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Antifungal drugs: What brings the future?

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Abstract

The high burden and growing prevalence of invasive fungal infections (IFIs), the toxicity and interactions associated with current antifungal drugs, as well as the increasing resistance, ask for the development of new antifungal drugs, preferably with a novel mode of action. Also, the availability of oral or once-weekly alternatives would enable ambulatory treatment resulting in an improved patient's comfort and therapy adherence. However, only one new azole and two new posaconazole-formulations were marketed over the last decade. This review focuses on the antifungal drugs in the pipeline undergoing clinical evaluation. First, the newest azole, isavuconazole, with its improved safety profile and reduction in DDIs, will be discussed. Moreover, there are two glucan synthase inhibitors (GSIs) in the antifungal pipeline: rezafungin (CD101), a long-acting echinocandin with an improved stability that enables once weekly administration, and SCY-078, an orally available GSI with efficacy against azole- and echinocandin resistant isolates. A new oral formulation of amphotericin B will also be presented. Moreover, the first representative of a new antifungal class, the orotomides, with a broad spectrum and no cross-resistance with current antifungal classes, will be discussed. Finally, an overview of other antifungals that are still in earlier clinical development phases, is provided.

Key words: antifungal drugs, pipeline, invasive fungal infections, treatment, review.

Introduction

Invasive fungal infections (IFIs) have a major impact on morbidity and mortality in humans. Many fungal species cause infections with mortality rates exceeding 50%, and IFIs are responsible for about one and a half million deaths every year. Especially *Cryptococcus*, *Candida*, *Aspergillus*, and *Pneumocystis* species contribute to those fungal related-deaths.[1] It even seems that this amount is still increasing, despite the current available antifungal medication.[2]

As IFIs are not common in healthy people, the increasing prevalence is probably due to the growing group of immunosuppressed hosts who are sensitive to this kind of infections.[3] Even though our modern healthcare is able to treat previously life-ending diseases, this often comes at the cost of immunosuppression. Solid organ and blood or marrow transplantations are performed, immunosuppressive drugs are administered, cancers are treated with aggressive chemotherapy, complicated surgery is carried out, and more patients live with underlying comorbidities.[2,3] Also, human immunodeficiency virus (HIV) is still an important cause of immunosuppression worldwide.[3]

The current antifungal armamentarium consists of four different classes of antifungal drugs: the polyenes, azoles, echinocandins, and flucytosine.

The polyene amphotericin B (AmB) acts by binding to ergosterol after which the fungal cell membrane disintegrates; the resulting leakage of intracellular compounds leads to fungal cell death.[4] AmB has a broad spectrum of fungicidal activity, covering yeasts, moulds, and dimorphic fungi; however, its clinical use is hampered by the lack of an oral formulation, by acute infusion-related toxicity, and by dose-limiting acute as well as chronic nephrotoxicity due to the interaction with human cholesterol-containing membranes. Although various lipid-based formulations of AmB (including liposomal AmB and AmB lipid complex) display a more favorable tolerability and toxicity profile, the nephrotoxic side effects and associated electrolyte disturbances, albeit diminished, are not fully eliminated.[3,5–7]

Azoles (in particular fluconazole, itraconazole, voriconazole, posaconazole) are commonly used for preventing and treating IFIs and are available as oral (PO) and intravenous (IV) formulations. They block the synthesis of ergosterol, the most important sterol of the fungal cell membrane, by inhibiting the lanosterol 14α-demethylase enzyme. Although considered as drugs of choice in many clinical instances (e.g., first line therapy of invasive aspergillosis or prevention of IFI in prolonged neutropenic patients), the class of azole antifungals is characterized by a number of major shortcomings, including (but not limited to) potentially hazardous drug-drug interactions through interactions with the cytochrome P450 enzyme system (3A4, 2C9, and 2C19), erratic absorption (itraconazole and posaconazole oral solution) resulting in unpredictable exposure, nonlinear and saturable pharmacokinetics with need for therapeutic drug monitoring (voriconazole), hepatobiliary adverse events (a class effect), QTc prolongation (ECG) with an associated (potentially fatal) arrhythmia, such as *torsades de pointes*, reluctance to use the cyclodextrins-containing intravenous formulation in renally impaired patients (itraconazole, voriconazole, posaconazole), acute adverse events (e.g., hallucinations and voriconazole, photosensitivity reactions) as well as toxicities associated with their prolonged use (such as cardiotoxicity, neuropathy, squamous skin cancer, fluoride-associated periostitis), and the emergence of azole resistance in *Aspergillus fumigatus* species.[3,4,7–9]

The echinocandins (caspofungin, anidulafungin, micafungin) target the biosynthesis of the fungal cell wall, a structure not present in mammalian cells. Collectively they inhibit the fungal 1,3-β-glucan synthase. This depletes the fungal cell wall of 1,3-β-glucan, one of its main components, which results in osmotic ballooning and lysis of the fungal cell. Echinocandins have very few clinically significant drug-drug interactions and display a very favorable tolerability and toxicity profile. Currently they are recommended as drugs of choice for the treatment of invasive candidiasis, including candidemia.[3,7] Unfortunately, these drugs are only available as a once-daily intravenous therapy.

Flucytosine interferes with the nucleic acid synthesis but is not routinely used in monotherapy because it is prone to drug resistance development. Bone marrow suppression is a major side effect. It is mostly used in combination with a polyene in the treatment of cryptococcal meningitis.[3]

Why do we need novel antifungal agents and/or agents with novel mode of action?

A wide antifungal armamentarium is useful to select the best therapeutic option for each patient. For example, when administering antifungals in combination with other medication, drug-drug interactions are to be considered. Important are the CYP450-interactions, which take place on the level of the cytochrome P450 enzymes. These enzymes are predominantly present in the liver and are responsible for phase I metabolism of a wide range of drugs. There are molecules that can inhibit or induce the CYP450-enzymes, and this will influence the metabolism and exposure of drugs metabolized by these enzymes (substrates). In the presence of a CYP450-inducer, for example, the metabolism of substrates will be increased. A CYP450-inhibitor will influence vice versa. Moreover, there are multiple iso-enzymes belonging to the total group of CYP450-enzymes, and metabolism, induction, and inhibition are selective for each iso-enzyme. For this reason, it is important to know for which CYP450-enzymes an antifungal drug is a substrate, inhibitor or inducer.[10–12] Next to CYP450 enzymes, phase II enzyme systems (involved in among others glucuronidation processes) are relevant for selected antifungal drugs.

Apart from many of the shortcomings already identified, resistance to currently available antifungal drugs is a growing problem.[13] Even in drug-naive patients, an increase in resistant *Candida* and *Aspergillus* species has been observed, but also acquired antifungal resistance is gaining importance.[8,14] Especially azole resistance in both non-*Candida albicans* species and *Aspergillus fumigatus*, as well as echinocandin resistance in *C. glabrata*, are rising.[8] In 2012, Pfaller et al. even found that 11% of the fluconazole-resistant *C. glabrata* bloodstream infections were also resistant to echinocandins.[15] Another species that recently gained a lot of attention is *Candida auris*, with up to 90% of the isolates showing reduced susceptibility to fluconazole, 35% to amphotericin B, and 7% to echinocandins.[16] Moreover, this *Candida* species can form biofilms, which even further impedes antifungal treatment.[17] Some fungal species are intrinsically resistant to all major antifungal groups (e.g., *Lomentospora prolificans*).[18]

Consequently, there is a need for new antifungals, preferably with a novel mode of action (to avoid cross-resistance and/or cross-toxicities). Also, the availability of oral alternatives would enable ambulatory treatment resulting in an improved patient's comfort and therapy adherence. However, only one new antifungal (isavuconazole; see below)[19] and two new formulations of posaconazole were marketed over the last decade. This low

Table 1. Summary antifungal drugs undergoing clinical evaluation.

