Official journal of the Spanish Society of Chemotherapy

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Trends in infectious diseases

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New trends in antifungal treatment: What is coming up?

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Revista Española de Quimioterapia
doi:10.37201/req/s01.14.2023

ABSTRACT

New antifungal agents are needed to overcome limitations of available ones such as poor pharmacokinetic traits, toxicity, drug-drug interactions, limited clinical efficacy, and emerging antifungal resistance. New antifungal drugs belong to well-known families (azoles, polyenes, or beta-d-glucan synthase inhibitors) or to drug families showing completely new mechanisms of action. Some drugs have a head start in terms of potential to reach the clinical setting and are here reviewed.

Keywords: Fosmanogepix, olorofim, ibrexafungerp, rezafungin

BACKGROUND

Understanding of invasive fungal infections requires taking into account multidirectional interactions among patients, causative agents, and antifungal drugs (Figure 1). New antifungal agents are needed to overcome limitations of available antifungals such as poor pharmacokinetic traits, toxicity, drug-drug interactions, limited clinical efficacy, and emerging antifungal resistance. Mapping out new drugs lies on expanding the number of the ones belonging to well-known families (azoles, polyenes, or beta-d-glucan inhibitors) or designing molecules showing completely new mechanisms of action. Some drugs have a head start in terms of potential to reach the clinical setting and are here reviewed (Figure 2); their main pharmacokinetic properties and potential clinical niches are summarised in Tables 1 and 2.

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NEW AZOLES

Opelconazole [1,2]. It is a new synthetic azole designed for topical use and nebulised administration; the drug shows high exposure and long retention at the site of infection (lungs). Since it is not absorbed, systemic effects such as toxicity and liver drug-drug interactions are avoided. It is an inhibitor of *Aspergillus* sterol 14-alpha-demethylase (CYP51 enzymes), similarly to posaconazole. Its spectrum of activity has not been well studied yet but it shows *in vitro* activity against *C. auris*, *C. albicans*, *C. glabrata*, *C. krusei*, *Cryptococcus*, *A. terreus*, and *A. fumigatus* (synergistic activity combined with voriconazole or posaconazole has been observed against the latter). *In vitro* activity against *A. flavus*, *A. niger*, and Mucorales is poor. It shows dose-dependent activity, and the best PK/PD index predictor is unknown. Data from animal models showed efficacy of opelconazole for the treatment and prevention of invasive pulmonary aspergillosis. Clinical data from humans is still very limited.

Oteseconazole [3,4]. It is a synthetic tetra-azole showing a high affinity to the fungal Cyp51 that confers the drug an enhanced specificity for fungal Cyp51 and fewer drug-drug interactions and good tolerability. It has shown *in vitro* activity against *Candida* and the potential activity against moulds is unknown. It has been under clinical evaluation for the treatment of superficial *Candida* infections including vaginitis and onychomycosis; it was approved by the FDA in 2022 for the treatment of vulvovaginal candidiasis.

POLYENES

Encochleated amphotericin B [5,6]. Amphotericin B was marketed in the 50's and shows the broadest fungicidal spectrum of *in vitro* activity. Its use is hampered by toxicity

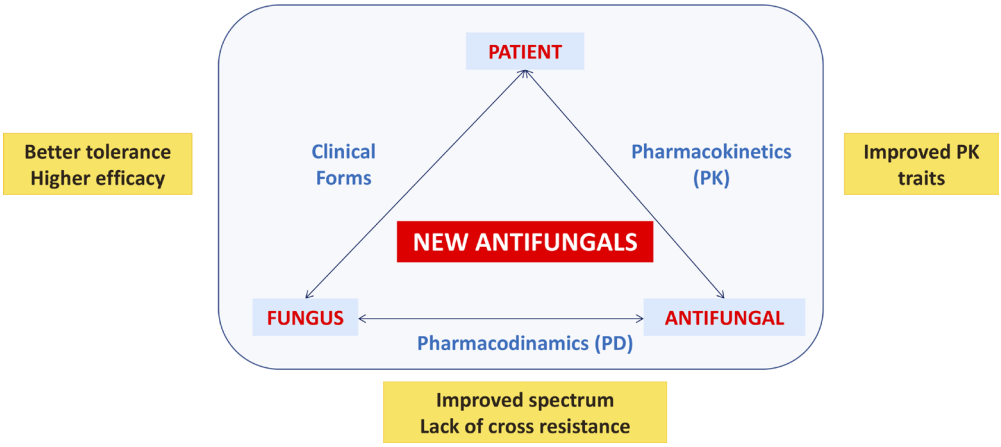

Figure 1 Graph showing interactions among the three elements playing a role in invasive fungal infections (patients, aetiological agents, and antifungal drugs)

