Antifungals in Clinical Use and the Pipeline

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KEYWORDS

• Antifungal drugs • Polyenes • Azoles • Echinocandins • Pipeline
• Invasive fungal infections • Novel therapies • Review

KEY POINTS

- Polyenes, azoles, echinocandins, and the antimetabolite agent flucytosine are the most common antifungals currently used for treatment and prevention of systemic fungal infections.
- Current systemic antifungal therapy choices have unique profiles and challenges related to spectrum of activity, pharmacokinetic/pharmacodynamic properties, development of resistance, toxicities, and drug interactions.
- At least 7 new antifungals are in phase 2 or phase 3 clinical trials for invasive fungal infections and have potential advantages over older agents in terms of activity against resistant organisms, dosing/pharmacokinetics, and tolerability.
- This article reviews pharmacologic facets and clinical use of Food and Drug Administration–approved and pipeline antifungal agents.

INTRODUCTION

Over the past 15 years, there has been an increase in development and utilization of newer antifungal agents. The ideal antifungal agent in regard to spectrum of activity, pharmacokinetic/pharmacodynamic properties, development of resistance, safety, and drug interaction profile remains elusive. This article reviews pharmacologic aspects of currently available systemic antifungal agents in use for treatment and prevention of invasive fungal infections (IFIs). The discussion of pharmacokinetic and dosing parameters focuses on adults, but there are emerging data for children, reviewed comprehensively elsewhere.[1,2] Promising antifungal candidates in clinical development also are discussed.

POLYENES

Amphotericin B (AmB) was the first antifungal approved for clinical use in systemic fungal infections and remains the sole polyene available today for this use. In addition

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to AmB deoxycholate (AmBd), there have been 3 Food and Drug Administration (FDA)–approved commercially available lipid formulations of AmB (LFABs): AmB lipid complex (ABLC), AmB colloidal dispersion, and liposomal AmB (LAmB). Only 2 of these lipid formulations (ABLC and LAmB), however, currently are marketed in the United States.

Mechanism of Action

Polyenes exert their antifungal activity by interacting with sterols in the fungal cell membrane, creating nonaqueous and aqueous channels that lead to leakage of cellular contents such as potassium through these pores.[3] This leads to loss of membrane potential and subsequent cellular collapse.

Spectrum of Activity/Resistance

Polyenes have a broad spectrum of antifungal activity including yeasts, such as *Candida* spp, *Rhodotorula* spp, and *Cryptococcus* spp; molds, such as *Aspergillus* spp*, Rhizopus* spp*, Mucor* spp, *Rhizomucor* spp; and endemic fungi, such as *Histoplasma* spp*, Coccidioides* spp, and *Blastomyces* spp. AmB lacks activity, however, against a few fungi, including A*spergillus terreus*, *C lusitaniae*, *C haemulonii* species complex, *Scedosporium apiospermum*, *Lomentospora prolificans*, and some *Fusarium* spp.[4] Higher AmB minimum inhibitory concentrations (MICs) also have been reported for numerous strains of *C auris.*[5] Alterations in fungal cell wall composition have been correlated with resistance to AmB in some species.[6,7] A recent study of *C auris* also identified 4 single-nucleotide polymorphisms in protein-encoding regions that were associated with AmB resistance.[8]

Formulations/Pharmacokinetics

AmB and LFABs have poor oral bioavailability, so are typically administered intravenously (IV) for systemic infections. Each of these preparations has differential pharmacokinetic properties (**Table 1**). None of these formulations is metabolized by the cytochrome P450 (CYP) enzyme system; therefore, these agents have few drug-drug interactions (**Table 2**).

In addition to IV administration, AmBd or LFAB can be nebulized and delivered via inhalation. This frequently is performed in some centers as prophylaxis in high-risk patients, such as allogeneic hematopoietic stem cell transplant, and lung transplant, or as adjunctive therapy in difficult-to-treat pulmonary fungal infections.[50–52]

Adverse Events

AmB has myriad associated adverse events that complicate IV administration, including infusion-related reactions (IRRs), nephrotoxicity, and electrolyte disturbances (hypokalemia/hyperkalemia and hypomagnesemia). IRRs have been reported in as many as 70% to 90% of patients receiving systemic AmBd.[53] Research over the past decade has illuminated the potential mechanism of AmBd-associated IRRs. Derived from *Streptomyces*, AmB is a ligand of Toll-like receptor 2 and CD14 on mononuclear cells, and, when recognized, initiates signaling pathways that lead to release of proinflammatory agents, such as interleukin (IL)-1b, IL-6, IL-8, and tumor necrosis factor α, that may be responsible for the IRRs that are observed.[54,55]

AmB-associated nephrotoxicity likely is multifactorial. First, administration of AmB leads to vasoconstriction of the afferent renal arterioles, resulting in reduced renal blood flow and a drop in glomerular filtration.[54] In addition, binding of AmB to cholesterol in cell membranes of the renal tubules and uptake through low-density-lipoprotein–AmB complexes may lead to high concentrations of AmB and subsequent

Table 1
Key pharmacokinetic properties of approved antifungals and phases 2/3 pipeline agents

Drug Class/ Antifungal Agent	Status	Oral Bioavailability	Vss (L/kg)	AUC$\mu g_{(0\text{-}24\ h)}$ $\mu g \cdot h/mL$	Peak Concentrations ($\mu g/mL$)	Protein Binding	P-gp Substrate/ Inhibitor	Metabolism/ CYP Inhibition	Half-Life (h)[a]
Polyenes									
AmBd[9–14]	FDA approved	<5%	5.2	17.1	1.4	>95%	ND	Minor hepatic	6.8/127[b]
LAmB[9,10,12]	FDA approved	<5%	0.1–0.4	171–1286	22.9	>95%	ND	None apparent	6.4–13.1/152[b]
ABLC[9,10,15]	FDA approved	<5%	131	16.5–19.2	2.4–3.7	>95%	ND	None apparent	173.4–393
MAT2203[16]	Phase 2	ND	ND	2.0–2.2	0.06	ND	ND	ND	ND
Antimetabolite									
5-FC[10,17]	FDA approved	78%–89%	0.6	62	80	3%–4%	No	Minimal hepatic metabolism	2–5
Azoles									
Fluconazole[18,19]	FDA approved	95%	0.7	359–409	12.1–25	12%	Possible inhibitor	CYP2C19, CYP2C9, CYP3A4 inhibitor	30
Isavuconazole[20–22]	FDA approved	97%–98%	6	60–64	5–7.5	>99%	Weak inhibitor	CYP3A4, CYP3A5 substrate Moderate CYP3A4 inhibitor	110–115