Agent	Phase	Class	Mechanism of action	Advantage	Disadvantage	Potential use
Azoles						
Isavuconazole	Phase IV	Azole	Inhibition of lanosterol 14α-demethylase	• Oral and IV formulation • Improved safety profile • Reduction in DDIs	• Price compared to other azoles	Invasive mould disease (for example: invasive aspergillosis, mucormycosis)
Glucan synthesis inhibitors						
Rezafungin (CD101)	Phase III	GSI	Inhibition of β-1,3-glucan synthesis	• Improved stability • Long half-life = > front-loaded administration • Safety profile • Minimal interaction with CYP450 enzymes	• No oral formulation	Broad antifungal spectrum, also activity against *Candida auris* and PJP.
SCY-078 (MK-3118)	Phase III	GSI (novel subclass)	Inhibition of β-1,3-glucan synthesis	• Oral and IV formulation • Activity against resistant strains		• *Candida* and *Aspergillus* spp. • *Scedosporium prolificans* • *Candida auris*
Polyenes						
Coch-AmB	Phase II	Polyenes	Pore formation by binding to ergosterol	• Broad spectrum • Minimal DDIs • Oral administration		Broad spectrum (*Candida* spp., *Aspergillus* spp., . . .)
Orotomides						
Olorofim	Phase III	Orotomides	Inhibition of dihydroorotate dehydrogenase	• Oral and IV formulation • No evidence of cross-resistance • Activity against *Lomentospora prolificans*	• DDIs • Little or no activity against *Candida* spp., *Mucorales* spp. and *Cryptococcus neoformans*	• *Aspergillus* spp. • *Scedosporium* spp. (including *Lomentospora prolificans)*

number underscores some of the hurdles that need to be overcome before an antifungal can be commercialized: the spectrum and indication has to be determined, toxicity should be well characterized, the cost of the development should be manageable, a prolonged trial duration should be possible, the sample size needs to be sufficient but achievable, and so forth.[3] Consequently, not every molecule with antifungal activity will result in an approved drug: approximately 80% of the potential antifungal targets published in literature were not further developed because of undesirable features.[20]

This review will only discuss the antifungal drugs in the pipeline that are currently undergoing clinical evaluation. This overview is structured by antifungal classes: azoles, glucan synthase inhibitors, polyenes, and orotomides. For each molecule, information concerning mechanism of action, pharmacokinetics, drug-drug interactions (DDIs), spectrum, resistance, and (ongoing) studies are presented. A summary is provided in Table 1. Moreover, a table (Table 2) is added with potential antifungals under investigation that were not discussed in detail in the first part of this review. Finally, an overview of the different fungal targets for the discussed molecules is provided in Figure 1.

Azoles: isavuconazole (BAL8857)

Isavuconazonium sulfate, a highly water soluble prodrug, is the most recently developed azole. Following administration, the prodrug is immediately hydrolyzed by plasma esterase into an active (isavuconazole) and an inactive moiety.[21,22] Figure 2 shows the chemical structure of this active molecule.[23] The drug is available as an oral and an intravenous formulation, which does not contain cyclodextrin.[24] The mechanism of action is not different from the other azoles, i.e. inhibition of lanosterol 14α-demethylase.[21]

Isavuconazole is given (IV or oral) at 200 mg (372 mg isavuconazonium sulfate) once daily, following a loading dose of 200 mg every 8 hours for the first 48 hours.[22,24] Oral isavuconazole can be administered with or without food and is readily absorbed with a bioavailability of 98%.[25] The absorption is not influenced by gastric pH, nor by the co-administration of proton pump inhibitors or H2-blockers.[25] Isavuconazole can be administered orally in patients with mucositis, although there was a statistical difference in oral bioavailability in patients with versus without mucositis, the drug exposures and clinical outcomes did not differ significantly.[26]

Table 2. Other antifungal drugs in development.[3,4,19]

Agent	Phase	Class	Mechanism of action	Advantage	Disadvantage	Potential use(*in vitro* or *in vivo* data)
Azoles						
VT-1598	Preclinical	Azole	Inhibition lanosterol demethylase	• Selectivity for fungal CYP51 so consequently fewer potential DDIs • Longer half-life • Broad spectrum		• *Candida* spp., including *Candida auris in vitro* • *Cryptococcus neoformans* and *Cryptococcus gattii* • *Aspergillus* species • *Rhizopus arrhizus* • *Blastomyces dermatitidis* • *Coccidioides* spp. • *Histoplasma capsulatum*
VT-1129	Phase I	Azole	Inhibition lanosterol demethylase	• Selectivity for fungal CYP51 so consequently fewer potential DDIs • Long half-life • Oral agent		Designed to treat cryptococcal meningitis
VT-1161	For vaginal candidiasis or onychomycosis: • Phase II (NCT02267382, NCT02267356, NCT01891331, NCT01891305) • Phase III will start soon (NCT03561701, NCT03562156)	Azole	Inhibition lanosterol demethylase	• Selectivity for fungal CYP51 so consequently fewer potential DDIs • Long half-life		Designed to treat *Candida* spp.
Molecules with new mechanisms of action						
ASP2397	Preclinical	Precise target unknown	Disruption of intracellular environment of the fungi after uptake via specific siderophore iron transporter (Sit1)	• Selective fungal target • Activity against azole-resistant *Aspergillus* spp.		• *Aspergillus fumigatus* • *In vitro* activity against few *Candida* spp. and some rare moulds and yeasts (*Fusarium* spp. and *Trichosporon* spp.)
Aureobasidin A	Preclinical	Glycolipid inhibitors	Inhibition of inositol phosphorylceramide synthase (important step in fungal sphingolipid biosynthesis)	Broad-spectrum		
T-2307	Phase I	Arylamidine	• Transported into cells by a specific polyamine transporter • Inhibits intracellular mitochondrial membrane potential	Preferential uptake by fungal cells		• *Candida* spp. • *Cryptococcus* spp. • *Aspergillus* spp.
AR-12	Phase I (NCT00978523)		Two mechanisms of action: 1. Inhibition of fungal acetyl-CoA synthetase 1 2. Downregulation host chaperone proteins with increase of host immune response			• *Cryptococcus neoformans* and *Candida albicans* • Moulds, including Mucorales, *Fusarium* spp. and *Scedosporium* spp.
Nikkomycin Z (VFS-1)	• Phase I (NCT00834184) • Two other phase I/II studies have been terminated (NCT01647256 and NCT00614666) because of recruitment challenges and lack of funding	Chitin synthases inhibitors	Competitive inhibitor of chitin synthase (fungal cell wall synthesis)	• Additive or synergistic *in vitro* and *in vivo* activity with the 1,3-β-glucan synthase inhibitors • Fungal specific target PO and IV	Poor antifungal activity in monotherapy	• In combination with echinocandins for both yeasts and moulds, e.g., coccidioidomycosis, histoplasmosis and blastomycosis. • Especially developed as an orphan drug for the treatment of coccidioidomycosis.

Table 2. (*Continued*).

