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SUPPLEMENT ARTICLE

Pipeline of Novel Antifungals for Invasive Fungal Disease in Transplant Recipients: A Pediatric Perspective

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Invasive fungal disease (IFD) remains a significant cause of morbidity and mortality in children undergoing transplantation. There is a growing armamentarium of novel antifungal agents recently approved for use or in late stages of clinical development. The overarching goal of this review is to discuss the mechanisms of action, spectrum of activity, stage of development, and pediatric-specific data for the following agents: encochleated amphotericin B deoxycholate, fosmanogepix, ibrexafungerp, isavuconazole, olorofim, opelconazole, oteseconazole, and rezafungin. Additionally, key drug attributes of these novel agents and their potential future therapeutic roles in pediatric transplant recipients are discussed.

Key words. invasive fungal disease; novel antifungals; pediatrics; transplantation.

INTRODUCTION

Invasive fungal disease (IFD) causes significant morbidity and mortality in pediatric transplant recipients. Various prevention and management guidelines have improved the approach to IFD, but often there is a paucity of therapeutic choices [1–4]. Fortunately, several novel antifungal agents have been recently approved or are in late stages of development, providing optimism for an expanded antifungal armamentarium in the future. Pediatric studies are currently being planned or underway for many of these novel antifungals as required by the United States Food and Drug Administration (FDA) regulatory stipulations which state that pediatric studies be planned before the initiation of phase III studies [5]. Herein, we present a pediatric-specific overview for novel agents including encochleated amphotericin B deoxycholate (eAMB), fosmanogepix, ibrexafungerp, isavuconazole, olorofim, opelconazole, oteseconazole, and rezafungin. We review mechanisms of action (Figure 1), pharmacokinetic (PK), and spectrum of activity data when available (Table 1 and Figure 2), and highlight the future utility of these agents in pediatric transplant recipients.

Current IFD Epidemiology and Therapy Recommendations in Pediatric Transplantation

The incidence of IFD after allogeneic hematopoietic cell transplantation (HCT) is 10% or more [1], with case fatality rates ranging from 20% to 70%. *Candida* and *Aspergillus* species (spp.) are the most frequently identified pathogens. Rates of IFD in the early post-transplant period are lower in pediatric solid organ transplant (SOT) recipients (2.2%) than in HCT recipients, with incidence highest in heart/lung and lung recipients [6].

In pediatric HCT recipients, prophylaxis is recommended pre-engraftment, post-engraftment before immune reconstitution, and with treatment of graft-versus-host disease. The prophylactic antifungal recommended varies based on the risk period with echinocandins or mold-active triazoles favored for periods of invasive mold risk (such as pre-engraftment with absent phagocytes and with graft-versus-host disease due to dysfunctional phagocytes, cell-mediated immunity dysfunction, and barrier breakdown) and fluconazole when candidiasis is the primary IFD of concern (central venous catheters with neutropenia for invasive candidiasis (IC) and low CD4+ T cells before immune reconstitution for mucosal candidiasis) [1, 2]. At the time of prolonged fever and neutropenia, empiric therapy with caspofungin or liposomal amphotericin B is recommended in evidence-based guidelines [3]. In SOT recipients, targeted prophylaxis is recommended for individuals with risk factors for IC and invasive aspergillosis (IA) [7–9]. *Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole is recommended until T-cell recovery for HCT recipients and for 6–12 months post-transplant in SOT recipients [7, 10–12].

Limitations of Currently Available Antifungal Agents in Pediatric Transplantation

The current armamentarium of antifungals is limited due to rising antifungal resistance, serious drug toxicities, and significant drug–drug interactions. Fluconazole as well as