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Table 1
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Drug Class/ Antifungal Agent	Status	Oral Bioavailability	Vss (L/kg)	AUCμg$_{(0\text{-}24\ h)}$ μg·h/mL	Peak Concentrations (μg/mL)	Protein Binding	P-gp Substrate/ Inhibitor	Metabolism/ CYP Inhibition	Half-Life (h)[a]
Itraconazole[18,23]	FDA approved	55%[c] SUBA-itraconazole 81%	11	AUC$_{(0-\tau)}$ Capsule 14.9 SUBA-itraconazole 15.6	1.1–2	>99%	Substrate and inhibitor	CYP3A4 substrate CYP2C9, CYP3A4 inhibitor	34–42
Ketoconazole[24–26]	FDA approved	84%	0.4	24	3.6	>93%	Inhibitor	CYP3A4 substrate and inhibitor	2–8
Posaconazole[18,27]	FDA approved	Susp: 8%–44% DR tab: 54% fasting (high fat meal ↑ 1.5 ×)	7–25	Susp: 8.5 DR tab 31.4 IV 42.9	Susp 0.6 DR tab 2 IV 2.6	>98%	Substrate	Glucuronidation by UGT1A4 Strong CYP3A4 inhibitor	18.7–29.2
Voriconazole[18,28]	FDA approved	96%	4.6	AUC $_{(0–12)}$ 34	4.6	58%	No	CYP2C19, CYP2C9, CYP3A4 substrate and inhibitor	6

Oteseconazole[29–32]	Phase 3	73%[d], ↑ with food	1.4[d]	AUC $_{(0–8)}$ 1.9–4.2[e]	0.4–1[e]	>99%	ND	Weak inhibitor CYP2C9, CYP2C19, CYP3A4	76–160 d
Glucan-synthase inhibitors									
Anidulafungin[19,33]	FDA approved	<5%	30–50L	55–93	3.9–7.7	>95%	No	Chemical degradation	24–26
Caspofungin[19,33,34]	FDA approved	<5%	9.5L[f]	52–170	3.9–13.8	>95%	No	Minor CYP3A4 substrate	9–11
Micafungin[33]	FDA approved	<5%	18L	158	0.24	>95%	No	Minor CYP3A4 substrate	10–17
Rezafungin[35–38]	Phase 3	<5%	28.5L	AUC $_{(0–168)}$[g] 813	12.4[g]	>98%	ND	Minimal P450 interaction	140
Ibrexafungerp[39–41]	Phase 3	>30%	>5	13.4	0.83	>99%	Substrate	CYP3A4 substrate CYP2C8 inhibitor	20–30
Orotomide									
Olorofim[42,43]	Phase 2	45%–82%	~3	35–55	4.6	>99%	ND	Multiple CYP enzymes CYP3A4 substrate Weak CYP3A4 inhibitor	20–30

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Glycosylphosphatidylinositol inhibitor									
Fosmanogepix[44–46]	Phase 2	>90%	ND	315[h]	21.3[h]	ND	ND	Possible substrate of CYP2C19, CYP2D6, CYP3A4, and CYP3A5	52.6[h]

Abbreviations: Vss, Volume of distribution at steady state; P-gp, P-glycoprotein; CYP, Cytochrome P450; Susp, suspension; [Up Arrow Symbol], increase; DR tab, delayed-release tablets; ND, has not been determined, still investigational.

[a] Assuming normal organ function with standard dosing in adults.
[b] Represents terminal half-life, due to triphasic elimination.
[c] Bioavailability for capsules highest when taken immediately after a full meal; solution is 30% higher under fasted conditions.
[d] Based on preclinical data in animal models.
[e] After day 1 of dosing.
[f] Likely larger than this due to limitations of experimental methods.
[g] Day 8 of 200 mg daily.
[h] Day 7 of 1000 mg daily.

Table 2
Pharmacodynamic characteristics and therapeutic drug monitoring recommendations for current and phases 2/3 pipeline antifungal agents[47,48]

Drug Class or Investigational Agent	Concentration Dependent	Prolonged PAFE	PD Index Predictive of Efficacy	Serum Concentration Monitoring Recommended
Polyenes	Yes	Yes	Cmax/MIC	No
Antimetabolite	No	No	*T* > MIC	Yes
Azoles	No	Yes	AUC/MIC	Yes: voriconazole, itraconazole, posaconazole, possibly isavuconazole ND for oteseconazole
Echinocandins	Yes	Yes	Cmax/MIC or AUC/MIC	No
Ibrexafungerp[40]	Yes	ND	Cmax/MIC or AUC/MIC	ND
Fosmanogepix[45]	Yes	Yes	AUC/MIC	ND
Olorofim[42]	No	ND	Cmin/MIC[49]	Yes

Abbreviations: PAFE, Post Antifungal Effect; PD, Pharmacodynamic; Cmax, peak concentrations; Cmin, trough concentrations; DR tab, delayed-release tablets; ND, has not been determined, still investigational; *T*, time.

toxicity. Furthermore, higher proinflammatory cytokine/chemokine levels have been observed in patients with AmB-associated nephrotoxicity and may contribute to this phenomenon.[55]

Nephrotoxicity may occur in a substantial number of patients receiving IV AmBd. In a recent Cochrane analysis of 10 randomized clinical trials, AmBd was associated with a greater than or equal to 2-fold increase in serum creatinine in approximately 26% of patients.[56] Saline loading prior to AmBd infusions has been proposed to help mitigate this toxicity, but there is a lack of data demonstrating clear benefit of this approach.[53,54] Presence of factors, such as comorbid illnesses, receipt of concurrent nephrotoxins, AmB daily and total doses, and intensity of hospital care, have been associated with increased risk of AmBd-associated nephrotoxicity.[53]

LFABs generally have yielded lower rates of IRRs and nephrotoxicity than AmBd, because the lipid moiety prevents interaction of amphotericin with cholesterol in cell membranes and allows more selective and controlled release of drug over time. In the Cochrane analysis of 10 randomized clinical trials, LAmB was associated with a greater than or equal to 2-fold increase in serum creatinine in approximately 10% of patients, with an overall risk ratio of 0.49 (95% CI, 0.40–0.59) compared with AmBd.[56] In a broader recent systematic review and meta-analysis, including 5 different LFABs compared with AmBd, LFABs were found to be associated with lower IRRs (fever [odds ratio (OR) 0.49; 95% CI, 0.26–0.94]; chills [OR 0.44; 95% CI, 0.21–0.92]; vomiting [OR 0.64; 95% CI, 0.46–0.88], and nephrotoxicity [OR 0.32; 95% CI, 0.25–0.41]).[57]

Clinical Use

AmB has a potential role in management of a wide variety of fungal infections, including candidiasis, cryptococcosis, aspergillosis, and mucormycosis. It also has been effective in endemic mycoses, such as histoplasmosis, coccidioidomycosis, blastomycosis, and sporotrichosis.[58] LFABs often are substituted for AmBd for

many of these infections due to their improved tolerability.[59] LFABs are recommended by European Society for Clinical Microbiology and Infectious Diseases/European Confederation of Medical Mycology guidelines as options for treatment of fusariosis, invasive aspergillosis due to *Aspergillus calidoustus*, and invasive aspergillosis due to *Aspergillus* isolates with voriconazole MIC greater than or equal to 2.[60,61] AmB also may have a role in treatment of infections due to *Acremonium* spp and *Purpureocillium lilacinum*, based on limited clinical data.[60]

NOVEL POLYENE FORMULATIONS IN DEVELOPMENT

Other formulations have been extensively investigated to facilitate oral delivery of AmB with a favorable efficacy and safety profile.[62] Of these, a cochleated form of AmB (MAT2203; Matinas BioPharma Nanotechnologies, Bedminster, NJ), is furthest along in clinical development. This agent currently is in phase 2, having completed a study in vulvovaginal candidiasis (VVC) (NCT02971007) with ongoing studies in mucocutaneous candidiasis (NCT02629419) and cryptococcal meningitis (NCT04031833). MAT2203 has been designated as a fast track, qualified infectious diseases product (QIDP) with orphan drug designation by the FDA for treatment of invasive candidiasis and aspergillosis, prevention of IFIs in patients receiving immunosuppressants, and treatment of cryptococcosis.

