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REVIEW

Antifungal resistance, combinations and pipeline: oh my!

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Abstract

Invasive fungal infections are a strong contributor to healthcare costs, morbidity and mortality, especially amongst hospitalized patients. Historically, *Candida* was responsible for approximately 15% of all nosocomial bloodstream infections. In the past 10 years, the epidemiology of *Candida* species has altered, with increasing prevalence of resistant species. With rising fungal resistance, especially in *Candida* spp., the demand for novel antifungal therapies has exponentially increased over the last decade. Newer antifungal agents have become an attractive option for patients needing long-term therapy for infections or those requiring antifungal prophylaxis. Despite advances in coverage of non-*Candida* pathogens with newer agents, clinical scenarios involving multidrug-resistant fungal pathogens continue to arise in practice. Combination antifungal therapy can lead to a host of side-effects, some of which can be drug limiting. Additional antifungal therapies with enhanced fungal spectrum of activity and decreased rates of adverse effects are warranted. Fosmanogepix, ibrexafungerp, olorofim and rezafungin may help fill some of these gaps in the antifungal armamentarium.

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Introduction

Invasive fungal infections are a strong contributor to healthcare costs, morbidity and mortality, especially amongst hospitalized patients. In epidemiological studies conducted in 2014, *Candida* was responsible for approximately 15% of all nosocomial bloodstream infections.[1,2] In the past 10 years, the epidemiology of *Candida* species has altered, with increasing prevalence of *Candida glabrata* in place of the historically more susceptible *Candida albicans*.[3]

Beyond *Candida*, there are also increasing incidences of *Cryptococcus* and mould species such as *Aspergillus*, *Scedosporium*, Mucorales, *Rhizopus*, *Fusarium* and others.[4] Resistant invasive fungal infections have been associated with mortality rates of up to 60%, and disproportionately affect already vulnerable or immunosuppressed patients.[3]

Currently approved antifungal therapies are limited to only four therapeutic classes and are plagued by toxicities and resistance that limit use in some populations. As the concerns for resistant fungal infections grow, clinicians should be familiar with the current and upcoming antifungal therapies to best manage their patients. The purpose of this review is to discuss resistance mechanisms and challenges with currently available agents, provide evidence for combination therapy, and evaluate the newly available and upcoming antifungal agents and their proposed place in the treatment of challenging fungal infections. We have chosen to focus this review on three of the four prominently used classes as use of flucytosine is clinically limited to selected infections (predominantly combination therapy for cryptococcal meningitis).

Methods

A systematic literature search of the PubMed, Google Scholar and ClinicalTrials.gov databases was performed with the search terms "antifungal", "novel antifungals", "resistance", "amphotericin", "flucytosine", "echinocandin", "azole" and "combination therapy". References of relevant articles were reviewed and added as appropriate. English-language clinical trials, meta-analyses, randomized clinical trials, reviews or systematic reviews evaluating antifungal therapy, combinations or antifungal resistance were reviewed. Relevant articles were included in the appropriate sections below.

Review

Mechanisms of resistance to currently available antifungals

From a clinical perspective, understanding mechanisms of antifungal resistance has often proved challenging due to the biological diversity represented amongst the medically important fungi. Broadly speaking, the differing metabolic capacity, cellular machinery and reproduction cycles of various yeasts, moulds and dimorphic fungi make general trends regarding antifungal activity difficult to discern. This is further compounded by the significant amount of genetic diversity exhibited even within a given genus such as *Candida*. Haploid organisms, such as *C. glabrata*, can acquire resistance easily by simple genetic duplications, deletions or other chromosomal modifications. This contrasts with the development of resistance in diploid organisms like *C. albicans*, which requires genetic modifications in both chromosome pairs for antifungal resistance to become readily apparent. Molecular studies continue to define the differences amongst organisms, ultimately culminating in a taxonomic reclassification (Table 1) of many medically important fungi.[5] These cases of relative genetic dis-similarity amongst *Candida* species provide context to the differing susceptibility patterns amongst various organisms previously classified based on morphological relationships.