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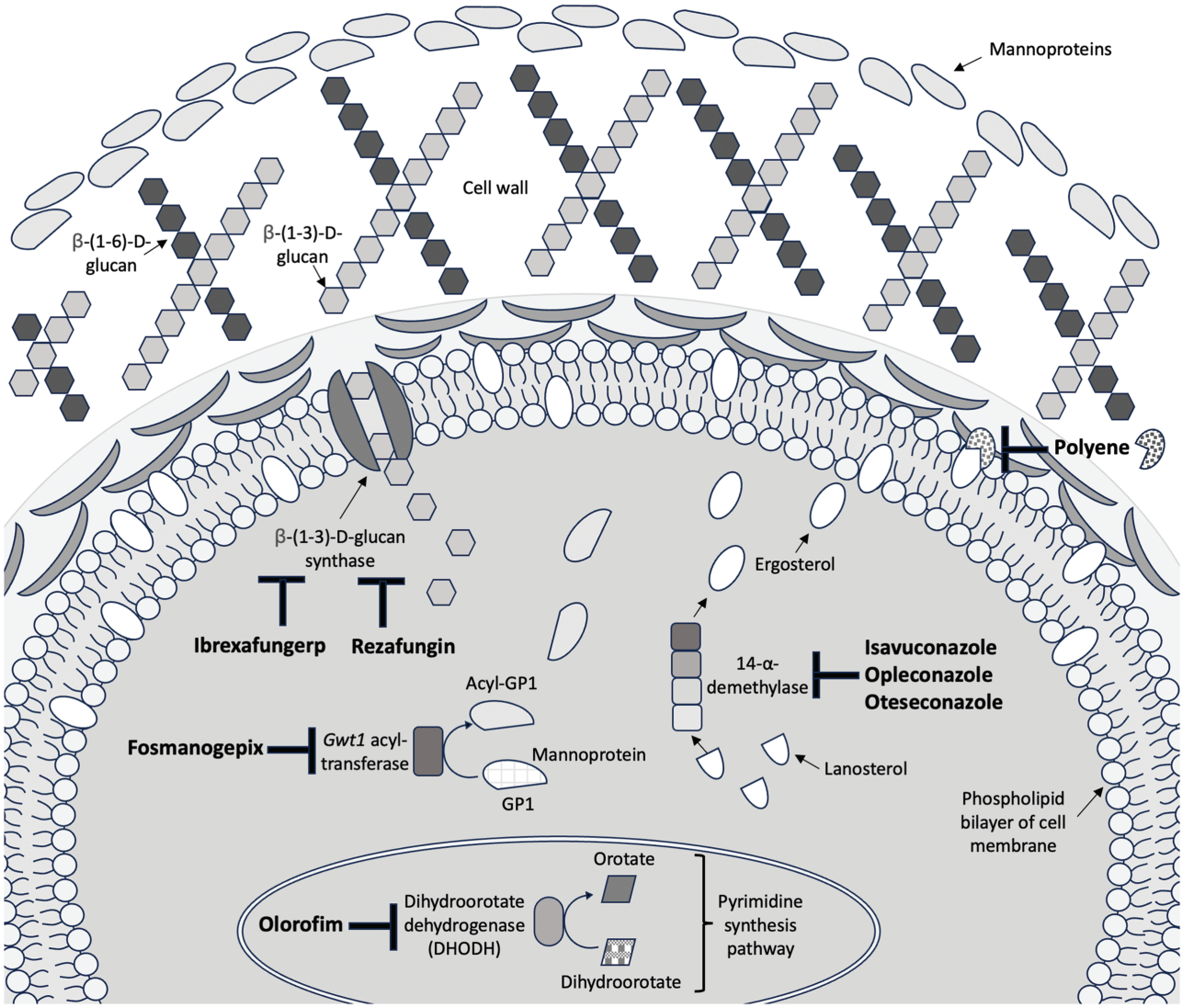

Figure 1. Mechanism of action for novel antifungals. Antifungal agents are depicted in bold with dark bars indicating the target of activity in the fungal cell.

echinocandin resistance has been on the rise for non–*C. albicans* species, and the recent emergence of multi–drug-resistant *C. auris* pose significant challenges with treatment [13, 14]. Existing formulations of amphotericin B can be nephrotoxic and/or cause significant electrolyte disturbances and infusion reactions, whereas triazoles can precipitate liver enzyme elevations, QTc prolongation, and significant drug–drug interactions due to CYP450 inhibition, especially with immunosuppressants like tacrolimus, sirolimus, and cyclosporine [15]. Lastly, currently available agents have limited efficacy for difficult-to-treat pathogens like *Scedosporium* spp., *Lomentospora* spp., *Fusarium* spp., and Mucorales order pathogens. The novel antifungal agents discussed herein provide more favorable safety profiles with fewer drug–drug interactions and fill some of the gaps in coverage with our current armamentarium. Clinical breakpoints have not been established for these novel antifungal agents, unless otherwise specified.

ENCOCHLEATED AMPHOTERICIN B

Formulation/Mechanism of Action

eAMB, or MAT2203, is a novel formulation of amphotericin B deoxycholate for oral (PO) administration and enteral absorption [16]. This formulation leverages a nanocrystal, referred to as a cochleate, that combines a negatively charged lipid bilayer with a calcium cation resulting in a spiral configuration. Hydrophobic amphotericin molecules contained in this spiral are protected from digestive tract degradation. Once absorbed, the cochleate is phagocytosed by cells of the reticuloendothelial system (eg, monocytes and macrophages) with deposition