Agent	Phase	Class	Mechanism of action	Advantage	Disadvantage	Potential use(*in vitro* or *in vivo* data)
APX001 (E1211) (is prodrug of E1210)	• Phase I (NCT02957929, NCT02956499, NCT03333005) • Phase II planned	Glycosyl phosphatidylinositol (GPI) inhibitor	Inhibition of Gwt1 (a GPI-anchor protein)-synthesis by inhibiting inositol aceyltransferase. This leads to disruption of the fungal wall and increased recognition of *Candida* by immune cells.	• Broad spectrum • Fungal-specific target • PO and IV • Synergizes with approved antifungals		• *Candida* spp. • No activity against *Candida krusei* • *Aspergillus* spp. • Difficult to treat moulds like *Fusarium* spp. and *Scedosporium* spp.
VL-2397	Phase II (NCT03327727)	Siderophore	• Effect on an (unknown) intracellular target. • It is transported intracellular by siderophore transporter Sit1.			• Invasive aspergillosis • Invasive candidiasis
MGCD290	Phase II (NCT01497223)	Histone deacetylase (Hos2) inhibitor	Inhibits Hos2, which removes acetyl groups from lysines on core histones, HSP90 and other cellular proteins (regulation of gene transcription and control other cellular functions)	• Broad spectrum • Synergizes with approved antifungals	Combination of MGCD290 + fluconazole was not better than fluconazole in monotherapy in severe vulvovaginal candidiasis (VVC) in humans	Effective in combination with both azoles and echinocandins

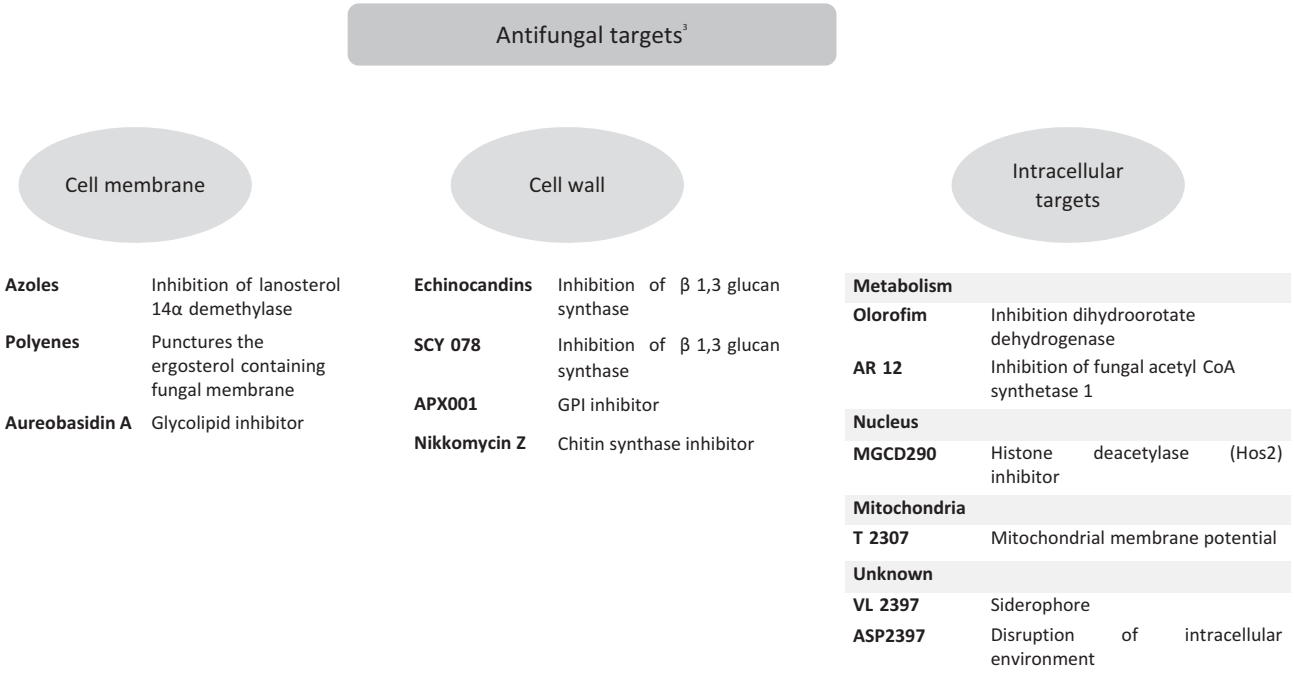

Figure 1. Overview of antifungal targets.[3]

Isavuconazole is extensively distributed with a volume of distribution (Vd) around 450 l.[21,22] It is highly bound to human plasma proteins (> 99%)[22,24] and has a long half-life (130 hours).[24]

Isavuconazonium sulfate and the cleavage product are (partially) further metabolized. Excretion of the molecules and their metabolites takes place via urine (45.5%) and feces (46.1%). The unchanged, active, isavuconazole is eliminated predominantly in the feces (33%) and for less than 1% in the urine.[24,27]

To determine population pharmacokinetics (PPK), Desai et al. pooled data of nine phase I studies and one phase III study to develop a PPK model. They developed a two-compartment model with linear and dose proportional pharmacokinetics (up to 600 mg a day[22]).[21] The mean $AUC_{0\text{-}24}$ was about 100 mg.h/l and the mean estimated clearance (CL) was 2.360 l/h. Race was the only statistically significant covariate on clearance, as Asians had an approximately 36% lower CL value than the white population.[21]

Regarding DDIs, preclinical studies suggest that mostly CYP3A4 and to a lesser extent CYP3A5 are responsible for metabolism of isavuconazole. Secondary metabolism is conducted by UDP-glucuronosyltransferase (UGT). Isavuconazole is not a substrate of P-glycoprotein.[22,24,28] Isavuconazole itself

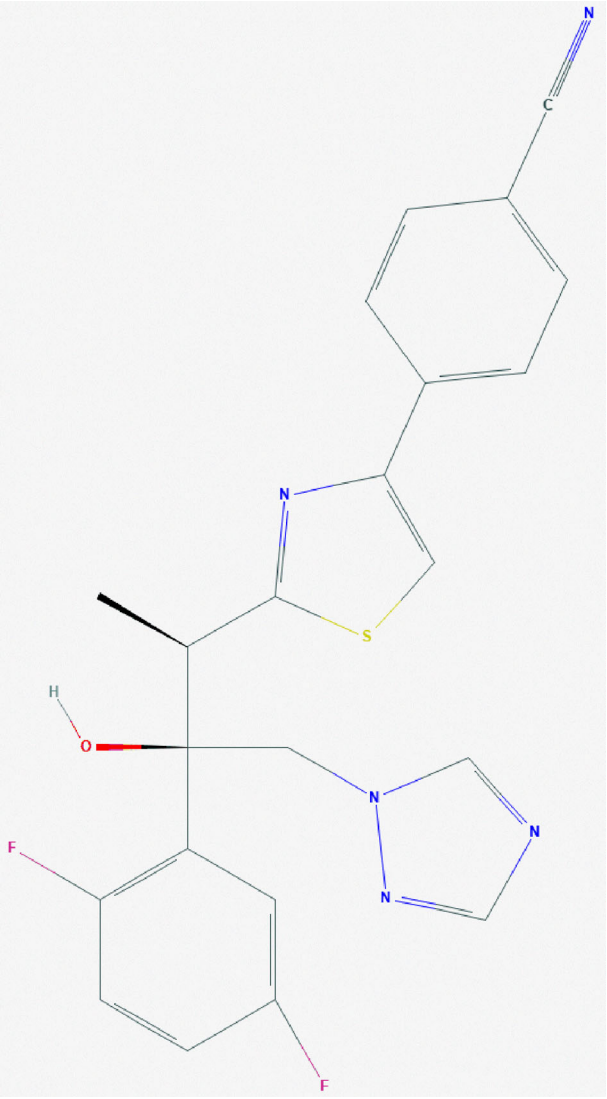

Figure 2. Chemical structure isavuconazole.[23]

is a moderate inhibitor of CYP3A4/CYP3A5, a mild inhibitor of P-gp, OCT2 and UGT and a mild inducer of CYP2B6.[22,28] There is a relative absence of CYP2C9 and CYP2C19 interaction.[29,30] The CYP3A4 inhibition, however, takes place to a lesser degree than is the case for the other triazole antifungals, but caution and possible dose adjustment can still be necessary.[28,31]

Two phase III and one phase II clinical trials were conducted to assess the role of isavuconazole. The double-blind, controlled SECURE-trial (NCT00412893)[32] demonstrated the noninferiority of isavuconazole to voriconazole for all-cause mortality throughout day 42 (week 6) in the treatment of proven, probable, and possible invasive mould disease (mainly invasive aspergillosis). However, isavuconazole was associated with fewer drug-related adverse events and drug discontinuations. Statistically significantly lower frequencies of hepatobiliary, eye and skin, or subcutaneous tissue disorders were seen.[32] Of note, isavuconazole shortens the QTc interval (ECG) and is contra-indicated for patients with congenital short QT syndrome (a rare cardiac condition characterized by an abnormally short QT interval and so increased risk of atrial and ventricular fibrillation).[33]