Cochleates are lipid delivery systems that have been investigated since the 1970s. MAT2203 is composed of a lipid bilayer rolled into a cigar-like spiral, encapsulating and protecting hydrophobic AmB in its interior.[63] Once in the body, cochleates fuse with target cell membranes and release AmB to the cytoplasm; MAT2203 also is thought to be readily taken up by macrophages, which facilitate delivery to sites of infection.[63] Experimental data from mice indicate that cochleated AmB is readily distributed into tissues with effective concentrations in the lungs, liver, kidneys, and spleen.[64,65] MAT2203 also demonstrated measurable brain tissue concentrations after enteral administration in mice infected with *Cryptococcus neoformans*, although this was somewhat lower than that of AmBd.[66]

In a small study evaluating MAT2203 for moderate to severe VVC, MAT2203 (100 mg or 200 mg orally, twice daily for 5 days) was compared with a single dose of fluconazole (150 mg orally) (NCT02971007). These results have not been published in a peer-reviewed journal, but clinical cure at day 12 reportedly was achieved in approximately 53% of MAT2203 recipients compared with 75% of fluconazole recipients.[67] No patients died or had a serious adverse event, and the most common adverse events included gastrointestinal disturbances, bacterial vaginosis, and urinary tract infections.

Phase 1 pharmacokinetic data recently were published and suggested similar exposures after MAT2203 doses of 1 g, 1.5 g, and 2 g daily, ranging from a median area under the concentration curve $(AUC)_{(0\text{-}24\ h)}$ of 1970 to 2180 ng•h/mL (see **Table 1**).[16] Dividing the total daily dose into 4 to 6 divided doses in this study seemed to reduce some of the gastrointestinal disturbances compared with a previous MAT2203 phase 1 study where single doses of 800 mg were used. Based on these results, a total daily dose of 2 g was selected for induction therapy in combination with flucytosine (5-FC) followed by 1.5 g daily in divided doses plus fluconazole for cryptococcal meningitis.[16]

Additional studies are needed to fully evaluate optimal dosing, efficacy, and safety of MAT2203 but this is a promising option for oral polyenes in the treatment or prevention of systemic fungal infections, such as candidiasis, aspergillosis, and cryptococcosis.

ANTIMETABOLITE

The antimetabolite antifungal 5-FC was approved by the FDA in the 1970s and is used primarily as adjunctive therapy for a variety of fungal infections.

Mechanism of Action

The antimetabolite 5-FC exerts its effect inside fungal cells after conversion to its active form, 5-fluorouracil, by fungal specific cytosine deaminase. It then disrupts several cellular processes, including RNA, protein, and DNA synthesis.

Spectrum of Activity/Resistance

Cryptococcus spp, *Aspergillus* spp, some dematiaceous fungi, and many *Candida* spp (except *C krusei*) are susceptible to 5-FC.[17,68,69] Fungal resistance to 5-FC can be intrinsic or acquired. Given concerns about resistance, 5-FC is combined most often with other antifungals for treatment of IFIs.

Formulations/Pharmacokinetics

5-FC is administered orally in the United States and has high bioavailability (see **Table 1**). 5-FC distributes widely into tissues, including cerebrospinal fluid (CSF). It is eliminated renally and requires dose adjustment in those with renal impairment.[17]

Adverse Events

Most commonly, 5-FC side effects include gastrointestinal disturbances and hepatic effects, including elevations in liver enzymes. Bone marrow suppression can also occur, especially with 5-FC concentrations above 100 mg/L.[70] Coadministration with AmB can lead to reduced excretion of 5-FC in patients who experience AmB-induced nephrotoxicity, leading to higher 5-FC concentrations. Coadministration with other myelosuppressive agents can be problematic and compound bone marrow effects of 5-FC.[70]

Clinical Use

The antimetabolite 5-FC is first line in combination with AmB for treatment of cryptococcal meningitis and severe cryptococcal pneumonia.[71] It also may be used adjunctive therapy (mostly combined with AmB formulations) for difficult-to-treat invasive *Candida* spp infections and alone or in combination for certain clinical cases of fluconazole-resistant *C glabrata* cystitis/pyelonephritis.[72] 5-FC was used historically for some cases of chromoblastomycosis, but its use has been supplanted by more effective agents, such as itraconazole and terbinafine.[73] It still may be useful in combination with other antifungals for mycetoma and cerebral infections with certain dematiaceous fungi, such as *Cladophialophora*.[74]

AZOLES

Triazoles are the most common antifungal class administered systemically in the United States and have 3 nitrogens on their azole ring. This imparts increased enzyme specificity and a better safety profile than most imidazoles, which typically are reserved for topical administration. There is 1 imidazole that is FDA approved for systemic use, ketoconazole, as well as 5 triazoles: fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole.

Mechanism of Action

Azoles inhibit ergosterol formation in fungal cell membranes by targeting the enzyme CYP-dependent 14α-demethylase (CYP51), which converts lanosterol to ergosterol. This results in accumulation of methylsterols, disruption of fungal cell membranes, and inhibition of cellular growth and replication.[53]

Spectrum of Activity/Resistance

Differences in chemical structure and affinity for sterol 14α-demethylase imparts differential antifungal activity between the azoles. Fluconazole is active against most *Candida* and *Cryptococcus* spp, whereas ketoconazole, itraconazole, voriconazole, posaconazole, and isavuconazole have activity against yeasts and molds.

Intrinsic resistance to some azoles, such as fluconazole, may occur naturally due to amino acid substitutions in sterol 14α - demethylase encoded by the gene CYP51A (ERG11).[75] Such mutations also may develop within a formerly susceptible species and lead to decreased affinity for binding of the azole to the enzyme. Several other mechanisms of azole resistance have been reported, including up-regulated ERG11 expression, leading to overproduction of sterol 14α - demethylase or overexpression of efflux pumps.[76] Increasing resistance among formerly susceptible *Candida* spp and *Aspergillus* spp has been noted and occurs more often in settings where previous azole exposure has occurred through therapeutic or environmental applications.[77–82]

Formulations/Pharmacokinetics

Many azoles are available in formulations for oral as well as IV delivery, which allow versatile dosing options in a variety of conditions. There is no IV form of ketoconazole, however, and the IV form of itraconazole has been withdrawn from the US market. Each of the azoles has distinct pharmacokinetic properties (see **Table 1**), and there have been notable challenges in achieving reliable systemic concentrations with some of these agents/formulations.