Table 1. Adult and Pediatric Approval Status for Novel Antifungal Agents

Novel Antifungal, Route of Administration (Pronunciation)	Approval Status and Adult Approved/Investigational Dose	Pediatric Dosing Currently Under Investigation	Pediatric Clinical Trials Registered at clinicaltrials.gov[a]	Key Advantages/Attributes	Key Toxicities/Precautions
Azole antifungals					
Isavuconazonium sulfate, PO/IV (eye sa vue koe na ZOE nee um sul FATE) NOTE: Dosing based on the pro-drug Isavuconazonium sulfate (372 mg of Isavuconazonium = 200 mg of Isavuconazole)	FDA and EMA approved for the treatment of IA and IM: Loading dose: 372 mg of Isavuconazonium (200 mg of Isavuconazole) IV/PO q8h × 6 doses on days 1–2 Maintenance dose: 372 mg of Isavuconazonium (200 mg of Isavuconazole) IV/PO q24h, to start 12–24 hr after last loading dose	6 months to <1 year: Loading dose: 6 mg/kg/dose of Isavuconazonium IV/PO q8h × 6 doses on days 1–2 Maintenance dose: 6 mg/kg/dose of Isavuconazonium IV/PO q24h, to start 12–24 hr after last loading dose 1 to <18 years: Loading dose: 10 mg/kg/dose of Isavuconazonium IV/PO q8h × 6 doses on days 1–2 Maintenance dose: 10 mg/kg/dose of Isavuconazonium IV/PO q24h (max 372 mg of Isavuconazonium/dose) to start 12–24 hr after last loading dose	NCT03241550, NCT03816176	More predictable pharmacokinetics and less inter- and intra-patient variability when compared to voriconazole; potential for less toxicity (hepatobiliary, skin, CNS, and QT prolongation) compared with voriconazole and posaconazole	Not recommended for the treatment of candidal infections due to inferior efficacy; moderate inhibitor of and substrate for CYP3A4, screen for drug–drug interactions; causes shortening of QTc interval (contraindicated in familial short QT syndrome)
Oteseconazole, PO (oh TES e KON a zole)	FDA approved for recurrent vulvovaginal candidiasis: Day 1: 600 mg PO × 1 Day 2: 450 mg PO × 1 Starting on day 14: 150 mg PO once weekly × 11 weeks	Not available	Studies including children ≥12 years: NCT03840616, NCT03562156, NCT03561701	Tetrazole moiety more selective for fungal CYP450 compared with triazoles, leading to less potential for drug–drug interactions and side-effects; active against fluconazole-resistant strains of *C. glabrata* and *C. krusei*	Fetal harm demonstrated in animal studies; due to long half-life, may cause embryo-fetal toxicity within 2 years after administration.
Opelconazole, inhaled (oh-PUHL-e-KON-a-zole)	No approval to date	Not available	No active pediatric clinical trials registered	Inhaled long acting triazole antifungal with activity against *Candida* spp. and *Aspergillus* spp.; minimal toxicities and less potential for drug–drug interactions due to minimal systemic absorption; potential role in non-angioinvasive pulmonary aspergillosis	If used for angioinvasive pulmonary aspergillosis, would likely need to be in combination with systemic antifungals
Echinocandin antifungal					
Rezafungin, IV (RE-za-FUN-jin)	FDA approved for candidemia and IC in adults with limited or no alternative treatment options: 400 mg loading dose, 200 mg once weekly thereafter	Not available	NCT05534529	Long acting echinocandin allowing for once weekly dosing; has activity against *Pneumocystis* spp.	Risk of infusion-related reactions, photosensitivity, abnormal liver tests

Table 1. Continued

Novel Antifungal, Route of Administration (Pronunciation)	Approval Status and Adult Approved/Investigational Dose	Pediatric Dosing Currently Under Investigation	Pediatric Clinical Trials Registered at clinicaltrials.gov[a]	Key Advantages/Attributes	Key Toxicities/Precautions
Triterpenoid antifungal					
Ibrexafungerp, PO/IV (eye-BREX-uh-FUNJ-erp)	PO FDA approved for treatment/prevention of vulvovaginal candidiasis: Acute infection: 300 mg PO twice daily × 2 doses Recurrent infection: 300 mg PO twice daily × 2 doses; repeat monthly for a total of 6 months Investigational adult dose for oral step-down therapy for invasive candidiasis and for invasive mold infections: 750 mg PO twice daily × 2 days, then 750 mg PO once daily	≥12 years: vulvovaginal candidiasis, same as adult dose	Studies including children ≥12 years: NCT03987620, NCT03734991, NCT04029116	Oral formulation; highly active against triazole-resistant *Candida* spp. and *Aspergillus* spp.	Fetal harm demonstrated in animal studies; current labeling advises females of reproductive potential to use effective contraception during treatment; potential for drug–drug interactions as ibrexafungerp is metabolized by CYP3A4
Gwt1 inhibitor					
Fosmanogepix, PO/IV (faas-MEN-a-GE-piks)	No approval to date Investigational adult dose for treatment of IFD: 1000 mg IV twice daily on day 1, then 600 mg IV once daily on days 2 and 3, then 600 mg IV once daily or 700–800 mg PO once daily thereafter	Not available	No active pediatric clinical trials registered	Novel mechanism of action with IV and highly bioavailable PO formulations and activity against difficult-to-treat molds such as *Fusarium* and *Scedosporium* spp.	Well tolerated (most common side-effects include headache and diarrhea)
Orotomide antifungal					
Olorofim, PO/IV (oh-LOHR-oh-fim)	No approval to date Investigational adult dose for treatment of IFD: 150 mg PO twice daily on day 1, then 90–150 mg PO twice daily thereafter	Not available	No active pediatric clinical trials registered	Novel mechanism of action with both IV and PO formulations; active against triazole-resistant-*Aspergillus*, *Scedosporium* spp., and *Lomentospora* spp.	Limited data thus far, possible increased risk for dizziness; potential for drug–drug interactions as olorofim is metabolized by multiple CYP450 enzymes including CYP3A4, and it is also a weak inhibitor of CYP3A4
Polyene antifungal					
Encochleated Amphotericin B, PO (en-KOK-lee-ey-tid am-foe-TER-i-sin-bee)	Granted orphan drug status for cryptococcosis but no approval to date	Not available	No active pediatric clinical trials registered	Novel oral formulation of amphotericin B deoxycholate that increases drug delivery to infection sites with potential for reduced toxicity (nephrotoxicity and electrolyte disturbances) compared to intravenous amphotericin products	Increased gastrointestinal disturbance with higher once daily dosing

Abbreviations: EMA: European Medicines Agency; FDA: Food and Drug Administration; IA: invasive aspergillosis; IC: invasive candidiasis; IM: invasive mucormycosis; IV: intravenous; kg: kilograms; mg: milligrams; PO: by mouth.