The open-label VITAL-study (NCT00634049) included patients with mucormycosis, with rare fungal pathogens, as well as patients with renal impairment. A subanalysis showed activity of isavuconazole in the primary or salvage treatment for patients with mucormycosis; the overall end-of-treatment complete and partial response was 32% and 36%, respectively. Other subanalyses suggest activity of isavuconazole in patients with cryptococcosis and dimorphic fungal infections, patients with mixed fungal infections, and patients with underlying renal impairment.[34–36]

Finally, the preliminary results of the ACTIVE-study (NCT00413218)[37] presented at ECCMID 2016 showed no non-inferiority of isavuconazole to caspofungin(/voriconazole) for the primary endpoint of successful overall response at the end of IV therapy for candidemia and other invasive *Candida* infections. The secondary endpoint of successful overall response at end of treatment + 2 weeks and all-cause mortality at day 14 and 56, were similar between the two groups. Both drugs were safe and well tolerated.[37] Recently, the final results of the ACTIVE trial were published.[38]

Studies are ongoing to investigate the exposure of isavuconazole in pediatric patients (NCT03241550) and for prophylaxis in patients undergoing hematopoietic stem cell transplantation (NCT03149055) and in neutropenic patients with acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) (NCT03019939).

The absolute need for therapeutic drug monitoring (TDM) for isavuconazole is still unclear. To date, no clear relationship between isavuconazole exposure and both efficacy or safety has been determined,[39,40] so consequently no clear target range is determined in the literature. Moreover, the linear pharmacokinetics and the low intra-subject variability (< 30%) assume predictable pharmacokinetics.[40] Although there is no strong evidence for a general need for TDM, it may be considered for individual cases (e.g., treatment of central nervous system infections or infections with non-wild type pathogens).[41]

In summary, the major advantage of isavuconazole lies in its improved safety profile and reduction in DDIs with preserved efficacy against a broad spectrum of IFIs. However, from an economic point of view, the patented isavuconazole looks less attractive than the off-patent voriconazole.

Given the novelty of this molecule, additional information is needed on long term safety data, treatment of sanctuary site infections, cross-resistance with other azoles and issues related to special patient populations (pediatric and critically ill patients, patients treated with extracorporeal circuits, etc.).

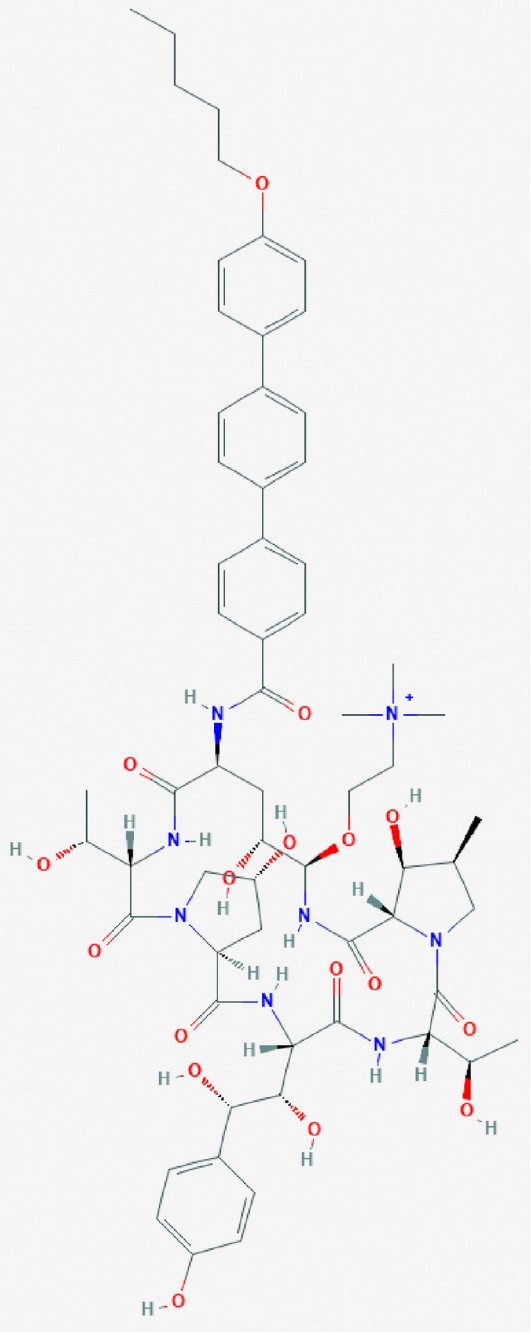

Figure 3. Chemical structure rezafungin.[42]

Glucan synthase inhibitors (GSI): rezafungin (CD101) and SCY-078 (MK-3118)

Rezafungin (CD101)

Rezafungin or CD101 is a structural analog of anidulafungin in which the hemiaminal region at the C5 ornithine residue in the cyclic echinocandin core is replaced with a choline aminal ether (as shown in the chemical structure; Fig. 3).[42] It shares the mechanism of action with the other echinocandins, i.e. inhibition of β-1,3-glucan synthesis, but the chemical modification comes with a greater stability and solubility. Rezafungin is being developed as a subcutaneous and IV formulation; no oral formulation will be available.[43–45]

CD101 has dose-proportional kinetics[46–48] and is highly protein bound ($\geq$ 98%).[49] Both the clearance of CD101 and the interindividual variability on this clearance (13%) in healthy volunteers are lower compared to the other echinocandins.[46] Only a small fraction ($\leq$ 0.26%) of CD101 is excreted in urine.[48]

The currently used dose consists of a loading dose of 400 mg in week one and a maintenance dose of 200 mg in week 2 and 3 (Dr. R. Brüggemann, personal communication).

Another remarkable characteristic of CD101 is its very long half-life in humans, namely, > 80 h after the first dose and approximately 150 h following the second or third dose.[48,50] Because of this long half-life, as well as the concentration-dependent fungal killing and limited toxicity, the possibility for nondaily dosing was explored in a murine model of disseminated candidiasis. The following dosing frequencies were compared: 0.29 mg/kg daily for 7 days, 1 mg/kg twice-weekly, and one single 2 mg/kg (front-loaded approach) administration. The front-loaded dosing regimen demonstrated a greater degree of fungal killing than the more-fractionated regimens, despite achieving the same area under the curve (AUC).[47] The once-weekly dosing regimen also appeared to be safe and well tolerated in healthy adults for multiple doses up to 400 mg once weekly for 3 weeks.[48] Moreover, this once weekly front-loaded approach is beneficial for maximizing the drug effect early in therapy, potentially reducing drug resistance, enhancing patient compliance and facilitating outpatient use, which could be economically interesting.[47,48]

Because of its extensive tissue distribution and quick penetration into abscesses, rezafungin might also be indicated in infections that are difficult to reach with the conventional antifungal drugs. In a mouse model, an intraperitoneal administration of CD101 was able to reach the necrotic core so it could interact with the main fungal population. Moreover, concentrations above the mutant prevention concentration (MPC) were reached so that resistance development might be limited.[51]

Because of its chemical stability, there is no evidence of biotransformation in rat, monkey, dog, and human liver microsomes and hepatocytes and even not of spontaneous chemical degradation; therefore, no reactive intermediates are formed. It has been suggested that those reactive intermediates might play a role in the induction of hepatotoxicity by echinocandins; as such, CD101 might have a better safety profile because of its stability.[48,49] Indeed, when compared to IV anidulafungin, IV CD101 showed less toxicity in Sprague-Dawley rats. For example, there was no influence on body weight, hematology, and coagulation. Remarkably, there were also no microscopic changes in the liver, in contrast with minimal to moderate single-cell necrosis of the hepatocytes in some female rats

with anidulafungin.[49] Whether this reduced hepatotoxicity will translate into the human model remains to be seen.