Therapeutic drug monitoring (TDM) has been proposed for many of the mold-active azoles, including itraconazole, voriconazole, and posaconazole (see **Table 2**).[47,83] TDM for these azoles may be especially relevant in patients with hypermetabolic conditions, drug-drug interactions, treatment failure, conditions that increase risk of poor absorption when receiving oral azoles, or if toxicity is suspected.[61,83] Additional data are needed to fully establish exposure-response relationships with isavuconazole, but it appears that patients in initial clinical trials achieved effective plasma concentrations with standard dosing.[20] Newer data suggest there may be a role of TDM for isavuconazole in certain clinical situations.[61,84–86]

Itraconazole and its active metabolite, hydroxyitraconazole, have nonlinear and variable pharmacokinetics. Dissolution of the drug is pH dependent and requires an acidic environment for adequate absorption, especially in capsule form. Newer oral formulations have been developed to try to overcome these pharmacokinetic limitations, including a cyclodextrin suspension and more recently superbioavailability itraconazole (SUBA-itraconazole [Tolsura], Mayne Pharmaceuticals, Raleigh, NC). SUBA-itraconazole capsules contain a pH-dependent polymer matrix with a solid dispersion of itraconazole. In an analysis of 7 studies, SUBA-itraconazole showed enhanced bioavailability (173% [95% CI, 156%–190%]) and lower variability (by 21%) in absorption compared with itraconazole capsules.[87] Pharmacokinetic models suggested 58 mg of SUBA-itraconazole yielded similar concentrations as 100 mg of itraconazole capsules. Food appeared to reduce absorption of both SUBA-itraconazole and

itraconazole capsules similarly, with a reduction of approximately 20% in AUC and 35% in peak serum concentrations.[87]

Voriconazole is known to have substantial intrapatient and interpatient pharmacokinetic variability, with nonlinear pharmacokinetics. Voriconazole has high bioavailability (96%) and moderate protein binding (58%), with CSF/plasma concentration ratios of 0.22 to 1.0.[18] It is metabolized by CYP2C19, CYP3A4, and more minimally CYP2C9. Genetic polymorphisms in CYP2C19, and possibly CYP3A4, have been shown to have an impact on voriconazole pharmacokinetics.[88] Five metabolizer phenotypes of CYP2C19 now have been identified, ranging from poor to ultrarapid metabolizers.[89] Poor and heterozygous extensive CYP2C19 metabolizers have 4-fold and 2-fold higher concentrations than homozygous extensive metabolizers, respectively[90]; 15% to 20% of Asian populations and 3% to 7% of whites and blacks are poor metabolizers, whereas 1% of Asians and more than 30% of whites and blacks may be ultrarapid metabolizers.[90,91] Recommendations from the Clinical Pharmacogenetics Implementation Consortium (2017)[89] suggest use of an antifungal other than voriconazole in patients who are rapid and ultrarapid CYP2C19 metabolizers since attaining target concentrations with standard dosing is unlikely. Use of alternative antifungals for primary therapy or voriconazole dose reduction with TDM is recommended for poor CYP2C19 metabolizers, because higher concentrations are likely in this population and may increase the risk of adverse events.[89] Altered fluconazole and voriconazole pharmacokinetics have been reported in patients on extracorporeal membrane oxygenation (ECMO), due to drug sequestration within the circuit.[92] In addition, dosing of voriconazole for obese patients based on total body weight has been associated with higher concentrations in some studies.[93,94] TDM, therefore, also is recommended for voriconazole in patients on ECMO or with obesity.

Posaconazole has 3 available formulations: oral suspension, delayed release tablets, and solution for IV injection. Posaconazole oral suspension displays saturable absorption, whereby doses above 800 mg are not absorbed readily.[95] Overall concentrations were 2.5-fold higher when posaconazole suspension was administered as 200 mg 4 times daily compared with 400 mg twice daily.[96] The delayed-release tablets of posaconazole have overcome some of the limitations of its oral suspension, providing better absorption and higher concentrations.[97] For this reason, dosing of oral posaconazole is formulation-dependent, and careful attention to formulation must be considered when making dosing recommendations for this agent.

Isavuconazole is available in both IV and oral formulations as the more water-soluble prodrug, isavuconazonium acetate, which is rapidly converted by plasma esterases to active isavuconazole.[98] It exhibits dose-dependent kinetics, with wide tissue distribution. In studies to date, there has been limited interpatient variability reported, although altered concentrations have been reported in those receiving renal replacement therapy or ECMO/Cytosorb (Monmouth Junction, NJ) adsorber therapy.[84] Low concentrations also have been reported in CSF or brain tissue in the presence of uninflamed meninges, with higher concentrations in infected brain tissue or in the presence of inflammation.[85]

All of the currently marketed azoles are substrates and/or inhibitors of CYP isoenzymes. Some also are inhibitors of P-glycoprotein (see **Table 1**). Together these features lead to substantial and unique drug interactions profiles of each azole that must be considered.[99] In a large study evaluating data from 150 hospitals, at least 88% of patients receiving mold-active azoles were administered at least 1 interacting concomitant drug.[100] Some of the more frequent interactions in clinical practice occur with antinausea medications, proton pump inhibitors, fentanyl, midazolam, immunosuppressants, and oral anticoagulants. Other interacting drugs include statins,

amiodarone, vincristine, venetoclax, midostaurin, oral anticoagulants, and anticonvulsants.[100,101]

Safety

Cross-inhibition of some CYP-dependent enzymes in humans by azoles leads to some toxicities and drug interactions. Adverse effects common to azoles as a class include QTc prolongation, with torsades de pointes and hepatic enzyme elevations/hepatotoxicity.[53] Isavuconazole, however, has been reported to shorten QTc interval, so does not follow this class effect.[102] Some adverse effects may be even more apparent with long-term azole exposure, such as alopecia, peripheral neuropathy, and hormone-related adverse effects.[103] Azoles in current clinical use are not recommended for use in pregnant women due to concerns about teratogenicity.[104–107]

Most azoles also are known to cause gastrointestinal side effects, such as nausea and diarrhea. Itraconazole also has been associated with rash, hypokalemia, headache, fever, and dizziness. In addition to these effects, voriconazole-related photopsia occurs in approximately 20% to 30% of patients; this effect seems related to the level of serum concentrations and typically subsides in the first week of therapy.[53] Visual hallucinations and central nervous system (CNS) effects also have been reported with voriconazole, especially at higher serum concentrations.[108,109] Skin rash, photosensitivity, and Stevens-Johnson syndrome also have been reported with voriconazole. More recently, an increase in squamous cell carcinomas has been observed in patients receiving voriconazole, especially with long-term exposure.[110] Periostitis and exostoses have been reported in patients receiving voriconazole and may relate to accumulation of fluoride over long periods of voriconazole intake and osteogenic impact of voriconazole on osteoblasts. Fluconazole, posaconazole, and isavuconazole contain a lower amount of fluoride than voriconazole, and these side effects have not been reported with these other azoles to date.[103]

