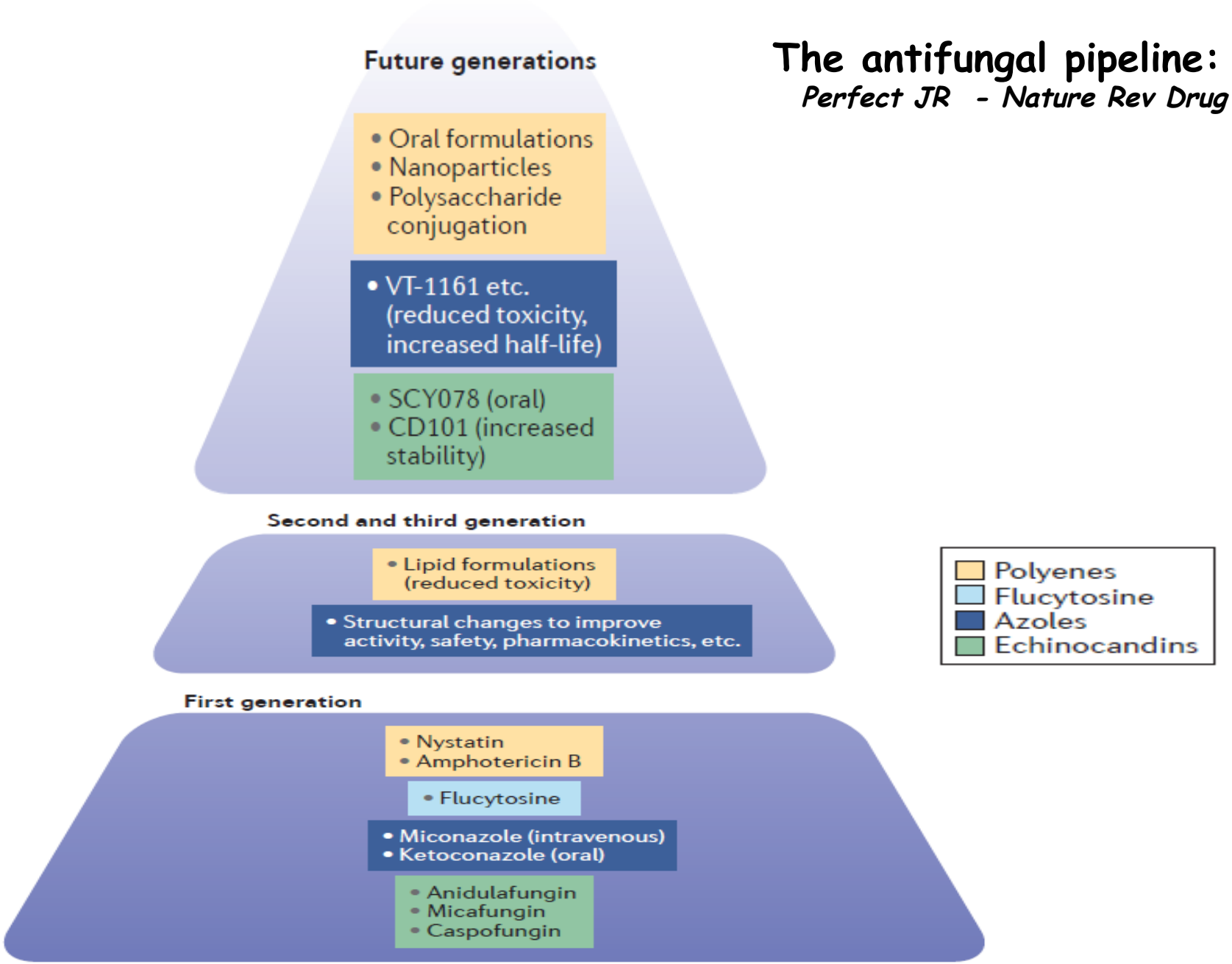

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Improving existing antifungals

Oral formulation for polyene treatment

An oral drug delivery formulation consisting of amphotericin B cochleate lipid–crystal nanoparticles has shown *in vivo* activity in animals and is now in clinical trials (NCT02971007 and NCT02629419).