A general favorable safety profile is seen in humans. In the phase I study by Sandison et al. in healthy adults, there were no serious adverse events (SAEs), severe adverse events (AEs), withdrawals due to an AE, or deaths. There was a tendency toward a higher incidence of treatment-emergent adverse events (TEAEs) in the cohort treated with the highest dose and the longest duration. Infusion reactions were also primarily seen but occurred and disappeared within minutes of infusion without the need for interrupting or discontinuing the antifungal drug. The only noninfusion-related TEAE related to the study drug in more than two subjects was mild or moderate constipation.[48]

The enhanced stability might also explain the minimal interaction with CYP450 enzymes (nor as substrate, nor as inhibitor) that were observed in an *in vitro* study,[49] but an effect on CYP450-enzymes can still be possible.

In vitro studies have demonstrated potent antifungal efficacy against *Candida albicans, Candida tropicalis, Candida krusei, Aspergillus fumigates,* and *Aspergillus flavus* (azole-susceptible and azole-resistant strains). This efficacy is comparable to that of the other echinocandins.[49,52,53]

As fungal resistance is emerging, Locke et al.[54] studied the potential of *in vitro* resistance development of CD101 in *Candida* species. A low potential for resistance development, similar to anidulafungin and caspofungin, was seen. Cross-resistance between these three molecules was broadly observed. *Fks* mutant strains of *Candida* also exhibit an elevated MIC value for CD101.[52] But rezafungin has the advantage that it reaches a much higher plasma drug exposure (C_{max}/AUC) due to the front-loaded dosing regimen, which can even further lower the resistance development.[54] As expected, CD101 has only limited activity against *C. neoformans* isolates.[53]

Moreover, rezafungin seems to possess potent *in vitro* activity against *C. auris*, similar to anidulafungin and greater than caspofungin and micafungin.[55] In immunocompromised mice, superior activity (lower $\log_{10}$ cfu/g of kidney tissue) against this isolate was demonstrated compared to amphotericin B on all days (day 1, 4, 7, and 10) and micafungin on day 10.[56]

A randomized phase II study (STRIVE trial, NCT02734862)[57] was conducted to assess the safety, tolerability, and efficacy of a once-weekly dosing of rezafungin compared to once-daily dosing of caspofungin (with possible step down to oral fluconazole) in patients with candidemia and/or invasive candidiasis. Two rezafungin dosing regimens were possible: one group received 400 mg rezafungin IV once weekly for 2 to 4 weeks (group 1) and a second group was treated with 400 mg rezafungin IV for the first week, followed by 200 mg once weekly for up to four weeks in total (group 2). CD101 attained its primary safety and efficacy objectives. The dosing regimen of rezafungin group 2 had the highest efficacy rate (overall success D14 of 22%, compared to 19% in rezafungin group 1 and 18% for daily caspofungin). There was a good toleration in both rezafungin groups. Severe adverse events occurred in 37.1% of rezafungin group 1, 27.8% in rezafungin group 2, and 39.4% in caspofungin-treated patients.[57]

Interestingly, data in immunosuppressed mice showed that CD101 has the potential to prevent infections with *Pneumocystis* spp. CD101 was intraperitoneally administered in doses of 20, 2, or 0.2 mg/kg once or 3 × each week. For most (but not all) CD101 doses, there were statistically significant reductions in both nuclei and asci counts of *P. murina* compared with untreated controls and the effect was comparable with that of the trimethoprim (TMP)/sulfamethoxazole (SMX) group.[58] Further studies need to address if CD101 is a good alternative in PJP treatment or prophylaxis, but CD101 has a favorable safety profile and might have a place in TMP/SMX-resistant PJP species.

Rezafungin can not only penetrate abscesses but might also be indicated in biofilm infections. In an *in vitro* model, *C. albicans* cells were adhered to silicone elastomer catheter discs to study exposure in biofilms. Rezafungin had the ability to prevent the adhesion-phase cells developing into mature biofilms and to eradicate a mature *Candida* biofilm.[59] This is probably due to the inhibition of the glucan synthesis, which is also a part of biofilms.[60]

Those promising results have led to the launch of phase III studies with rezafungin: the ReSTORE trial will investigate the non-inferiority of rezafungin versus caspofungin in treatment of candidemia and/or invasive candidiasis. The ReSPECT trial will evaluate rezafungin's potential to prevent *Candida*, *Aspergillus,* and *Pneumocystis* in high risk-patients (including allogeneic hematopoietic cell transplant recipients).[57]

The development of topical formulations is shut down due to unfavorable result in a phase II (RADIANT, NCT02733432) trial of CD101 in vulvovaginal candidiasis (VVC) since the efficacy was lower compared to oral fluconazole.[61]

However, CD101 already received a qualified infectious disease product (QIDP) and Fast Track designation by the Food and Drug Administration (FDA) for both topical use in treatment of VVC and prevention of recurrent VVC[62] and as well for IV treatment of candidemia and invasive candidiasis.[63]

In summary, rezafungin is a new, long-acting echinocandin with an improved stability. This molecule seems to be safe and is most effective in front-loading dose regimen of a once weekly administration, also enabling outpatient therapy. CD101 has antifungal activity against different *Candida* and *Aspergillus* spp. Moreover, it might also be useful in a broad range of antifungal indications like PJP, *C. auris*, intra-abdominal candidiasis, and biofilms.

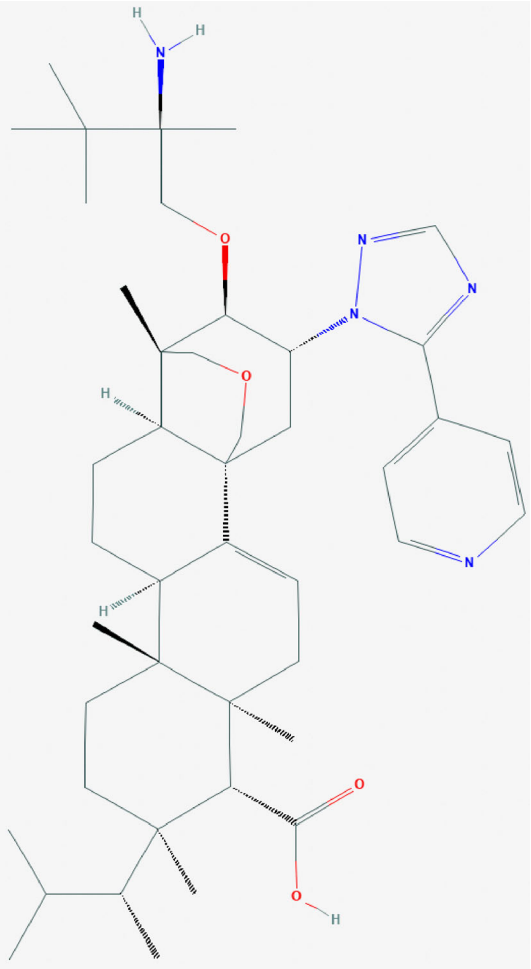

Figure 4. Chemical structure SCY-078.[66]

SCY-078 (formerly MK-3118)

SCY-078 is the first member of a new glucan synthase inhibitor (GSI) subclass, namely, the triterpenoid antifungals that are derived from the naturally occurring enfumafungin.[64] It has the same fungal target as the echinocandins (β-1,3-glucan synthase), but the two classes have another chemical structure and interact differently with the target-enzyme[65] (chemical structure of SCY-078 is shown in Fig. 4).[66]

The pharmaceutical formulation of SCY-078 is innovative since it is the first GSI that can be administered both intravenously and orally. That is due to the good oral bioavailability and permeability through Caco-2 monolayers (i.e., human colon carcinoma cell lines used to determine drug permeability).[67,68] SCY-078 also has a pH-dependent solubility, reaching the highest concentrations in acidic media like gastric and intestinal fluids.[65]