Fungi broadly express some mechanisms of resistance that would be relatively familiar to those with an awareness of general mechanisms of bacterial resistance. These mechanisms can be largely classified as (1) target-site modification, either through overexpression or changes to the drug target itself; (2) upregulation of drug transporters (largely analogous to efflux pump upregulation); (3) cellular changes induced by stress response to antifungal therapy; (4) restricted access to the target site via biofilm production or increased chitin synthesis; and (5) non-target effects related to mRNA processing and loss of mitochondrial DNA in certain species. Similarly to bacteria, fungi may also express one or more of these resistance factors at a given time, affecting the extent and degree of antifungal resistance. Several mechanisms are implicated in the development of resistance to multiple antifungal agents and may also result in cross-resistance.

Table 1. Taxonomic reclassification of medically important fungi.

Previous name	Current name
Candida glabrata	*Nakaseomyces glabrata*
Candida guillermondii	*Meyerozyma guilliermondii*
Candida krusei	*Pichia kudriavzevii*
Rhizopus microsporus var *chinensis* var *oligosporus* var *rhizopodiformis*	*Rhizopus microsporus* (varieties no longer recognized)
Rhizopus oryzae	*Rhizopus arrhizus*
Rhizomucor variabilis	*Mucor irregularis*

Data taken from ref.[5]

Azole antifungals

The azole antifungal class is widely used clinically, ranging across pathogens and infectious syndromes depending on the agent selected. The primary mechanism for azole antifungals is the enzyme lanosterol 14α-demethylase, which is responsible for synthesizing ergosterol, a component of the fungal cell membrane.

Efflux pumps

Before azole-enzyme complex binding, efflux pumps can effectively reduce intracellular azole concentrations.[6] The two primary drug efflux pumps responsible for azole resistance are the ATP-binding cassette (ABC) and major facilitator superfamily (MFS) systems. Regulation of these efflux pumps is dependent on a variety of transcriptional and transacting factors, several of which contain drug-responsive elements that allow for efflux pump induction in the presence of certain drugs, including azoles.[7] Upregulation of these drug transporters is one of the most common mechanisms of azole resistance in yeasts, particularly *Candida* species. Although these systems can also be found in *Aspergillus* species, they less commonly contribute to resistance in these organisms.[8]

Varying numbers of ABC transporters have been identified in multiple *Candida*, *Cryptococcus* and *Aspergillus* species.[9–11] CDR1 and CDR2 are the primary ABC trans-

porters responsible for azole resistance in *C. albicans*.[6] CgCDR1, CgCDR2 and CgSNQ2 have been associated with azole resistance in *C. glabrata*, whilst Afr1 plays a similar role in *C. neoformans*.[12] Beyond CDR1B (formerly AfuMDR1), specific ABC transporters involved in azole resistance amongst *Aspergillus* species remain largely unknown at present.[13] Several MFS transporters have been identified in genomic studies of *Candida* species, though only MDR1 has been demonstrated to increase azole efflux when overexpressed in *C. albicans* and *C. dubliniensis*.[14] Upregulation of the MFS transporter AfuMDR3 in *Aspergillus* species has been identified in itraconazole-resistant isolates.[15]

Target-site modification

Resistance to azole antifungals can occur through a variety of modifications to the lanosterol 14α-demethylase encoding genes, particularly *ERG11* in yeasts and *CYP51* in moulds. Modifications to or near the enzyme's haeme moiety can block azole binding, whilst overexpression of ERG11 or CYP51 can reduce azole susceptibility by increasing target abundance and thereby requiring larger amounts of drug for inhibition.[16,17] ERG11 overexpression in *C. albicans* can result from atypical chromosome formation, via isochromosomes or duplication, as well as activating mutations in the transcription factors regulating ergosterol biosynthesis.[18–21] Overexpression of ERG11 has also been identified in azole-resistant isolates of *C. glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei*.[22–26] In contrast to overexpression of ERG11, loss-of-function mutations in the *ERG3* gene can also reduce azole susceptibility. The loss of function in *ERG3* and the subsequently reduced synthesis of precursor sterols used as substrates by ERG11 modify the sterol membrane content and allow the cell to grow in the presence of azole antifungals.[27] Whilst this rarely results in high-level azole resistance, this modification to ERG3 can also provide cross-resistance to polyene antifungals by depletion of target ergosterol.[28] At present, these changes have not been observed in *Aspergillus* species.[8]