Echinocandin CD101

A new 1,3-β-glucan synthase inhibitor.
Phase II trials (NCT02733432 and NCT02734862) have been initiated for this long-acting echinocandin (weekly dosing).

SCY078 (also known as enfumafungin)

A new 1,3-β-glucan synthase inhibitor.
Oral bioavailability. Similar activity against yeasts to that of the echinocandins, but has some *in vitro* antifungal activity against echinocandin-resistant yeasts.
Phase II trials for treatment of yeast infections (NCT02679456).

New "modified" azoles

Reduced interactions with cytochrome P450 → less drug-drug interactions.
VT-1161 (only for superficial mucoses), VT-1129 (a very potent anti-cryptococcal compound), VT-1598 (endemic mycosis and cryptococcosis).

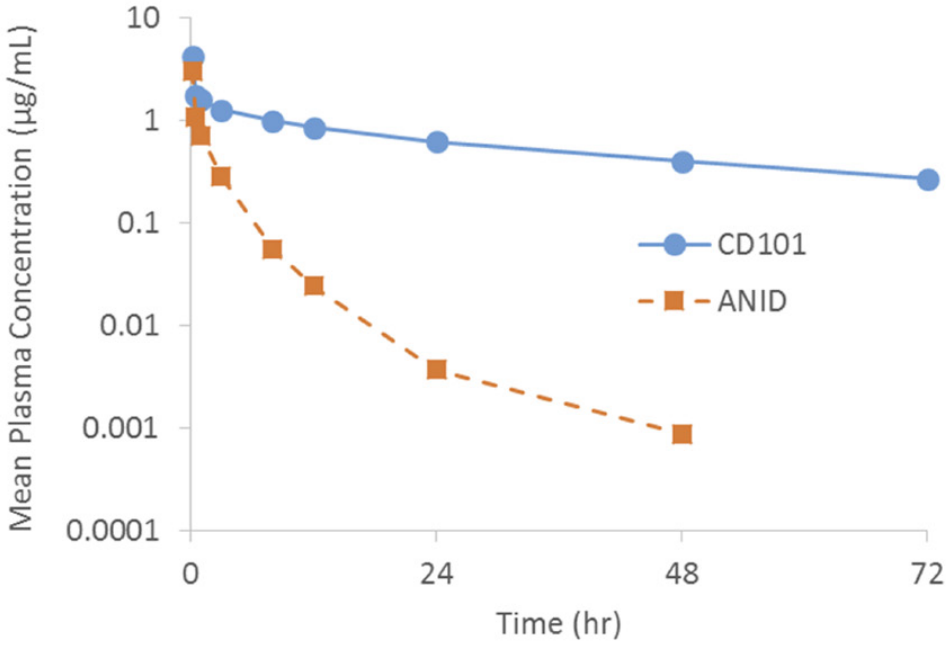
Cellular Microbiology (2016) **18**(9), 1308–1316