SCY-078 is characterized by an extensive tissue distribution (Vd ~ 10-fold higher than body water volume)[65] but no CNS penetration (Dr. J. Maertens, personal communication). This is supported by the observation of a 20- to 25-fold $AUC_{0-\infty}$ and C_{max} in kidney tissue compared to plasma values in mice after oral administration.[65] The molecule also has a high plasma protein-binding but probably with a rather low affinity, still allowing extensive tissue distribution.[65] Orally administered SCY-078 had an approximately linear PK over the studied dose range in a neutropenic murine model of invasive candidiasis,[69] and the PD target is expressed as AUC/MIC, which indicates that it is a concentration-dependent molecule with associated time-dependency.[69,70] Once-daily dosing is suggested in humans because of the moderate hepatic clearance and the long half-life.[65]

Unpublished *in vitro* data by Wring SA and Park SM showed that SCY-078 is a possible inhibitor of CYP2C8. The potential for inhibiting other CYP450-enzymes was also studied and appeared to be lower than for CYP2C8.[71] However, in a phase I study in healthy volunteers, little clinical impact of SCY-078 on rosiglitazone, a known substrate of CYP2C8, was observed. Both the exposure and C_{max} for rosiglitazone and its metabolite were not significantly affected by SCY-078. So there probably is a low risk for interaction with drugs metabolized via CYP450-enzymes.[71] The only weak CYP3A-inhibitory properties of SCY-078 are confirmed in another study in which the influence of SCY-078 on tacrolimus, a substrate of CYP3A and P-glycoprotein, was studied. There was a modest 1.4-fold increase in $AUC_{0-\infty}$ of tacrolimus in the presence of SCY-078. The C_{max} and T_{max} of tacrolimus were similar with versus without SCY-078. So, the authors of this study concluded that there is a lower risk for clinically meaningful influence of SCY-078 on tacrolimus exposure compared with the azoles.[72]

However, SCY-078 itself is *in vitro* metabolized by CYP3A-enzymes, especially CYP3A4, so inhibitors/inducers could influence the SCY-078 concentrations. Tacrolimus, a mild inhibitor of CYP3A4, had no effect on SCY-078 concentrations, but only one reduced dose of tacrolimus was given so further research is needed.[72]

In vitro studies demonstrated a good—primarily fungicidal—activity of SCY-078 against *Candida* and *Aspergillus* species.[70,73–76] Wild-type (WT) susceptibility in *Candida* spp. for SCY-078 was compared to the available echinocandins. The activity of SCY-078 was similar for *C. parapsilosis, C. lusitaniae, C. guilliermondii,* and *C. orthopsilosis,* but SCY-078 was 4-66-fold less active against WT strains of the other tested species.[77] In another study micafungin and SCY-078 seemed to be equally effective, yet there was a difference in MIC values between the two molecules.[73]

Moreover, the activity of SCY-078 against biofilms was tested *in vitro* using a 96 well microtiter-based method. SCY-078 showed activity against both the sessile and planktonic *Candida* forms, so it could be used in biofilm infections.[73]

Concerning *Aspergillus* spp., excellent *in vitro* activity of SCY-078 against both wild-type and itraconazole-resistant

Aspergillus spp., was shown. However, in general, SCY-078 was less active (higher MEC_{90} values) than caspofungin in the studied collection of *Aspergillus* strains.[75]

Regarding the non-*Aspergillus* moulds, this new antifungal has little activity against *Mucoromycotina* spp., *Fusarium* spp., and *Purpureocillium lilacinum* but was highly active against *Paecilomyces variottii*. More importantly, it was the only molecule to be (modest) active against *Scedosporium prolificans*, a usually panresistant isolate.[78] Orally administered SCY-078 is also reported to display prophylactic activity, expressed as a reduction in organism burden and improved survival, against PJP in a murine model.[79]

The resistance profile of SCY-078 is a major advantage for this new molecule since it has activity against both azole and echinocandin resistant strains.[65,73,74,77,80,81] This is mostly studied for *Candida* spp. For example, when compared *in vitro* with the three available echinocandins, SCY-078 seems to experience less influence of common *fks* mutations, most probably due to different enzyme-drug interactions.[77] On the other hand, echinocandin-resistant (ER) *Aspergillus* strains have rarely been observed, although SCY-078 was tested against one ER strain of *A. fumigatus* and showed a MIC value 133 times lower than caspofungin.[80] So, despite the similar mechanism of action, there is no complete cross-resistance between echinocandins and SCY-078.[77] This was confirmed by Jiménez-Ortigosa et al. who showed an independent but partially overlapping binding site on β-1,3-glucan synthase.[82]

Another possible indication for SCY-078 is the treatment of *C. auris* infections. Larkin et al. proposed SCY-078 for this indication since it showed an *in vitro* potent antifungal activity and was effective against the formed biofilm.[83] Overall, SCY-078 could be an important added value against emerging multiresistant isolates.

Those preclinical findings were further studied in humans in phase II clinical trials of which the results were presented at the 27th ECCMID congress.[84,85] The first study (NCT02244606)[84] for oral step-down treatment of invasive candidiasis after initially treatment with an echinocandin was conducted in 27 subjects. The goal was to identify an oral dosing regimen for SCY-078 by comparing two study-arms, a loading dose (LD) of 1000 mg followed by a maintenance dose (MD) of 500 mg once daily (arm 1) or a loading dose of 1250 mg followed by 750 mg once daily (arm 2). They evaluated the safety, tolerability and efficacy and compared this with the standard of care (arm 3, fluconazole or micafungin in case of fluconazole resistance). SCY-078 appeared to be a relatively safe molecule with similar rates of (serious) AE in the three study arms. The most common AEs in all study arms were gastrointestinal disturbances. The dosing regimen of 1250 mg LD/750 mg MD had the highest probability of reaching target exposure (84% vs 56%). The response rate was also the highest in the 750 mg SCY-078-arm compared to the 500 mg SCY-078-arm and standard of care (86% vs 71% vs 71%).[84]

The second study (NCT02679456)[85] evaluated SCY-078 in the treatment of moderate to severe vulvovaginal candidiasis. Three oral study-arms were compared: SCY-078 1250 mg LD/750 mg MD for 2 days, SCY-078 1250 mg LD/750 mg MD for 4 days or fluconazole 150 mg for 1 day. Comparing the two SCY-078 groups with the fluconazole-arm, SCY-078 showed a greater clinical cure, mycological eradication at day 24 and therapeutic cure (respectively 78% vs 66%, 70.% vs 69%, and 56% vs 56%). After 4 months, there was a higher clinical cure rate (88% vs 65%) and less recurrent infection (4% vs 15%) in the SCY-078 groups. There were no serious adverse events but a higher rate of GI AEs was reported in the SCY-078 arms. However, only 96 subjects were enrolled in this pilot-study.[85]

Ongoing clinical trials with SCY-078 are the phase III, open-label FURI-study (NCT03059992) in patients with an invasive and/or severe fungal disease that are refractory or intolerant to standard-of-care treatment and the phase III CARES-trial (NCT03363841) focusing on patients with *C. auris*-candidiasis. A recently completed study is the phase II DOVE-trail (NCT03253094) that explored five dose regimens of oral SCY-078 versus fluconazole in patients with acute VVC. Results still have to be published.

A QIDP and Fast Track designation was already given by the FDA to intravenous SCY-078 for treatment of patients with IFIs and to oral SCY-078 in treatment for VVC and prevention of recurrent VVC.[86,87]

In summary, SCY-078 is the first representative of a novel GSI class that can be administered both orally and intravenously. There seems to be a low risk for clinically relevant interactions with CYP450-substrates. SCY-078 has a broad activity against *Candida* and *Aspergillus* species. A major advantage is the increased efficacy against azole- and echinocandin resistant isolates.