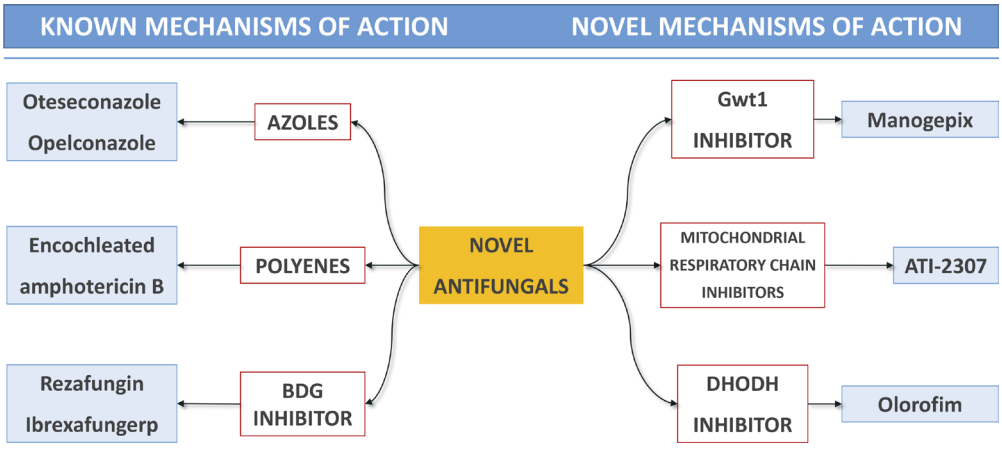

Figure 2 New antifungal agents in the horizon for the treatment of fungal infections

and formulation problems (highly water-insoluble and self-aggregate tendency). Vehicles in the formulation are needed and current formulations allow intravenous administration exclusively. The molecule gets protection into encochleating lipid-based vehicles, which means increasing chemical stability, safety and clinical efficacy, and allowing oral absorption. Encochleated amphotericin B is more stable than liposomes and less prone to oxidation, resists enzyme degradation, and shows slow release of the drug. The spectrum of activity is similar to other formulations of the drug (with limited activity against *A. terreus*, *A. flavus*, and *A. nidulans*) and shows dose-dependent activity; the best PK/PD index predictor is unknown. Data from animal models showed efficacy of encochleated amphotericin B for the treatment systemic candidiasis, cryptococcal meningitis, and invasive pulmonary aspergillosis. Clinical data from humans is still very limited.

NEW BETA-D-GLUCAN INHIBITORS

Rezafungin [7,8]. It is a second generation echinocandin whose mechanism of action and spectrum of activity is similar to the currently available echinocandins, including *C. auris*. It is a derivative of anidulafungin in which the modification cyclic core conferred the drug a safer profile and long half-life (130 hours) which in turn resulted in high drug exposure, one-week single dose administration, and lower induction of FKS mutations. It shows concentration-dependent activity (*in vitro*) or dose-dependent activity (animal models); the best PK/PD index predictor is AUC / MIC (*Candida*), or AUC / MEC or C_{max} / MEC (*Aspergillus*). Rezafungin showed non-inferiority compared to caspofungin for the treatment of patients with candidaemia and FDA approved the drug for the treatment of candidaemia (it is under evaluation by EMA now). Clinical trials

Table 1 Main pharmacokinetic properties of the new antifungal agents

Drug	Administration			Penetration				Expected drug-drug interactions	Excretion
	Oral	IV	Other	CNS	Eye	Urine	Tissue distribution		
Opelconazole	Unavailable	Unavailable	Available (Nebulised)	No	No	No	Topical use (lungs)	Non expected	Unknown
Oteseconazole	Available	Unavailable	Unavailable	No	No	Yes	Unknown	Non expected	Faeces and urine
Enclocheated amphotericin B	Available	Unavailable	Unavailable	Yes	Yes	Yes	Wide	Non expected	Unknown
Rezafungin	Unavailable	Available	Unavailable	No	No	No	Wide	Non expected	Biliary elimination
Ibrexafungerp	Available	Available	Unavailable	No	No	Yes (uvea)	Wide	Moderate	Biliary elimination
Manogepix	Available	Available	Unavailable	Yes	Unknown	Unknown	Wide	Moderate	Unknown
Olorofim	Available	Available	Unavailable	Yes	Unknown	Unknown	Wide	Moderate	Unknown

IV, intravenous; CNS, central nervous system

assessing the role of rezafungin for the prevention of invasive fungal infections in allogenic SCT, and evaluating pharmacokinetic properties in paediatric patients, are underway.