doi:10.1111/cmi.12640
First published online 22 July 2016

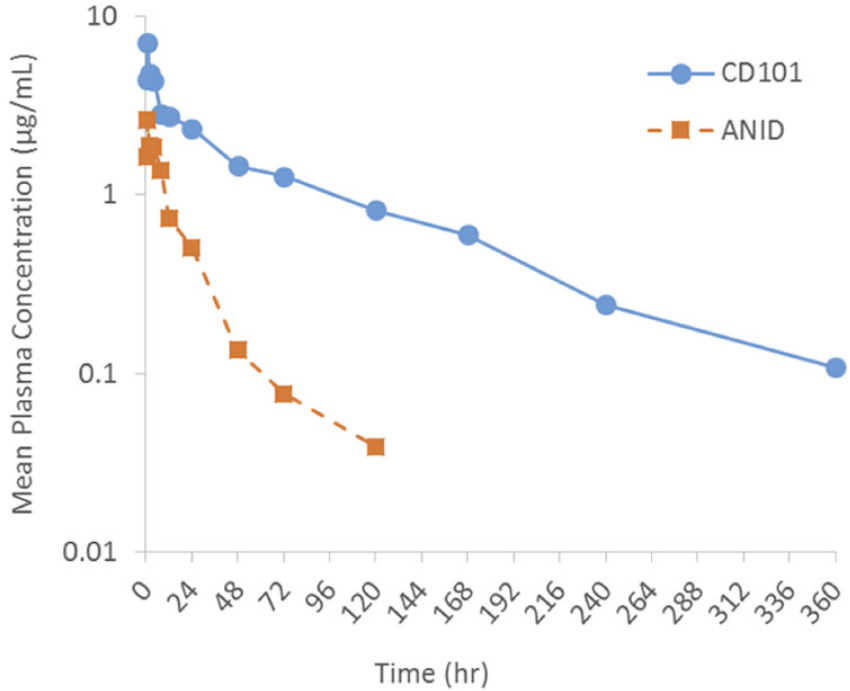
CD101: a novel long-acting echinocandin

Pharmacokinetics of the Novel Echinocandin CD101 in Multiple Animal Species Ong V et al , Antimicrob Agents Chemother 2017; 61:e01626-16.

(c) Cynomolgus Monkey (n=3/group)



(d) Chimpanzee (n=2/group)



CD101's concentration-dependent pattern of fungicidal activity in combination with its slow clearance from the body, has important implications for dose regimen selection and front-loading drug exposure (i.e., maximizing drug effect early in the course of therapy to increase the rate and extent of pathogen killing, reduce and prevent resistance, and ultimately improve clinical outcomes)

The antifungal pipeline: a reality check

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New agents in development

APX001

It is an inhibitor of glycosyl phosphatidylinositol (enzyme for the biosynthesis of glycerophospholipids, sphingolipids and ergosterol) .

Antifungal activity *in vitro* against *Candida* spp., *Aspergillus* spp., some drug-resistant yeasts and difficult to treat moulds, such as *Fusarium* spp. and *Scedosporium* spp.

It has some direct antifungal activity against the Mucorales *in vitro*.

A present it is in phase I (NCT02956499 and NCT02957929), and phase II clinical trials are planned.

Nikkomycin Z

It has a protracted history.

It is a competitive inhibitor of chitin synthase, involved in trehalose biosynthesis essential for fungal pathogen virulence

Very potent fungicidal agent for the treatment of murine coccidioidomycosis, histoplasmosis and blastomycosis.

Additive or synergistic *in vitro* and *in vivo* activity with the 1,3-β-glucan synthase inhibitors (echinocandins).

New agents in development

MGCD290

An histone deacetylase 2 (Hos2) inhibitor, able to reverse azole resistance when co-administrated

This compound has the potential to be a potent enabler to increase fungicidal activity, overcome resistance and broaden the activity of other antifungal drugs (*in vitro* and in animal models). Now studied only in VVC

Aureobasidin A

Inhibitor of inositol phosphorylceramide synthase an essential and unique enzyme involved in fungal sphingolipid biosynthesis.

Now under study novel derivatives of aureobasidin A.

Antifungal activity against yeasts and moulds.

The antifungal pipeline: a reality check

John R. Perfect - Nature Rev Drug Discov. 2017 May 12

Repurposing old drugs

Rifampin, an antibacterial RNA polymerase inhibitor

Verapamil, a calcium channel blockers

Immunosuppressive compounds such as **cyclosporine, tacrolimus and rapamycin**, if manipulated, could have reduced immunosuppressive action and more fungicidal effect.

Tamoxifen, an oestrogen receptor-targeting drug, has anti-cryptococcal activity and could be combined with fluconazole as an all-oral treatment option to enhance anti-cryptococcal activity.

Sertraline, a selective serotonin reuptake inhibitor, has been shown to potentiate the anti-cryptococcal activity of azoles. After a successful exploratory phase II study with the use of sertraline as adjunctive therapy for cryptococcal meningitis, the investigators are approximately half-way through a phase III study to determine the value of adding this compound to a standard induction therapy for cryptococcal meningitis (NCT01802385).

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Host immune cell-targeted approaches

There have been promising results using adoptive transfer of activated immune cells in infections with *Candida* spp., *Aspergillus* spp. and Mucorales in animal models.

Therapeutic fungal vaccines: A *Candida* spp. vaccine has been used in phase I and phase II studies (NCT01447407 and NCT01926028).

Antifungal biological agents

The use of monoclonal antibodies to attack fungi has been validated in animal models as a potential treatment strategy.

- Efungumab
- efungumab-C28Y variant

… to be continued …