Polyenes: Encochleated amphotericin B (Coch-AmB, MAT2203)

Currently, there are no new polyenes in phase II or III clinical trials. The polyene that is most progressed in its development process is enchochleated amphotericin B (Coch-AmB), a new formulation of amphotericin B (chemical structure shown in Fig. 5).[88]

Amphotericin B (AmB) is known for its broad spectrum of activity and minimal DDIs. Currently, AmB is already available in different (liposomal and lipid complex) pharmaceutical formulations. The newest achievement is the inclusion of AmB in cochleates. These are phospholipid bilayers precipitated with divalent cations to form a multilayered structure, rolled up in a spiral without internal aqueous space. This structure protects the molecule inside which makes it stable and enables oral administration. AmB is readily released upon interaction of the cochleate with target cells.[19,89,90] The drug-cochleates open in presence of the low intracellular calcium concentrations after which the drug is released.[91]

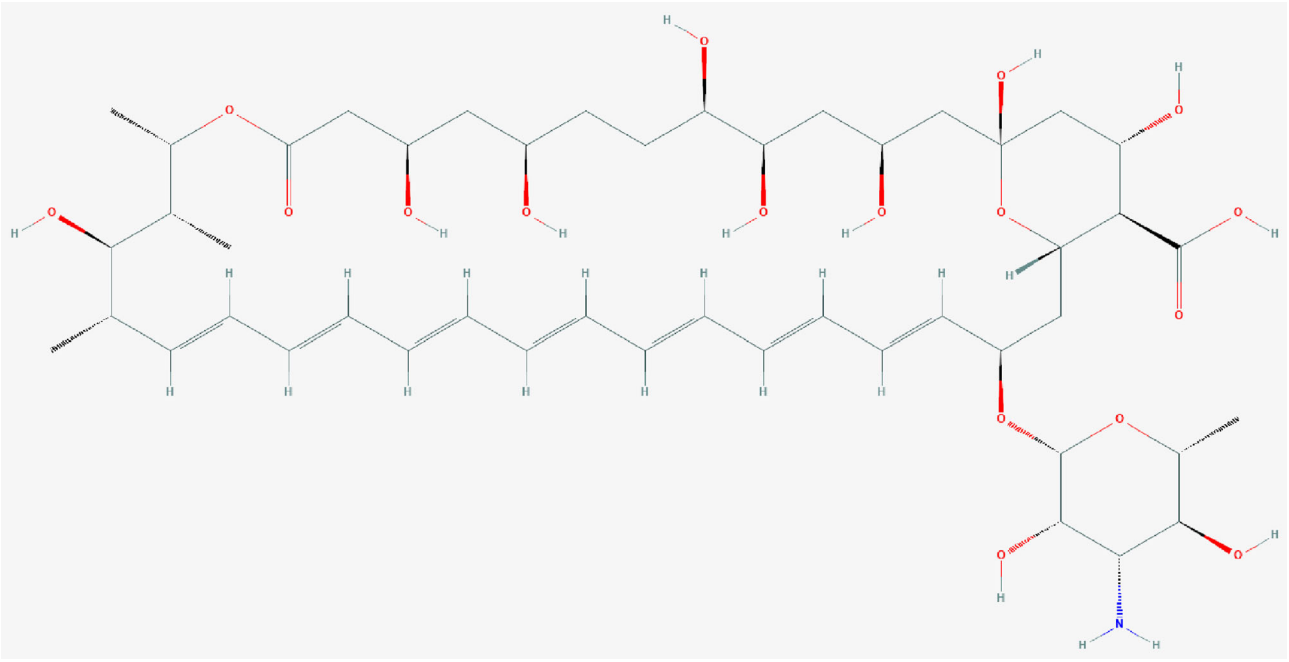

Figure 5. Chemical structure amphotericin B.[88]

Coch-AmB is extensively distributed into tissues in mice. Coch-AmB 10 mg/kg (oral) led to quantifiable and reproducible levels of AmB in liver, lungs, and kidneys. Moreover, the maximal levels were already achieved in early treatment duration, in contrast with deoxycholate AmB (D-AmB) that achieved higher AmB levels but at a later timepoint.[91] Of all tissues, the liver and spleen have the highest AmB-exposure, probably due to the removal of Coch-AmB by the macrophages.[89] Efficacious intracellular drug concentrations are reached with lower plasma levels, so there may be less systemic toxicity.[91] Moreover, it is suggested that the liver is a reservoir for AmB, releasing it at a slow rate.[89]

The activity of Coch-AmB PO was studied in a *Candida* murine model; all mice treated with oral Coch-AmB survived the 16 day-study period, in contrast with the untreated mice, that all died within 12 days. There also was a dose-dependent reduction in *C. albicans* from the kidneys and lungs. Intraperitoneally D-AmB showed similar results at a dose of 2 mg/kg/day.[90] Moreover, high oral Coch-AmB doses (10 and 20 mg/kg/day) showed no additional toxicity compared to low (1 and 2 mg/kg/day) intraperitoneally doses of D-AmB[90] and in contrary with D-AmB no hemolysis was observed with Coch-AmB *in vitro*.[92]

Effectivity was not only shown in *Candida* spp. but also in other fungi. In a murine model of disseminated aspergillosis, for example, a dose-dependent reduction of mortality and fungal tissue burden was seen.[93] And Coch-AmB did also have a similar *in vitro* activity as D-AmB against *Leishmania chagasi* with lower toxicity to macrophages.[94]

To assess the activity and safety of the oral formulation of Coch-AmB (MAT2203) in humans, multiple studies are being conducted and are planned in the near future. A phase I study in healthy volunteers was performed for three different dosing regimens (200 mg, 400 mg, and 800 mg). Single oral doses of 200 mg and 400 mg appeared to be well tolerated with AEs primary being mild gastrointestinal disturbances (6% and 38%, respectively). In the 800-mg cohort, gastrointestinal adverse events were seen in 56% of the subjects. Mean plasma concentrations (C_{max}, 28.11 vs 37.09 vs 40.76 ng/ml for the respective doses) and exposure ($AUC_{0\text{-}24}$, 407.4 vs 522.9 vs 624.5 ng.h/ml) were calculated.[95]

Multiple phase II studies are being or will be conducted. In prophylaxis, a study is planned to evaluate the efficacy and safety in patients undergoing chemotherapy for acute myelogenous and lymphoblastic leukemia (NCT03187691). For treatment, Coch-AmB is studied for use in cryptococcal infections (NCT03196921) and non-IFIs, like fluconazole-resistant VVC and mucocutaneous candidiasis (NCT02971007, NCT02629419, NCT03167957).

In 2015 and 2016, MAT2033 was granted a QIDP and Fast Track status by the FDA for treatment of *Aspergillus*, invasive candidiasis and prevention of IFIs.[96–98]

In summary, Coch-AmB is the first polyene formulation for oral administration. It is shown to be well tolerated and is probably active against multiple fungi. However, more information is still needed on efficacy, tolerability, and toxicity.

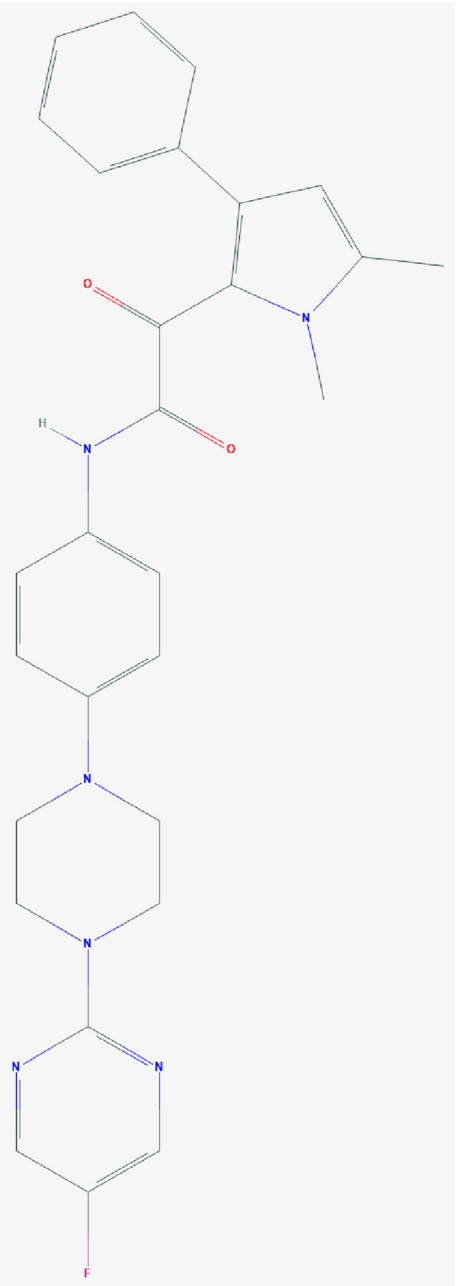

Figure 6. Chemical structure olorofim.[99]