Ibrexafungerp [8,9]. It is a semi-synthetic derivative of enfumafungin, a tri-terpenoid non-competitive inhibitor of 1,3-B-D-glucan synthase enzyme complex. It is not an echinocandin from a chemical point of view, but its mechanism of action is similar to the one of the echinocandins, yet the exact point of drug binding to the enzyme might not be identical. It retains some activity against echinocandin-resistant *Candida* isolates, can be orally administered, and has shown high penetration into intra-abdominal lesions. It shows concentration-dependent activity (*in vitro*) or dose-dependent activity (animal models); the best PK/PD index predictor is AUC / MIC (*Candida*), or AUC / MEC or C_{max} / MEC (*Aspergillus*). Ibrexafungerp has shown encouraging results on treatment of non-neutropenic patients with invasive candidiasis, women with vulvovaginitis (current approved indication), and is under evaluation for the treatment of patients with IFI refractory to other treatments, patients with *C. auris* infections, or patients with invasive aspergillosis (treatment combined with voriconazole).

ACYLTRANSFERASE ENZYME (GWT1) INHIBITORS

Fosmanogepix [10,11]. It is a prodrug (manogepix is the active moiety) that inhibits the fungal acyltransferase enzyme (Gwt1), an important component of the glycosylphosphatidylinositol (GPI)-anchored protein maturation pathway, that is essential for trafficking mannoproteins to the fungal cell membrane and wall. Given its new mechanism of action, it shows a broad spectrum of antifungal activity against *Candida* spp. (except for *C. krusei*), *Cryptococcus* and other non-Candida yeasts, *Aspergillus* spp and *Fusarium* spp, and lacks of cross-resistance. The best PK/PD indexes predictor of response are AUC/MIC and AUC/MEC (aspergillosis), and AUC/MIC (invasive candidiasis). The drug is under clinical evaluation for the treatment of candidiasis (including *C. auris*), aspergillosis, and other mould infections (*Scedosporium* and *Fusarium*). Preliminary data (including tolerability and clinical efficacy) are encouraging.

MITOCHONDRIAL RESPIRATORY CHAIN INHIBITORS

ATI-2307 [12]. It is an aromatic diamidine pentamidine-like compound with antifungal activity against *Candida* spp, *Aspergillus* spp., *Fusarium*, and *C. neoformans*. ATI-2307 acts by means of selectively inhibition of yeast mitochondrial respiratory chain complexes III and IV. Animal models data have shown efficacy of the compound in the treatment of cryptococcal meningitis in rabbits.

DIHYDROOROTATE DEHYDROGENASE INHIBITORS

Olorofim [13,14]. It is a first-in-class drug belonging to a new family of antifungal agents, the orotomides, whose mechanism of action lies on the inhibition of the pyrimidine biosynthesis by blocking the action of the enzyme dihydroorotate dehydrogenase (DHODH). Olorofim shows a peculiar spectrum of activity and lacks *in vitro* activity against *Candida* spp and Mucorales. In contrast, it has potent activity against most of clinically relevant *Aspergillus* spp. (including azole-resistant strains) and *Scedosporium*. The ratio of the minimum total plasma concentration / MIC (C_{min}/MIC) was the PK/PD index that best predicts clinical response. Currently, olorofim is under evaluation for the treatment of invasive mould infections in patients with limited treatment options.

Table 2 Potential clinical niches for new antifungal agents

	Preclinical name	Company	Prophylaxis	Vaginitis	Candidaemia	Aspergillosis	Cryptococcosis	Other IFIs
Opelconazole	PC945	Pulmocide Ltd	++ (Lung transplant, cystic fibrosis)	+	+	++	-	-
Oteseconazole	VT-1161	Mycovia	+	++	+	+	+	+
Enclocheated amphotericin B	MAT-2203	Matinas Biopharma	-	-	+	+	++	-
Rezafungin	CD101 SP-3025 Biafungin	Cidara→ Mundipharma	++	-	++	+	-	+
Ibrexafungerp	SCY-078	Scynexis→ GSK	++	++	++	++	-	+
Manogepix	APX001A	Amplyx→ Pfizer→ Basilea	+	+	++	++	+	++
Olorofim	F901318	F2G	-	-	-	++	-	++

- no clinical trials and unlikely for the indication based on in vitro spectrum of activity and PK properties, or discouraging clinical data
+ no clinical trials but room for indication based on in vitro spectrum of activity and PK properties
++ clinical trials and likely for the indication based on in vitro spectrum of activity, PK properties, and clinical data

FUNDING

This study was supported by grants PI21/00450 from the *Fondo de Investigación Sanitaria* (FIS. Instituto de Salud Carlos III; *Plan Nacional de I+D+I* 2017-2020).

JG holds a permanent position at the *Fundación para Investigación Sanitaria del Hospital Gregorio Marañón*.

TRANSPARENCY DECLARATIONS

JG has received funds for participating in educational activities organised on behalf of Gilead, Pfizer, MSD, and Mundipharma; they also received research funds from FIS, Gilead, Scynexis, F2G, Mundipharma, and Cidara, outside the submitted work.

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