Hormone-related changes, derangements in electrolytes, and adrenal suppression are variable within the azole class, due to variations in binding affinity for CYP-dependent enzyme CYP51A1, which converts lanosterol to ergosterol in the steroidogenesis pathway. Ketoconazole, and to a lesser extent itraconazole, blocks several other enzyme target sites in the steroidogenesis pathway, having an impact on formation of testosterone and estradiol and leading to side effects, such as gynecomastia, impotence, decreased libido, oligospermia, and azoospermia.[103] Adrenal insufficiency has been reported with all of these azoles with the exception of isavuconazole to date; pseudohyperaldosteronism also has been reported with itraconazole and posaconazole.[103,111,112] Mineralocorticoid excess as well as potential direct damage to myofibroblasts or mitochondrial dysfunction with itraconazole may lead to cardiac toxicity and congestive heart failure with its use in some patients, but this does not appear to be a azole class effect.[113,114]

IV formulations of voriconazole and posaconazole contain the vehicle sulfobutylether-β-cyclodextrin (SBECD), which may accumulate in patients with renal impairment (estimated glomerular filtration rate <50 mL/min).[115,116] There have been concerns about necrosis of the liver and dose-dependent changes in renal histopathology, including vacuolation, in rats at high doses over prolonged exposure periods (1–6 months).[117] Thus, the labeling for these formulations states they should be used only in patients with renal impairment if the benefit outweighs the risk. More recent reviews and retrospective analyses have suggested that there is not strong evidence demonstrating worsening renal dysfunction in patients with renal impairment who received IV voriconazole, and SBECD may be removed by dialysis.[118,119] Itraconazole oral solution is solubilized with hydroxypropyl-β-cyclodextrin (HP-ß-CD), which has

been associated with pancreatic adenocarcinomas in rat but not murine carcinogenicity studies. Toxicity of HP-ß-CD at the concentrations present in itraconazole oral solution has not been apparent in humans to date.[120,121]

Clinical Use

Given their versatility, azoles are the most prescribed class of systemic antifungal agents in United States hospitals.[122] Fluconazole accounted for more than 80% of inpatient antifungal administrations from 2006 to 2012, with voriconazole comprising 6%.[122] Fluconazole may be used in certain clinical situations for the treatment or prevention of candidemia and invasive candidiasis, coccidioidomycosis, and less severe cryptococcosis or as consolidation therapy following induction with LAmB and 5-FC for cryptococcal meningitis. Itraconazole maintains a niche primarily in treating certain cases of histoplasmosis, sporotrichosis, coccidioidomycosis, and non-CNS blastomycosis.[123–126] Voriconazole is a first-line agent for invasive aspergillosis and also may be useful for fusariosis, *Scedosporium apiospermum* infections, certain clinical situations in *L prolificans* and other rare mold infections, candidemia/invasive candidiasis, and cryptococcosis.[60,71,72,124,127] Posaconazole is a first-line agent for prevention of fungal infections in patients with hematologic malignancies as well as treatment of some cases of aspergillosis, fusariosis, mucormycosis, histoplasmosis, blastomycosis, cryptococcosis, candidiasis, coccidioidomycosis, and certain other rare mold infections.[60,61,71,72,124,125,127–131] Isavuconazole has a first-line role for invasive aspergillosis, and there are evolving data to support use in mucormycosis as well as certain clinical scenarios with candidiasis, cryptococcosis and dimorphic fungi.[61,128,132]

NEW AZOLES IN DEVELOPMENT

In recent years, there have been at least 3 new tetrazole-based compounds in development: oteseconazole (formerly VT-1161), VT-1598, and quilseconazole (formerly VT-1129). These agents are highly selective for lanosterol 14α-demethylase, yielding potent antifungal activity with the potential for fewer off-target effects leading to toxicity and drug interactions.[133]

Oteseconazole and quilseconazole (Mycovia Pharmaceuticals, Durham, NC) have shown in vitro activity against fluconazole-resistant C krusei and fluconazole and echinocandinresistant C glabrata at clinically achievable concentrations, suggesting promise for more difficult to treat candida infections.[134] Oteseconazole (Mycovia Pharmaceuticals, Durham, NC) is being studied in phase 2 and phase 3 trials for acute/recurrent VVC (NCT02267382, NCT01891331, NCT03561701, NCT03562156, and NCT01891331) and has additional phase 2 data evaluating it in the treatment of onychomycosis (NCT01891305) and tinea pedis (NCT01891305). Oteseconazole has been awarded QIDP status and a fast track designation for recurrent VVC by the FDA.[135] Phase 3 trials for recurrent VVC recently have been completed, and a New Drug Application (NDA) for this indication is expectedto be filed in 2021.

In a phase 2 study of symptomatic acute VVC, oteseconazole oral doses of 300 mg daily, 600 mg daily, and 600 mg twice daily for 3 days were compared with fluconazole, 150 mg, as a single dose.[29] In intention-to-treat analysis, clinical and microbiologic cure at 28 days was similar for oteseconazole compared with fluconazole: 64.3% (300 mg daily), 75% (600 mg daily), and 78.6% (600 mg twice daily) versus 66.7%. With oteseconazole's long half-life, measurable drug concentrations were still observed at 168 days (127 ng/mL, 409 ng/mL, and 1300 ng/mL for initial 3-day courses of 300 mg daily, 600 mg daily, and 600 mg twice daily, respectively). No

patients treated with this new agent experienced recurrent VVC whereas 46% of fluconazole-treated patients had mycologically proved recurrence after 6 months.

VT-1598 (Mycovia Pharmaceuticals) currently is being evaluated in a phase 1 pharmacokinetic study and has shown activity against a range of fungi, such as *Candida* spp (including *C auris*), *Cryptococcus* spp, *Aspergillus* spp, *Rhizopus arrhizus*, and endemic fungi including *B dermatitidis*, *Coccidioides* spp, and *H capsulatum*.[136,137] It has been granted QIDP status and a fast track as well as orphan drug designation for coccidioidomycosis by the FDA.

Quilseconazole demonstrated efficacy with linear pharmacokinetics after oral dosing for cryptococcal meningitis in immunocompetent mice.[138] This agent has a long half-life of more than 6 days in mice and displayed excellent CNS penetration in this study. Quilseconazole has been identified as a QIDP and received fast track and orphan drug designations from the FDA for treatment of cryptococcal meningitis. At this time, however, there are no quilseconazole clinical trials registered in the United States.