Orotomides: Olorofim (F901318)

Olorofim is the first representative of a new antifungal class, the orotomides. Figure 6 shows the chemical structure of this molecule.[99] This class has a novel mechanism of action, namely inhibiting the dihydroorotate dehydrogenase (DHODH),[100] a key enzyme in the pyrimidine biosynthesis. Since pyrimidine is an important molecule in DNA, RNA, cell wall and phospholipid synthesis, cell regulation and protein production,[101] there will be a profound effect on fungi. The DHODH-target enzyme does exist in multiple (fungal) species but can structurally differ which explains the different susceptibilities. For example, there is a more than 2000-fold difference in IC_{50} between human and fungal enzymes.[100]

Olorofim can be administered both intravenously and orally, since this molecule has a good bioavailability.[102,103] At this moment, studies are conducted with the oral formulation only, but the IV formulation is expected to be available soon. The molecule is widely distributed into tissues, including kidney, liver, lung, and even brain, but the latter, however, at lower levels.[100] It was also shown that olorofim is highly protein bound (ca. 99%)[102] and undergoes an enterohepatic recirculation with multiple cycli.[104] Olorofim shows a linear PK in the studied dose-range and was fitted to a standard 2-compartiment PK model.[102] F901318 is a time-dependent antifungal and C_{min}/MIC is in current practice mostly used as PD-index.[102,105,106] Efficacy of olorofim, expressed as the reduction in serum galactomannan, was studied in a neutropenic murine and rabbit model with invasive pulmonary aspergillosis. The exposure to olorofim that is needed to achieve similar efficacy as posaconazole (murine model) or isavuconazole (rabbit model) at their expected human exposures, was determined. Equivalent efficacy was seen with total olorofim plasma C_{min} of 0.3 mg/l (murine model) and 0.1 mg/l (rabbit model).[102]

Olorofim is cleared by multiple CYP450-enzymes, with CYP3A4 being the dominant route. So the molecule is sensible to DDIs (Dr. R. Brüggemann, personal communication). It does not induce CYP450-enzymes itself, but it is a weak CYP3A4 inhibitor.[107]

Moreover, toxicity studies have not revealed major safety concerns up until now (Dr. J. Maertens, personal communication).

Olorofim is active against *Aspergillus* spp., including isolates less susceptible or resistant to other antifungals.[100,102,108–110] MIC-values below 0.1 mg/L were observed in the major subspecies (*Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger,* and *Aspergillus terreus*),[100] but olorofim also demonstrated effectivity against difficult-to-treat *Aspergillus* species, like *Aspergillus nidulans*, *Aspergillus tubingensis,* and *Aspergillus calidoustus*.[108] Initially the effect on *Aspergillus* spp. is fungistatic, but it becomes fungicidal if the exposure is prolonged.[105]

Olorofim is also active against other moulds[100,109] among which *Scedosporium* spp., including *Lomentospora prolificans* for which there are no therapeutic options at the moment[18,111] and effectivity was observed against *Coccidioides*, both *in vitro* and *in vivo*.[112] Unfortunately, olorofim has little or no activity against *Candida* spp., Mucorales spp., and *Cryptococcus neoformans*.[100,109] The activity against *Fusarium* spp. is not clarified yet since the results seems to be variable and species specific.[109]

The effect against resistant strains indicates no evidence of cross-resistance with other known antifungal resistance mechanisms, so an important role for the orotomides in the approach of resistant pathogens was suggested.[100,102,108,109] Moreover, it appeared that resistance to olorofim is not easily induced in *A.*

fumigatus since there was only a modest increase in MIC value after 40 passages on an agar plate.[100]

For the IV formulation, a 4-hour infusion duration was studied during development but is inconvenient in clinical practice. Kennedy et al. showed that a shorter duration is possible without significant increase in C_{max}, which is likely to correspond with toxicity, while still achieving C_{min}-concentrations $\geq$ 0.5 mg/l.[113]

For the oral formulation, the exact dosing regimen is being studied. At the moment, the provided dose consists of a loading dose of 4 mg/kg divided into two or three doses, respectively 12 h or 8 h apart. From day 2, a maintenance dose of 2.5 mg/kg/day divided into two or three doses will be administered. The maximum daily dose is 300 mg divided into two or three doses (Dr. R. Brüggemann, personal communication).

To confirm the activity and to further assess the appropriate dosing regimens in humans, phase II open label trials were initiated for use in systemic mould infections. Varying oral dosing regimens are being assessed in healthy volunteers (NCT03340597) and a study investigating metabolism in detail is ongoing (NCT02912026). A phase III randomized trial is planned to initiate in the beginning of 2019.

In summary, olorofim belongs to the new orotomide antifungal class which targets the pyrimidine synthesis. It can be administered both IV and orally but seems to be impacted by DDIs. It has a broad spectrum, including *Aspergillus* spp. and *Scedosporium* Spp. (*L. prolificans)*. Due to the novel mechanism of action, there seems to be no cross-resistance with other antifungal classes.

Overview of other possible new antifungal drugs in the pipeline

The molecules discussed above are already in a later stage of development. Next to these, also other promising antifungal drugs are being investigated. In Table 2, an overview of other antifungals which are still in earlier clinical development phases, is provided.

Discussion

Multiple evolutions in the fungal domain, like the increasing prevalence of potentially life-threatening IFIs, emerging fungal resistance, and disadvantages with the existing antifungals, demand the development of new antifungal drugs in clinical practice. Despite the fact that this is not easy to achieve, there are several drugs in the late stage of development. Some of them are favorable because of their improved resistance profile, like SCY-078 and olorofim. Others have a major advantage in formulation and administration, for example, CD101, SCY-078, and Coch-AmB. Moreover, isavuconazole has benefit over voriconazole because of its improved safety profile and reduction in DDIs while preserving the efficacy of azoles. And finally, a new antifungal class, namely, the orotomides, is developed for reducing cross-resistance and allowing oral administration.

Several additional molecules are still in development, so future will tell which of them will finally enter the drug market. Additional research is of course needed after commercialization in order to assess effectivity, safety, and resistance in clinical practice and in special patient populations.

Besides, efforts should be made to discover other strategies in the approach of fungal infections, like repurposing drugs, host immune cell-targeted approaches, and antifungal biological agents.[3]

Declaration of interest

R.V.D. has received travel support from Pfizer, Inc, and Gilead Sciences. I.S. has served as a consultant to and has received unrestricted travel and research grants from Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer, Inc and Cidara. All contracts were through and invoiced by UZ and KU Leuven. J.W. has received research grants from Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer, Inc. J.M. has received research grants from Merck/MSD, Gilead Sciences and Pfizer; is a consultant to Astellas, Basilea, Bio-Rad, Merck/MSD, Pfizer, Schering-Plough, F2G, Zeneus/Cephalon, Gilead, Cidara, Synexis and Luminex; and has served on the speaker's bureau of Astellas, Gilead, Bio-Rad, Merck/MSD, Pfizer, Schering-Plough, Zeneus/Cephalon, Basilea, Cidara, and Viropharma. T.M. has received lecture honoraria from Gilead and travel support from MSD and Gilead. S.V.H. has no conflicts of interest. R.J.M.B. has served as a consultant to and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharpe and Dohme Corp., and Pfizer, Inc. In addition, he has been a consultant to F2G. All contracts were through Radboudumc, and payments were invoiced by Radboudumc.

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