[a]Last accessed 11/7/23.

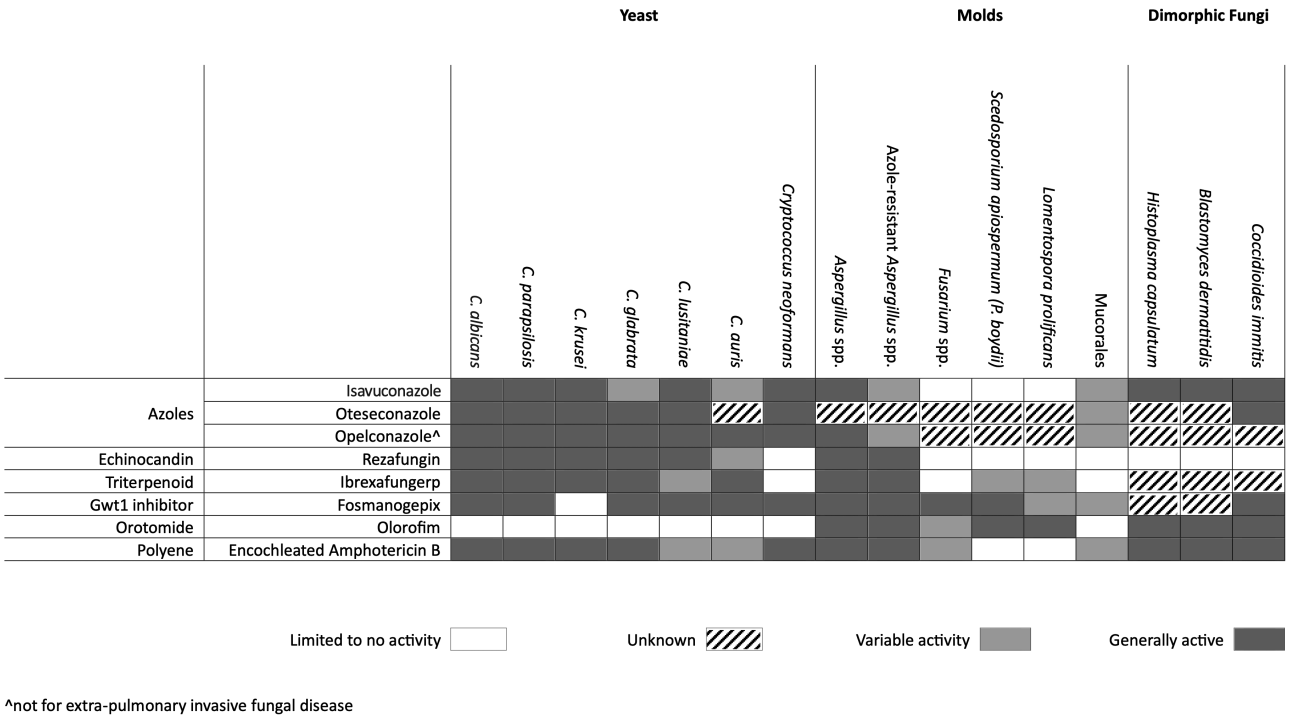

Figure 2. Spectrum of activity for novel antifungals. Antifungal agents organized by drug class and marked with activity for clinically relevant yeasts, molds, and dimorphic fungi.

of amphotericin into the cytoplasm. This mechanism of delivery results in high cellular concentrations of drug with reduced plasma concentrations relative to intravenous (IV) administration of liposomal amphotericin B and amphotericin B deoxycholate [16–18]. These pharmacokinetics result in higher concentrations of amphotericin at the site of infection with reduced toxicity risk. The excretion kinetics of eAMB are not well defined. One case series found minimal fraction of amphotericin in urine and feces [19]. The mechanism of action of eAMB is similar to other amphotericin products; it binds ergosterol in the fungal cell membrane with resultant membrane pores and fungal cell death.

Spectrum of Activity

eAMB's spectrum of activity is broad including *Candida* spp., *Aspergillus* spp., pathogens of the Mucorales order, *Cryptococcus* spp., and endemic mycoses. While not officially documented, it is likely that species with reduced intrinsic susceptibility to amphotericin products (eg, *A. terreus*, *A. nidulans*, and *A. versicolor*) will have reduced susceptibility to eAMB [20].

Approval Status

A phase I trial of eAMB for cryptococcal meningitis (NCT04031833, data not yet available) [21], a phase II trial of four subjects with hyper IgE syndrome and chronic mucocutaneous candidiasis (CMC) (NCT02629419) [22], and a phase II randomized trial comparing eAMB to fluconazole for vulvovaginal candidiasis (VVC) (NCT02971007) [23] have been completed. eAMB was associated with favorable responses in the four subjects with CMC [24] while clinical and mycological responses to eAMB in the VVC subjects were found to be not non-inferior to responses in fluconazole recipients. Notably, clinical cure rates of VVC among eAMB treated patients were substantially lower (54.5%) than fluconazole recipients (75%). The FDA granted eAMB orphan drug status on October 3, 2019, for cryptococcosis but has not yet approved eAMB for any indication.