ECHINOCANDINS

Echinocandins are the newest antifungal class approved for use and include anidulafungin, caspofungin, and micafungin. These compounds consist of an amphiphilic cyclic hexapeptide with an *N*-linked acyl lipid side chain. Differences in the side chain make each echinocandin structurally unique.[53]

Mechanism of Action

Echinocandins exert their antifungal effects by noncompetitively inhibiting the synthesis of (1→3)-β-D-glucan, an essential component of the fungal cell wall. They exert this effect by targeting the catalytic subunit of the enzyme complex (1→3)-β-D-glucan synthase, which is encoded by FKS genes.[139] Decreased production of (1→3)-β-D-glucan leads to a loss of cell wall integrity and subsequently, lysis of the cell.

Spectrum of Activity/Resistance

Echinocandins have fungicidal activity against *Candida* spp as well as fungistatic activity against *Aspergillus* spp. Echinocandins lack appreciable clinical activity against *Cryptococcus* spp, zygomycetes, *Fusarium solani*, and *Trichosporon* spp.[140,141] Mutations in FKS1 and FKS2 in *Candida* spp have been associated with higher echinocandin MICs and diminished clinical activity.[142–144] Echinocandins have variable activity against endemic fungi, with micafungin having the most potent activity in vitro against mycelial forms of *H capsulatum*, *B dermatitidis,* and *Coccidioides immitis* but little activity against yeast-like forms of these fungi. Echinocandins also have activity against the cyst forms of *P jirovecii* but not the trophozoite form.[141]

Formulations/Pharmacokinetics

Currently licensed echinocandins are available only in IV formulations. These compounds are large and do not penetrate CNS well. All are typically dosed once daily, but the half-life of these agents varies from 9 hours to 11 hours for caspofungin and 24 hours to 26 hours for anidulafungin. Echinocandins are not metabolized via the CYP system, so they have fewer drug interactions than azole compounds.[141] In addition, their large size and high protein binding seem to limit removal of drug by hemodialysis or hemofiltration, although adsorption of micafungin to polyacrylonitrile (AN-69) membranes during continuous venovenous hemodiafiltration has been associated with lower exposures in some patients.[145] Dose modifications for patients

receiving echinocandins while undergoing hemodialysis or hemofiltration are not universally recommended.[146] Recent data suggest, however, altered pharmacokinetics of micafungin but not caspofungin or anidulafungin in patients on ECMO.[146–150] Higher micafungin doses (at least 200 mg daily for adults) may be needed in these patients.

In addition, obese patients may experience inadequate target attainment due to lower-than-expected drug exposures with standard dosing of all echinocandins. Therefore, dose increases of these agents are recommended in obesity.[151–154] Although original product labeling recommended maintenance dose reduction of caspofungin to 35 mg in patients with moderate hepatic insufficiency, a more recent study in patients with decompensated Child-Pugh class B or class C cirrhosis suggested this would result in lower than comparable exposures in noncirrhotic patients and potentially suboptimal concentrations.[155]

Safety

Echinocandins have a favorable safety profile and are well tolerated by most patients. There is no synthesis of (1→3)-β-D-glucan in human cells as in fungal cell walls; thus, off-target effects of echinocandins in humans are less likely to occur. The most common adverse effects noted with echinocandins in clinical trials have been elevations in liver enzymes, gastrointestinal disturbances, hypokalemia, fever, and injection site reactions.[156–158] In preclinical toxicology studies of long-term high-dose micafungin exposure, liver tumors were observed in rats, leading to a black box warning in European product labeling.[159] An evaluation of more than 23,000 patients who received systemic antifungal therapy in US hospitals, however, found no signal of hepatocellular cancers with micafungin compared with other antifungals in this population after 71,285 person-years of follow-up.[160] Short-term risk of liver injury and kidney injury also was found to be similar for patients receiving micafungin and other systemic antifungals in a propensity score matched analysis.[161]

Clinical Uses

Echinocandins are considered first-line agents for the treatment of candidemia in neutropenic and non-neutropenic adults and have a role in certain other forms of invasive candidiasis, such as intra-abdominal infections, osteomyelitis/septic arthritis, esophagitis, and chronic disseminated candidiasis.[72] High-dose echinocandin therapy may be used for some cases of endocarditis, cardiac device infections, or suppurative thrombophlebitis due to susceptible *Candida* spp. Another role for echinocandins is salvage therapy or as part of combination therapy for invasive aspergillosis. Micafungin also has been shown to be noninferior to fluconazole as prophylaxis in hematopoietic stem cell transplant recipients in a randomized trial, and caspofungin demonstrated efficacy and better tolerability than LAmB in a randomized trial as empirical therapy of neutropenic fever.[162,163]

NEW AGENTS IN DEVELOPMENT TARGETING GLUCAN SYNTHESIS

Rezafungin

Rezafungin (CD101, Cidara Therapeutics, San Diego, CA) is a next-generation echinocandin that is a structural analog of anidulafungin, with the same side chain with a slight change in the cyclic core, which yields improved stability and solubility. Rezafungin has a much longer half-life (>130 hours) than precursor echinocandins, which facilitates less frequent dosing. It also exhibits dose-proportional pharmacokinetics with little interpatient variability and a favorable safety profile, including lack of apparent effects on QT interval at doses up to 1400 mg.[35,164] This agent has a

QIDP and fast track designation for prevention of IFIs in adults undergoing allogeneic bone marrow transplantation. It also is designated as a QIDP, fast track, and orphan drug designation for the treatment of candidemia/invasive candidiasis. Current phase 3 clinical trials are exploring rezafungin for both of these indications. In a phase 3 candidemia/invasive trial (ReSTORE, NCT03667690), rezafungin is administered as a 400-mg IV loading dose in week 1, followed by 200-mg IV weekly thereafter, and compared with daily caspofungin infusions with stepdown to oral daily fluconazole dosing. In the phase 3 prophylaxis trial (ReSPECT, NCT04368559), rezafungin is dosed similarly and compared with standard doses of trimethoprim/sulfamethoxazole (for *Pneumocystis jirovecii* prophylaxis) in combination with either fluconazole or posaconazole. Dosing in these trials was selected on the basis of prior dose-ranging studies and a phase 2 clinical trial evaluating rezafungin for candidemia/invasive candidiasis.

In a phase 2 randomized, double-blind multinational trial for candidemia and invasive candidiasis (STRIVE), rezafungin was compared with caspofungin (70 mg IV loading dose followed by 50 mg IV daily, with optional stepdown to oral fluconazole).[36] Rezafungin had 2 dosing schemes: either 400 mg IV weekly or 400 mg IV once during the first week followed by 200 mg IV weekly, for 2 weeks to 4 weeks total. Overall response in the modified intention-to-treat analysis at day 14 was 60.5% for rezafungin, 400 mg weekly; 76.1% for rezafungin, 400/200 mg weekly; and 67.2% for caspofungin; 30-day all-cause mortality rates were 15.8%, 4.4%, and 13.1% for these groups, respectively. There were several patients in the rezafungin 400-mg weekly arm with indeterminate responses at day 14 (13.2%, due to lack of data from mycologic cultures or assessment of systemic signs of infection), contributing to the trend in lower success rates in this group. These differences in outcome were apparent in mycological and clinical cure rates at day 5, after only a single 400-mg dose in each of the rezafungin groups. Median time to blood culture negativity was lower overall for patients receiving rezafungin (19.5 h) versus caspofungin (22.8 h; $P = .02$). The most common treatment emergent adverse events were hypokalemia (16.4%, rezafungin, and 13.2%, caspofungin), gastrointestinal disturbances, fever, and anemia. The rates of severe and serious treatment-related adverse events were similar between groups. Together these data support the comparative safety of rezafungin and proof-of-concept for efficacy with a front-loaded weekly dosing strategy in treating candidemia/invasive candidiasis.