Mutations in the lanosterol 14α-demethylase encoding genes or promoters of CYP51 are the most common mechanisms of azole resistance in *Aspergillus* species.[29,30] Widespread agricultural use of azole antifungals is believed to have propagated this mechanism in a variety of isolates.[31] Over 30 mutations have been identified in *CYP51A* (one of two CYP51 isoforms) alone, with the position and nature of the mutations influencing cross-resistance between various azoles.[32–34] All known mutations confer resistance to at least itraconazole, with various mutations imparting various degrees of resistance to voriconazole, posaconazole and isavuconazole.[35–41] Overexpression of CYP51A and CYP51B with subsequent reductions in azole susceptibility have also been observed in *Aspergillus* species.[42,43]

Cellular changes induced by stress response, biofilm formation and indirect-target effects

Cellular stress response and signalling allow fungal cells to survive membrane-related stress associated with exposure to azole antifungals.[8] One of the primary mechanisms associated with this response is heat shock protein 90 (Hsp90), a highly conserved, global regulatory protein involved in cellular signalling.[44] Mutations in Hsp90 or its upstream regulators can impact ergosterol biosynthesis, reduce matrix glucan levels and modulate biofilm resistance.[8,45–47] Compromise of Hsp90 has been specifically shown to reduce *Candida* species tolerance to azoles[48] and regulate azole resistance within biofilms.[49]

Biofilm formation is one of the key resistance mechanisms found in fungi, particularly *Candida* species.[50] The formation of dense carbohydrate, protein and nucleic acid networks combines with β-1,3-glucan in the cell wall to facilitate binding to a variety of surfaces and limit penetration of azoles into fungal cells. Biofilms produced by *Candida* species are particularly problematic as sequestration of azoles in the biofilm matrix and induction of efflux pumps can lead to high levels of azole resistance. Formation of biofilms amongst *Aspergillus* species is less well studied but has also been observed to contribute to azole resistance.[51]

A variety of non-specific mutations can modify or complement mechanisms of resistance, including efflux pumps and non-promoter-based transcriptional regulation. Azole resistance in *C. glabrata* can result from mitochondrial mutants, whereby partial or complete loss of mitochondrial DNA results in the formation of 'petite' mutants.[52] Upregulation of transcriptional activators and their associated genes, such as *cgPDR1* in *C. glabrata*, produces intrinsic resistance to azole antifungals in these petite mutants.[53] Conflicting data indicate that these mutants may or may not be avirulent.[53–55] Modifications in mRNA stability have also been implicated in azole resistance. Hyperadenylation of the polyA tail in mRNA encoding efflux pump CDR1 has been identified in an azole-resistant isolate of *C. albicans*. This post-transcriptional regulation with hyperadenylation extended CDR1 mRNA half-life by three times that observed in azole-susceptible isolates.[56,57] Similar to direct, promoter-based upregulation of CDR1, enhanced mRNA stability and half-life can contribute to increased levels of efflux pump and azole resistance.