Clinical and Pharmacokinetic Data in Children

Clinical trials to date have not included pediatric patients. Doses investigated in adults have ranged from 200 to 800 mg/day PO.

Key Drug Attributes and Potential Role in Pediatrics

eAMB is an oral polyene that results in lower plasma concentrations as compared to IV formulations, which is likely to result in reduced toxicity relative to IV polyenes, notably less renal toxicity and electrolyte wasting. Gastrointestinal disturbance (ie, nausea, diarrhea) is relatively frequent with higher once daily dosing, but this can be mitigated with smaller doses administered more frequently [16]. Furthermore, plasma levels of eAMB do not vary significantly with increasing once daily doses. While these features are advantageous in reducing toxicities, they do stimulate questions regarding potential effectiveness of this agent with specific IFD sites. This PK and

pharmacodynamic (PD) profile may be helpful to treat organisms contained in phagocytic cells or within granulomatous lesions where phagocytic cells (eg, macrophages) are enriched [16]. An experimental mouse model of cryptococcal infection suggests eAMB is effective at reducing fungal burden in the central nervous system which provides optimism for success with this agent for other focal sites of infection such as pulmonary aspergillosis [25]. However, the lower plasma levels could call into question the agent's ability to clear pathogens present outside phagocytic cells and thus it will be important to independently document efficacy of eAMB for non-focal sites of infection such as the bloodstream. Additionally, eAMB may have a role in combination therapy for multifocal infections as well as in the prevention of IFD in high-risk hosts.

FOSMANOGEPIX

Formulation/Mechanism of Action

Fosmanogepix, previously APX001A, a prodrug of the active moiety manogepix, acts as a potent inhibitor of Gwt1, an essential enzyme involved in biosynthesis of glycosylphosphatidylinositol (GPI) anchors. These anchors are integral to assembly and stability of fungal cell walls; hence, their disruption results in fungal cell death [26]. Both PO and IV formulations are being investigated. It is widely distributed into tissues and is primarily cleared by biliary excretion [26].

Spectrum of Activity

Fosmanogepix has demonstrated activity against resistant *Candida* spp. (except for *C. krusei*) [27, 28], *Coccidioides* spp. [29], *Cryptococcus* spp., molds including triazole-resistant *Aspergillus* spp. [30], and many *Fusarium* and *Scedosporium* spp [31]. Murine data suggest potential activity against some Mucorales order pathogens [32, 33].

Approval Status

The efficacy of fosmanogepix for IC is being assessed in a phase III study (NCT05421858) [34]. A phase II study (NCT04240886) [35] was opened to assess effectiveness of fosmanogepix for *Aspergillus* and other molds but was prematurely terminated to prioritize a phase III study inclusive of similar pathogens.

Clinical and Pharmacokinetic Data in Children

Clinical trials to date have not included pediatric patients. The investigational adult dose is 1000 mg IV twice daily on day 1, then 600 mg IV once daily on days 2 and 3, then 600 mg IV once daily or 700–800 mg PO once daily thereafter.

Key Drug Attributes and Potential Role in Pediatrics

Fosmanogepix has high oral bioavailability (~90%), a half-life of ~2.5 days [36], and effective tissue penetration, including brain, eyes, and intra-abdominal viscera. Animal models have demonstrated its potential efficacy at these typically challenging infection sites. It has been well tolerated with the most common side-effects reported to be headache and diarrhea [26, 36, 37]. These attributes, in combination with its broad spectrum of activity against difficult-to-treat molds such as *Fusarium* and *Scedosporium* spp., make fosmanogepix a valuable addition to the antifungal armamentarium for IFD treatment. Further research is required to elucidate its effectiveness against Mucorales order pathogens. Its role for the prevention of IFD has not been elucidated.

IBREXAFUNGERP

Formulation/Mechanism of Action

Ibrexafungerp is a semi-synthetic triterpenoid that inhibits glucan synthase, an enzyme involved in 1,3-β-D-glucan formation in fungal cell walls. This drug has a binding site similar to, but distinct from, echinocandins [38]. Ibrexafungerp is currently available as an oral formulation. A liposomal IV formulation of ibrexafungerp is in phase I of clinical development. It distributes well into all tissues except for the brain and eyes, and undergoes biliary excretion after hepatic metabolism via CYP3A4.

Spectrum of Activity

Ibrexafungerp has broad activity against *Candida* spp. (including most echinocandin-resistant strains of *Candida* spp.) [39, 40], *C. auris* [41], as well as *Aspergillus* spp. (including triazole-resistant *Aspergillus*) [42, 43].

Approval Status

Oral ibrexafungerp is approved by the FDA for the treatment of acute VVC based on two superiority phase III trials [44, 45]. Compared with fluconazole, it resulted in improved clinical outcomes and mycological eradication with sustained clearance [45]. It has also been approved for reducing the incidence of recurrent VVC in patients with a history of recurrent infections. Ibrexafungerp has been studied as oral step-down therapy from an echinocandin for the treatment of IC in phase II [46] and phase III trials (NCT05178862) [47]. Other adult phase III trials currently underway or awaiting publication include a study of *C. auris* (NCT03363841) [48] and other difficult-to-treat IFD (NCT03059992) [49]. Lastly, there is a phase II trial evaluating ibrexafungerp in combination with voriconazole for IA (NCT03672292) [50].