Rezafungin was also previously evaluated as a topical treatment (as 3% gel or 6% ointment) for acute VVC in a phase 2 trial (NCT02733432)[165]; 90% of participating women had *C albicans* infections, and 36% had a history of recurrent VVC. Although there was a relatively small number of nonalbicans isolates in this study, failure of nonalbicans infections was relatively high across all treatment groups (75%, rezafungin, and 100%, fluconazole). Overall, clinical cure rates were no better for either of the 2 rezafungin topical formulations than a single (150-mg) dose of fluconazole. Thus, topical rezafungin is not currently being developed further for the VVC indication.[166]

Ibrexafungerp

Ibrexafungerp (SCY-078, Scynexis Pharmaceuticals, Jersey City, NJ) is a glucan synthase inhibitor with a unique chemical structure as a triterpenoid derivative of enfumafungin. Although it is not an echinocandin, it inhibits glucan synthesis through interaction with enzyme complex (1→3)-β-D-glucan synthase at a site that is distinct but partially shared with echinocandins.[139] This leads to some potential cross-resistance with echinocandins; however, studies to date suggest that ibrexafungerp retains activity against many *Candida* isolates with FKS mutations associated with

echinocandin-resistance.[167] It also appears active against many *C auris* strains, including isolates that may be resistant to echinocandins and azoles.[168] Ibrexafungerp also has demonstrated in vitro activity against *Aspergillus* spp as well as *Paecilomyces variotii* and otherwise pan-resistant *L prolificans.*[169]

Ibrexafungerp is being studied in current clinical trials as an oral formulation. A liposomal formulation for IV administration is under development with plans for a phase 1 pharmacokinetic study in 2021.[170] This compound is widely distributed in tissues, including abscesses in experimental models, although it has relatively poor CNS penetration.[171,172] It exhibits linear pharmacokinetics with a terminal half-life of 20 hours to 30 hours.[39] It is a substrate of CYP3A4, and ibrexafungerp dosing may need adjusted when coadministered with potent CYP3A4 inhibitors.[39] Although in vitro data have suggested that ibrexafungerp is a possible inhibitor of CYP2C8, it did not appear to significantly impact concentrations of rosiglitazone (a CYP2C8 substrate) in a clinical pharmacokinetics study.[173]

Completed and ongoing clinical trials have focused on evaluating ibrexafungerp for the treatment of acute/recurrent VVC (NCT03987620, NCT03734991, NCT04029116, NCT02679456, and NCT03253094), *C auris* infections (NCT03363841), candidemia/invasive candidiasis after initial therapy with an echinocandin (NCT02244606), a variety of fungal infections refractory/intolerant to other antifungals (NCT03059992), and invasive pulmonary aspergillosis in combination with voriconazole (NCT03672292).

Initial results with ibrexafungerp for VVC have been promising but are not yet published in peer-reviewed journals. A dose of 300 mg, twice daily for 1 day, was studied in 2 phase 3 trials for acute VVC and was significantly more effective than placebo for both clinical and mycological response.[39]

In invasive candidiasis, results of a small (N = 27), phase 2, open-label study of step-down therapy after echinocandins indicated that ibrexafungerp had a similar response as standard of care (SOC), which was fluconazole step-down or micafungin for fluconazole-resistant isolates.[174] Ibrexafungerp had 2 dose groups: 1000-mg loading dose, followed by 50 mg daily, or 1250-mg loading dose, followed by 1000 mg daily, whereas fluconazole was given as an 800-mg loading dose, followed by 400 mg daily. Only 1 patient in the SOC arm received micafungin (100 mg daily) instead of fluconazole due to an azole-resistant *Candida* spp. Global responses at the end of therapy were 71% and 85% for ibrexafungerp maintenance doses of 500 mg and 750 mg, respectively, and 71% for SOC. The treatments were well tolerated, with the most common side effects of gastrointestinal disturbances (43%), infection/infestation (38%), and headache (24%). In a pharmacokinetic model, 85% of ibrexafungerp patients were found to achieve target steady-state $AUC_{0–24}$ exposures (15.4 μM·h, equivalent to 11.2 μg·h/ml).[40] One patient in the ibrexafungerp, 500-mg, maintenance dose group had suboptimal concentrations below the organism MIC but still responded to therapy. Only 1 patient in either ibrexafungerp group achieved the target $AUC_{0\text{-}24}$ on day 1 of dosing.[174]

The FURI study (NCT03059992) extends ibrexafungerp experience to infections refractory to or intolerant of other antifungals. Preliminary results of this open-label phase 3 study have suggested promising ibrexafungerp activity against a variety of deeply invasive *Candida* spp infections as well as some cases of mucocutaneous candidiasis.[175] In this study, ibrexafungerp is administered orally, at a dose of 750 mg twice daily for 2 days, followed by 750 mg daily for IFIs, with a dose reduction to 500 mg daily when combined with mold-active azoles.

Ibrexafungerp has been designated as a QIDP with fast track status by the FDA for treatment of VVC and prevention of recurrent VVC, and in 2020 an NDA was filed for the treatment of VVC with plans for priority review in 2021. It also has been designated

an orphan drug with QIDP and fast track status for oral use in treating invasive candidiasis, including candidemia, and invasive aspergillosis.[176]

OTHER NOVEL AGENTS IN THE PIPELINE (PHASE 2 OR PHASE 3)

Orotomides

Olorofim (F901318, F2G, Manchester, UK) is the first of a novel antifungal class, the orotomides. These agents inhibit dihydroorotate dehydrogenase (DHODH) in the pyrimidine biosynthesis pathway, which is an essential component of many cellular processes, including nucleic acid, cell wall, and phospholipid synthesis.[177] Fungal cell regulation and protein production are also affected. Olorofim leads to fungal cell lysis and lack of fungal cell viability by reducing available substrates for formation of the cell wall components chitin and (1→3)-β-D-glucan as well as impacting hyphal growth, septation, and vacuole formation.[42,178] Toxicity in humans is expected to be low, because olorofim's affinity for fungal DHODH is more than 2200-times greater than that of the human enzyme homolog.[177]