Polyenes

Despite being in clinical use since the 1950s, resistance to polyene antifungals, specifically amphotericin B, is

relatively rare.[57] Severe fitness trade-offs have been associated with acquired amphotericin B resistance, whilst its unique mechanism of action targeting ergosterol, a major protein in the fungal cell membrane, may also contribute to low rates of resistance development.[57,58] Nevertheless, amphotericin B resistance has been reported in *Candida* spp., with the most common mechanism involving modifications to the ergosterol biosynthesis pathway.[59,60]

Intrinsic and acquired amphotericin B resistance varies by species as well as broadly between pathogenic yeasts and moulds. Resistance to amphotericin B in *C. albicans* isolates is rare,[61–64] though loss-of-function mutations in *ERG11* and *ERG3* or *ERG5* can result in substitution of ergosterol for alternative and precursor sterols into the fungal cell membrane.[57,60,65] Similar substitution effects have also been observed with *C. glabrata* and *Candida lusitaniae*, though resulting from *ERG6* and *ERG2* mutations.[66,67] Whilst *C. glabrata* resistance to amphotericin B is uncommon,[61,68–70] *C. lusitaniae* susceptibility rates are variably reported.[71–74] However, the development of amphotericin B resistance in *C. lusitaniae* isolates whilst on treatment has been documented.[75] Of increasing concern for amphotericin B resistance are *Candida auris* and the *Candida haemulonii* complex (*C. haemulonii*, *C. haemulonii* var *vulnera* and *Candida duobushaemulonii*). Currently, mechanisms of polyene resistance in *C. auris* remain poorly understood, though mutations in *ERG6* and subsequent membrane sterol substitutions have been reported.[76] Multiple ergosterol biosynthesis modifications resulting from mutations in *ERG2*, *ERG3*, *ERG6* and *ERG11* have been identified in the *C. haemulonii* complex.[77] Amphotericin B resistance has also been reported in cryptococcal species, though this rarely exceeds 6% of isolates in surveillance studies.[78–81] Inactivating mutations in *ERG2* have been described in *Cryptococcus neoformans* but non-ergosterol biosynthesis-related mechanisms are thought to exist.[82]

Attenuation of polyene-induced oxidative stress is thought to be an important component of amphotericin B resistance, particularly in moulds such as *Aspergillus terreus*.[83,84] When comparing intrinsically resistant organisms such as *A. terreus* with amphotericin B-susceptible *Aspergillus fumigatus*, catalase levels are significantly elevated.[85] Increased production of this enzyme is thought to help inactivate the reactive oxygen species produced on polyene exposure, thereby minimizing any antifungal activity.[86] Mutations in cellular messengers, such as Hsp70 and Hsp90, may also play a role in facilitating the emergence and/or maintenance of amphotericin B resistance, though their role remains poorly defined at present.[87–89]

Structural changes in the fungal cell wall outside of sterol composition are also believed to contribute to amphotericin B resistance. Increased concentrations of cell wall protein 1,3-α-glucan conferred resistance to amphotericin B in an *Aspergillus flavus* isolate,[90] whilst increased 1,3-β-glucan concentrations yielded a similar result in a *C. tropicalis* isolate.[91] Whilst the increased glucan synthesis may represent the result of upregulation due to amphotericin B exposure, it has also been hypothesized that these enlarged cell walls served to inhibit the interaction between amphotericin B and sterols in the fungal membrane.[90]

Echinocandins

Target-site modification

Echinocandins are currently the primary agent recommended for the treatment of invasive candidiasis because of their reliable activity and improved efficacy and tolerability compared with other treatments.[92] They also play an important role in the prophylaxis and treatment of infections caused by *Aspergillus* spp. Whilst echinocandin resistance is rare, echinocandin non-susceptibility has been documented and its incidence is increasing, most notably in *C. glabrata*.[93,94]