Clinical and Pharmacokinetic Data in Children

Current ibrexafungerp dosing is for children aged 12 years and older, but no patients aged <18 years were enrolled in the phase III clinical trials for acute VVC [51]. Per the package insert, approval was based upon studies in adult nonpregnant

females and other safety data from post-menarchal pediatric females.

Key Drug Attributes and Potential Role in Pediatrics

Oral ibrexafungerp has a bioavailability of 35%–50%; its absorption is improved with a high-fat meal. Ibrexafungerp is expected to have fewer drug–drug interactions in comparison to triazoles because it neither induces nor inhibits CYP450 enzymes [52] but it is metabolized by CYP3A4 and dosage reductions are necessary when ibrexafungerp is given in combination with potent CYP3A4 inhibitors [53]. Side-effects are minimal with gastrointestinal discomfort being most common. It is important to note that fetal harm has been demonstrated in animal studies of ibrexafungerp; therefore, the current labeling advises females of reproductive potential to use effective contraception during treatment.

Given its broad spectrum of activity and availability as an oral formulation, ibrexafungerp is an attractive oral step-down option for IC due to resistant *Candida* spp. that would have otherwise required IV echinocandin therapy. It is also a more attractive option for VVC due to resistant *Candida* spp. or for treatment in patients with contraindications to triazole therapy. Its role for the treatment of IA in combination with voriconazole will likely be defined in the near future. Ibrexafungerp may have a potential role in IFD prophylaxis; however, further studies are needed.

ISAVUCONAZOLE (ISAVUCONAZONIUM SULFATE)

Formulation/Mechanism of Action

Isavuconazonium sulfate is a prodrug rapidly converted in the bloodstream to the active compound isavuconazole. Similar to other triazoles, isavuconazole inhibits 14-α-demethylase, a fungal CYP450-dependent enzyme responsible for fungal cell membrane ergosterol synthesis [54]. It is structurally similar to voriconazole except for an additional side chain that allows greater avidity for the binding pocket in the fungal CYP51 protein [55] and expanded antifungal activity to include Mucorales order pathogens [54]. Isavuconazole also has more predictable pharmacokinetics and less inter- and intra-patient variability when compared with voriconazole as a result of the structural differences [56]. It has high oral bioavailability (98%), is extensively distributed into tissues including the brain, and is hepatically metabolized by CYP3A4/5 [57]. Isavuconazole has a much longer half life (~80–120 hr) compared with other triazoles [57].

Spectrum of Activity

Isavuconazole exhibits activity against *Candida*, *Cryptococcus*, *Aspergillus*, *Histoplasma, Blastomyces*, and *Coccidioides* spp. It also has variable activity against Mucorales order pathogens and has limited to no activity against species in the *Fusarium* and *Scedosporium* genera. Species of *C. glabrata* that are fluconazole resistant are usually also resistant to isavuconazole [54]. Isavuconazole clinical breakpoints have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for some *Aspergillus* spp. [58] but not for yeasts [59].

Approval Status

Isavuconazole is FDA and European Medicines Agency (EMA) approved for the treatment of IA and invasive mucormycosis (IM) based on results from SECURE (NCT00412893) [60] and VITAL (NCT00634049) [61] clinical trials in adults, respectively. Isavuconazole failed to meet noninferiority in comparison to caspofungin for IC in the ACTIVE trial (NCT00413218) [62], and therefore, should not be used as first-line IC therapy.

Clinical and Pharmacokinetic Data in Children

Published pediatric experiences with isavuconazole are limited to a phase I PK study, case reports, and case series. Results of the phase I trial in 45 immunocompromised children predicted >80% of children receiving IV and >76% of children receiving PO isavuconazole at doses listed in Table 1 are expected to achieve targeted adult AUC exposures (NCT03241550) [63]. The pediatric case reports of isavuconazole [64–68] utilized trough targets of 2–4 μg/mL to mirror exposures similar to adult participants in the SECURE trial [60, 69]. In younger children, higher doses (~20 mg/kg/day of isavuconazonium sulfate) may be required to achieve target isavuconazole drug exposures [67, 70]. A case series of isavuconazole-treated pediatric hematologic malignancy/HCT patients revealed favorable outcomes and tolerability [68]. A phase II trial addressing pediatric efficacy and safety of isavuconazole for treating IA or IM recently completed (NCT03816176) [71]. Although adult data suggest that routine therapeutic drug monitoring (TDM) is not necessary when standard adult doses are prescribed, until the pharmacokinetics are well defined in those aged <18 years, TDM may be advised in pediatrics to ensure target exposures are achieved [69].

Key Drug Attributes and Potential Role in Pediatrics

Isavuconazole may prove most beneficial when toxicities preclude the use of voriconazole and/or posaconazole [72–74]. Specifically, hepatobiliary, skin, and neurotoxicity appear to be less frequent with isavuconazole compared with voriconazole [60], and isavuconazole is associated with QT interval shortening rather than QT prolongation [75, 76].