In in vitro studies, olorofim has demonstrated activity against *Aspergillus* spp, *Scedosporium* spp, *L prolificans*, *Penicillium, Paecilomyces*, *Purpureocillium*, *Talaromyces*, and *Microascus/Scopulariopsis* spp; and endemic fungi, such as *Coccidioides* spp, *Histoplasma* spp, and *Blastomyces* spp. It also has activity against some *Fusarium* spp but lacks activity against *Candida* spp, *Cryptococcus* spp, and Mucorales.[42,179]

Clinical studies to date have focused on establishing the pharmacokinetic (see **Table 1**) and drug-interaction profile of olorofim in multiple formulations. To solubilize the drug, early IV formulations contained a HP-ß-CD vehicle and oral tablets were formulated with hydroxypropyl methylcellulose acetate succinate.[42] Oral bioavailability of 45% to 82% has been reported as well as enterohepatic recirculation.[180] This compound appears to be widely distributed, with some CNS penetration. It is metabolized by multiple CYP isoenzymes, leading to concerns about possible drug-drug interactions with other agents, such as the CYP3A substrate midazolam, which was increased by approximately 30% after 7 days of concomitant olorofim dosing.[181]

A phase 2b clinical trial (NCT03583164) is currently evaluating oral olorofim (up to 300 mg a day, guided by TDM) in patients with difficult-to-treat IFIs due to *L prolificans*, *Scedosporium* spp, *Aspergillus* spp, and other resistant fungi. Several case reports presented in 2020 described successful treatment of infections due to *L prolificans* and *Coccidioides* spp, with oral olorofim in individual patients participating in this trial.[182–184]

Olorofim has been granted an orphan drug designation for coccidioidomycosis as well as a breakthrough drug designation for treatment of refractory/intolerant CNS *coccidioidomycosis.* In addition, it has an orphan drug designation for treatment of invasive aspergillosis and *Lomentospora/Scedosporium* infections. Olorofim also has been designated as a QIDP and breakthrough drug for treatment of difficult-to-treat mold infections, including invasive aspergillosis, scedosporiosis, lomentosporiosis, fusariosis, and infections due to *Scopulariopsis* spp.

Glycosylphosphatidylinositol Inhibitors

Fosmanogepix (APX001, Amplyx Pharmaceuticals, San Diego, CA) is a small molecule prodrug of the antifungal manogepix (APX001 A) that interferes with assembly of mannoproteins into cell wall glucan. By inhibiting the fungal Gwt1 enzyme, manogepix reduces cellular trafficking and anchoring of mannoproteins in cell membranes and the

outer cell wall, leading to a variety of detrimental effects on fungal cell integrity, growth, and virulence.[44,185]

In vitro studies have shown that manogepix has potent activity against a variety of *Candida* spp, including *C auris* as well as *Cryptococcus neoformans*, *Aspergillus* spp (including azole-resistant and echinocandin-resistant organisms), and *L prolificans*, with variable activity against *Scedosporium* spp and *Fusarium* spp.[44,45,186] Higher MICs generally have been observed for manogepix against Mucorales. Mutations in the Gwt1 target are likely to lead to manogepix resistance. This does not seem to impart cross-resistance with other antifungal classes. Some fluconazole-resistant *Candida* with efflux-related mutations, however, have exhibited higher MICs to manogepix; more data are needed to evaluate the clinical relevance of these findings.[44]

Fosmanogepix is being studied in both IV and oral formulations. Data from humans suggests it has a half-life of 2 days to 2.5 days with linear pharmacokinetics and, in preclinical studies, appeared to be distributed well in tissues, including the eye and brain. It appears to be metabolized in the liver via several pathways and may be a substrate of several CYP isoenzymes, including CYP2C19, CYP2D6, CYP3A4, and CYP3A5.[187]

Phase 2 clinical trials have focused on evaluating fosmanogepix for candidemia (NCT03604705), invasive *C auris* infections (NCT04148287), and invasive aspergillosis/rare mold infections (NCT04240886). In a small proof-of-concept phase 2, open-label study, 80% of non-neutropenic patients with candidemia experienced treatment success after 14 days of fosmanogepix (1 g twice daily IV for 1 day, followed by 600 mg daily IV or 700 mg daily orally after 3 days). AmB-resistant or anidulafungin-resistant Candida spp. infections occurred in 66% (N = 14) patients in the study; 71% (N=10) of these patients experienced treatment success. The most common treatment-emergent adverse effects were gastrointestinal disturbances.[188]

Fosmanogepix has an orphan drug and QIDP/fast track FDA designation for the treatment of invasive candidiasis, invasive aspergillosis, coccidioidomycosis, cryptococcosis, and rare mold infections.[189]

SUMMARY

This is an exciting time in antifungal development, with more than 7 agents in phase 2 or phase 3 clinical trials for a variety of IFIs. Polyenes, antimetabolites, azoles, and echinocandins all have a place in prevention or treatment of fungal infections. Given the challenges with dosing, pharmacokinetics, drug interactions, safety, and mycologic activity with each of these classes, however, there is room for new agents in the armamentarium. Additional studies are ongoing to optimize use of both new and older agents against highly morbid fungal infections.

CLINICS CARE POINTS

- Polyenes are the antifungal class with the broadest spectrum of activity and few drug-drug interactions but have poor oral bioavailability in currently approved forms. Side effects, such as nephrotoxicity, infusion-related reactions, and electrolyte disturbances, are a consideration when using agents in this class.
- Newer formulations of AmB include encochleated preparations, which may enable systemic concentrations with oral dosing.
- Azoles each have unique properties in regards to spectrum of activity, pharmacokinetics, drug-drug interactions, and safety profile. Availability in both oral and IV forms facilitates

administration of azoles in a variety of settings. TDM is recommended for several of the mold-active azoles to optimize efficacy and tolerability.

- Investigational azoles have greater selectivity for the target for lanosterol 14α-demethylase and may have fewer off-target effects, leading to favorable safety profiles while retaining potent antifungal activity.
- Echinocandins target (1→3)-β-D-glucan synthase in the fungal cell wall, leading to fungicidal activity against *Candida* spp and fungistatic activity against *Aspergillus* spp. They generally are well tolerated but are available only in IV formulations.
- A new echinocandin in development, rezafungin, has a much longer half-life than currently approved echinocandins, which will facilitate once-weekly dosing for IFIs.
- An investigational glucan synthase inhibitor, ibrexafungerp, is being studied in both IV and oral formulations and offers promise for candida infections, including *C auris*, as well as some invasive mold infections.
- Other agents include the antimetabolite 5-FC, which is used as adjunctive therapy in cryptococcal and candida infections. Its use is challenged by development of resistance and complexity of oral dosing due to its toxicity profile and need for TDM.
- Antifungals from novel classes, such as orotomides and glycosylphosphatidylinositol inhibitors, have entered phase 2 clinical trials and hopefully offer new alternatives with a wide spectrum of activity, IV and oral formulations, and favorable safety profiles.

DISCLOSURE

Dr M.D. Johnson has been a consultant to Cidara, Pfizer, and Astellas, and has research grants from Astellas, Scynexis, Charles River Laboratories, and Merck & Co.

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