Echinocandins bind reversibly to the FKS subunits of the enzyme 1,3-β-D-glucan synthase, thereby preventing synthesis of β-D-glucan cell wall components and weakening the cell wall structure.[95,96] The FKS subunits are encoded by similarly named genes: *FKS1*, *FKS2* and *FKS3*.[97] The primary form of developed echinocandin resistance in *Candida* species comes from point mutations that occur in these regions, with the majority occurring in FKS1. Additionally, the intrinsic reduced susceptibility of *C. parapsilosis* is also thought to be a naturally occurring substitution in this region.[98] The effects of mutations in the FKS genes on echinocandin minimum inhibitory concentrations (MICs) of *C. glabrata* and subsequent echinocandin treatment outcomes are well documented.[99] Whilst rarer, similar changes have been identified in *C. albicans*,[100,101] and the emerging pathogen *C. auris* has already shown evidence of these mutations.[99–102] The specific mutations vary but notable mutations include S663, S629 and P659 in *C. glabrata*, S645F, S645P and S645Y in *C. albicans*, and S652 or S639F in *C. auris*.[102,103] Echinocandin resistance through FKS gene mutations has been identified in *A. fumigatus* isolates but the prevalence appears low. The primary mechanism for detection of FKS mutations remains susceptibility testing. However, this detection method is limited because individual mutations do not lead to predictable changes in measured MIC, suggesting compensatory mutations.[97] Because a relatively small number of mutations are present in a large share of resistant organisms, rapid diagnostics may be useful in the identification of potentially resistant organisms.[104]

Cellular changes

Candida and *Aspergillus* species may also develop reduced echinocandin susceptibility through a stress-triggered response leading to increased chitin production. Hsp90 appears to play a significant role in mediating this increase via calcineurin. Hsp90 is believed to be one of the key factors in the observed 'paradoxical effect' or 'eagle effect', which describes the increased growth at increasingly high echinocandin concentrations.[105] Hsp90 or other members of this calcineurin pathway may be future targets of antifungal or combination treatments. Singh et al. showed that loss of function of Hsp90 led to decreased calcineurin activation, which led to echinocandin susceptibility.[106] Additionally, Lamoth et al. showed that exposure to the calcineurin inhibitor geldanamycin improved fungicidal activity of caspofungin against echinocandin-resistant *A. fumigatus*.[107] Other stress-induced responses have been investigated, including changes in lipid composition.[108]

Biofilm formation

Both *Candida* spp. and *A. fumigatus* have been shown to produce and persist in biofilms, reducing the susceptibility of echinocandins. The exact mechanism of this remains unclear but components include extracellular matrix creation, efflux activity, altered metabolic activity and oxygen gradients. One driver of *A. fumigatus* biofilm adhesion (*alaA*) has been identified and its deletion improved echinocandin susceptibility in a murine treatment model.[109,110]

Response to resistant infections

Current evidence and guidelines recommend susceptibility testing results should be used to guide decisions regarding treatment selection for *Candida* infections.[92] Whilst not as readily available, susceptibility testing may also be used to guide therapy for other fungal infections. Although limited, there are some data that suggest that *in vitro* susceptibility testing translates to clinical activity or lack thereof.[111,112] This may be particularly important in areas known to have high levels of resistance.[113] Currently, no specific therapeutic approach is universally recommended for infections with reduced susceptibility to antifungal agents. Repeated susceptibility testing may help identify patients in whom antifungal susceptibility has diminished during treatment. Re-evaluation of immunosuppression needs may also be appropriate for patients failing to respond to treatment.

Overview of antifungal combination therapies: difficulties and challenges

Although there have been many theoretical or *in vitro*-proposed mechanisms for antifungal synergy and enhanced antifungal activity in combination with other antifungals or alternative agents, clinical uptake of combination therapy for antifungal infections has been slow. One concern with combining antifungal agents is that indifference or even antagonism has been demonstrated in several combination evaluations.[114–117] For example, against several *Candida* species in *in vitro* assays, amphotericin B was demonstrated to be antagonistic in combination with azole antifungals, including miconazole, clotrimazole, ketoconazole, itraconazole and fluconazole.[114] In animal models, amphotericin was found to be antagonistic or indifferent in combination with itraconazole, posaconazole and fluconazole.[114] Caspofungin and fluconazole also demonstrated antagonism in an *in vitro* evaluation of the effect against *C. albicans* biofilms.[114] Amongst FDA-approved antifungal agents, synergy was only demonstrated *in vitro* between amphotericin and flucytosine for *C. albicans*; terbinafine and the azole antifungals for *C. albicans* and *C. glabrata*; and terbinafine and amphotericin for *C. albicans*. Against *C. albicans* biofilms, caspofungin and amphotericin were found to be additive *in vitro* but not synergistic. Given these concerns for indifference or antagonism that derived from *in vitro* and animal models and the challenges of additive toxicity, antifungal monotherapy is still primarily chosen for many clinically relevant fungal infections.