Although not FDA- or EMA-labeled for prevention of IFD, there have been observational reports of isavuconazole prophylaxis in adult allo-HCT and hematologic malignancy patients [77–82]. The rate of breakthrough candidemia and IA have been reported to be ~3% [77, 78] and ~3%–5% [79–81], respectively. Experience with isavuconazole for prevention of IFD in children is limited to one small study in which breakthrough

IFD was absent in 6 children who received prophylaxis for a median of 175 days [83].

OLOROFIM

Formulation/Mechanism of Action

Olorofim, previously F901318, is a first in class agent from the class of orotomides. Olorofim is being studied as PO and IV formulations. The former is an immediate release tablet with potential for once daily dosing and an oral bioavailability of 45%–80% based on animal studies [84–86]. It inhibits the fungal cell enzyme dihydroorotate dehydrogenase (DHODH) which is necessary for synthesis of pyrimidine. Inhibition of pyrimidine limits DNA synthesis, cell wall building, and cell division [87, 88]. Olorofim distributes rapidly into tissues based on rapid clearance of the drug from plasma and high volume of distribution; it also undergoes enterohepatic recirculation during its elimination phase [89].

Spectrum of Activity

Olorofim has broad coverage against *Aspergillus* spp. and endemic mycoses. It may offer a therapeutic option for multi–drug-resistant organisms such as *Scedosporium* spp., *Lomentospora prolificans*, and *Scopulariopsis* spp. Olorofim has variable coverage for *Fusarium* spp., no activity against yeasts, including *Candida* spp. and *Cryptococcus* spp., and no activity against Mucorales order pathogens.

Approval Status

Olorofim received orphan drug designation from the FDA for the treatment of IFD secondary to pathogens with limited therapeutic options (eg, resistant-*Aspergillus*, *Coccidioides* spp., *Scedosporium* spp., and *Scopulariopsis* spp.). A phase IIb open-label trial of olorofim (NCT03583164) enrolled patients with difficult-to-treat pathogens that had in vitro susceptibility to olorofim [90]. Data from the first 100 patients enrolled in this study were submitted as part of the New Drug Application (NDA) to the FDA but the FDA requested further data and thus approval is pending. The full data set of 203 enrolled patients is planned to be submitted as part of the revised NDA to the FDA [91]. A phase III randomized trial is ongoing to compare olorofim to liposomal amphotericin B for IA (NCT05101187) [92].

Clinical and Pharmacokinetic Data in Children

Clinical trials to date have not included pediatric patients. The currently investigated dose in adults for the treatment of IFD is 150 mg PO twice daily on day 1, then 90–150 mg PO twice daily thereafter.

Key Drug Attributes and Potential Role in Pediatrics

Olorofim will likely prove advantageous for pathogens with limited therapeutic options such as resistant-*Aspergillus*, *Scedosporium* spp., and *Lomentospora prolificans*. It also will extend options for endemic mycoses and *Talaromyces marneffei*. Olorofim is unlikely to have a role in prophylaxis against IFD due to its lack of activity against *Candida* spp. In limited healthy volunteer studies, the adverse effect profile has been favorable, with dizziness being the most common adverse event [89]. There is potential for drug–drug interactions as olorofim is metabolized via several cytochrome P450 pathways and it is also a weak inhibitor of CYP3A4 [89].

OPELCONAZOLE (INHALED)

Formulation/Mechanism of Action

Opelconazole, previously PC945, is a novel long-acting triazole designed for inhalation to treat pulmonary infections. It is a potent, tightly binding inhibitor of 14-α-demethylase. The inhaled route provides delivery of high concentrations to the lungs with minimal systemic absorption, resulting in low potential for drug–drug interactions and systemic toxicities [93].

Spectrum of Activity

Opelconazole has activity against *Candida* spp. including *C. auris* and *C. krusei*, *Cryptococcus* spp., *Aspergillus* spp., and some Mucorales order pathogens [94].

Approval Status

A phase I study including healthy volunteers and individuals with mild asthma found opelconazole to be well tolerated and escalating doses did not result in increases in adverse events [93]. In individuals with asthma, no acute bronchospasm or change in lung function was observed after inhaled administration. Systemic absorption was low after inhalation, reducing risk for systemic adverse effects and drug–drug interactions. Inhaled opelconazole is currently being studied in a phase III randomized trial comparing it in combination with systemic antifungal therapy vs. systemic antifungal therapy alone in adults with refractory pulmonary IA (NCT05238116) [95]. Additionally, a phase II trial is evaluating safety and tolerability of inhaled opelconazole for prevention of IFD in lung transplant recipients (NCT05037851) [96].

Clinical and Pharmacokinetic Data in Children

Clinical trials to date have not included pediatric patients. Opleconazole is currently being studied as a twice daily inhalation in adult clinical trials.

Key Drug Attributes and Potential Role in Pediatrics

Inhaled opelconazole may be an important therapeutic option for non-angioinvasive pulmonary IA in non-neutropenic patients [97]. Pending results from the ongoing phase III trial, it may also prove beneficial in combination with systemic

antifungal agents for angioinvasive pulmonary IA. Lastly, inhaled opelconazole may become an attractive prophylaxis option for those at high risk for pulmonary IFD, such as post lung transplant or HCT.

OTESECONAZOLE

Formulation/Mechanism of Action

Oteseconazole is a novel oral azole with a tetrazole moiety (unlike previous azoles that have an imidazole or triazole moiety) that is more selective for the fungal CYP51 protein and less interactive with human CYP450, reducing potential for drug–drug interactions as well as toxicity [98, 99]. High-fat (at least 50% fat), high-calorie (800–1000 calorie) meals improve absorption of oteseconazole. It is primarily eliminated via biliary excretion and has a very long elimination half-life of ~138 days [98].

Spectrum of Activity

It is more than 40-fold more potent than fluconazole against most *Candida* spp., including fluconazole-resistant strains of *C. glabrata* and *C. krusei* [98]. It has activity against *Coccidioides* spp., *Cryptococcus* spp., and possibly *Rhizopus* spp. based on data from neutropenic mice [100].

Approval Status

Because of its activity against resistant strains of *Candida* spp. and very long half-life (~138 days) [101], oteseconazole has been extensively studied for recurrent VVC. In a phase II randomized trial comparing oteseconazole with fluconazole, 28-day acute VVC cure rates were similar and recurrence rates were reduced at 3 and 6 months [102]. Additional phase III studies (NCT03840616, NCT03562156, and NCT03561701) [103, 104] assessing oteseconazole efficacy for preventing recurrent VVC led to its FDA approval for recurrent VVC in women with a history of recurrent VVC who are not of reproductive potential due to fetal harm observed in animal studies.

Clinical and Pharmacokinetic Data in Children

Clinical trials to date have not included pediatric patients.

Key Drug Attributes and Potential Role in Pediatrics

Currently, the use of oteseconazole will likely be restricted to superficial and mucosal candidal infections, particularly if caused by azole-resistant *Candida* spp. Additionally, studies suggest improved tolerability compared with fluconazole, including less liver enzyme elevations, QTc prolongation, and drug–drug interactions [98, 103, 104]. It is important to note that fetal harm has been demonstrated in animal studies of oteseconazole, and due to its long half-life, it may still cause embryo-fetal toxicity within 2 years after administration. Women of reproductive potential should be counseled about this warning. Given that oteseconazole has demonstrated in vitro activity against some Mucorales and in vivo animal models have demonstrated a protective effect against *Rhizopus* spp., future studies may explore a role for the prevention or treatment of IM in immunocompromised hosts.

REZAFUNGIN

Formulation/Mechanism of Action

Rezafungin, previously CD101, is an IV medication from the echinocandin class that inhibits the catalytic subunit of the β-1,3-D-glucan synthase enzyme complex, preventing synthesis of a structural carbohydrate of the fungal cell wall [105]. Rezafungin is a structural analog of anidulafungin with modifications that prolong the half-life and stability for storage. Rezafungin has poor urinary penetration and is eliminated in the feces as primarily unchanged drug [106].

Spectrum of Activity

Rezafungin has activity against most *Candida* spp. including azole-resistant species and some *C. auris* [107, 108], *Aspergillus* spp. [107, 109] including azole-resistant species [110], and *Pneumocystis* spp. [111, 112] Similar to other echinocandins, minimum inhibitory concentrations for *C. parapsilosis* are higher than seen for other *Candida* spp. [113] Rezafungin has increased potency compared to caspofungin for *Candida* strains with *FKS* mutations [109]. Provisional breakpoints have been established by the Clinical and Laboratory Standards Institute (CLSI) for *Candida* spp., but may be revised, including potential to raise breakpoints for *C. glabrata* and *C. auris* [114, 115].

Approval Status

Rezafungin received FDA approval for limited indications on March 22, 2023. The approval for IC in adults with limited or no alternative treatment options was based on the ReSTORE phase III trial (NCT03667690) and supported by the STRIVE phase II trial (NCT02734862) [116, 117]. In ReSTORE, rezafungin was shown to be non-inferior to caspofungin for treatment of IC in adults [116]. Primary endpoints were day-14 global cure and 30-day all-cause mortality. The EMA received the authorization application in August 2022, which is currently under review.

Clinical and Pharmacokinetic Data in Children

Clinical efficacy trials in children have not been conducted for rezafungin to date. A phase I PK study is planned in children (NCT05534529) [118].

Key Drug Attributes and Potential Role in Pediatrics

Rezafungin is unique among echinocandins for its long half-life and activity against *Pneumocystis* spp. The long half-life allows for once weekly dosing which would facilitate outpatient administration of IV prophylaxis or treatment regimens. A phase III trial evaluating rezafungin for prevention of *Candida* spp.,

Aspergillus spp., and *P. jirovecii* in adult allogeneic HCT recipients is ongoing (NCT04368559) [119]. The toxicity profile is favorable, although infusion-related reactions, abnormal liver tests, and photosensitivity may occur [120].

CONCLUSION

The growing armamentarium of novel antifungal agents provides promise for increased therapeutic options with novel mechanisms of action and administration, favorable safety profiles, and expanded coverage of resistant pathogens. However, as these agents reach the market with adult-based approvals, significant gaps in pediatric PK and efficacy data remain. Clinical trials conducted in pediatrics are needed to better define the role of these agents.

Notes

Potential conflicts of interest. BTF's institution receives funding from Allovir, Pfizer, and Merck for research he does unrelated to fungal therapies, and he serves as Chair of a Data Safety Monitoring Board for Astellas for a pediatric study of isavuconazole. AJH, BRH, and ARH have no relevant disclosures.

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