Beyond the well-known and widely accepted antifungal combination therapy of amphotericin and flucytosine for cryptococcal infections[116,118,119], limited evidence is available to support combination antifungal therapy with currently available agents.

Candida species

One study evaluated combination therapy of fluconazole and amphotericin for invasive candidiasis and infective endocarditis in murine and rabbit models.[120] In the neutropenic mouse model, survival was significantly prolonged with both amphotericin monotherapy and amphotericin–fluconazole combination therapy. In an invasive endocarditis rabbit model, fungal burden in cardiac vegetations were significantly decreased with both amphotericin monotherapy and combination therapy. No antagonism was noted but the combination was not found to be additive or synergistic in these models.

In a study of 85 patients living with HIV, investigators evaluated the efficacy of fluconazole monotherapy, itraconazole plus flucytosine, or placebo in the treatment of oesophageal candidiasis.[121] Clinical cure was experienced by 75.8% and 72.4% in the fluconazole and itraconazole-flucytosine combination therapy groups, respectively, and both were significantly better than the placebo group ($p<0.001$). Adverse effects were compa-

rable between groups, with no statistically significant difference from placebo. One limitation of this study is the choice of combination agents, as it is difficult to determine whether the combination of fluconazole and flucytosine may have provided different results than itraconazole and flucytosine. Although the combination of itraconazole and flucytosine was as effective as fluconazole monotherapy, clinicians should be aware of the challenges of multiple agents and possible additive toxicities in the context of limited additional benefits over monotherapy.

Aspergillus species

In an *in vitro* analysis, activities of posaconazole and caspofungin were evaluated alone and in combination against four *A. fumigatus* isolates with varying posaconazole MICs.[121] Isolates included one wild-type strain, one posaconazole-susceptible/caspofungin resistant strain and two posaconazole-resistant strains. Although combination therapy did not improve the activity for the two posaconazole-susceptible strains, synergistic activity was demonstrated in the posaconazole-resistant strains.[122] In another *in vivo* efficacy analysis comparing voriconazole monotherapy, anidulafungin monotherapy and combination therapy for invasive aspergillosis, combinations were found to be synergistic in voriconazole-susceptible isolates and additive in resistant isolates.[123] Based on these data, it may be reasonable to use a combination of an azole plus an echinocandin for infections caused by azole-resistant *Aspergillus* species.[124]

In another *in vitro* evaluation, ibrexafungerp (SCY-078) was tested in combination with amphotericin, voriconazole and isavuconazole against four wild-type strains of *A. fumigatus* and two azole-resistant strains.[125] In these checkerboard tests, combinations of ibrexafungerp plus voriconazole or isavuconazole were synergistic for the wild-type tested strains (4/4 and 4/4 tested wild-type strains susceptible, respectively). The combination of ibrexafungerp plus amphotericin was also found to be synergistic in wild-type strains (4/4), with synergy also demonstrated in one of two azole-resistant strains tested. Given these results and the relatively new FDA approval of this agent, the combination of ibrexafungerp plus amphotericin shows promise and should be investigated further in cases of azole-resistant invasive *Aspergillus*.

In addition to the *in vitro* evaluations, a number of clinical studies that have evaluated the utility of combination therapy for invasive aspergillosis in adult haematology patients have been reviewed by Candoni et al.[126] Many of these combinations were used for salvage therapy.[126] The majority of studies included in this review are retrospective, but three smaller prospective studies (patient number ranging from 30 to 454) were also included. Mortality rates ranged from 0% to 91%, and combinations of an echinocandin and liposomal amphotericin B had the best survival rates when used as first-line therapy (100% survival, *n*=30 patients).[127] Despite this, the current Infectious Diseases Society of America aspergillosis guidelines (2016) recommend monotherapy with a triazole as preferred first-line therapy.[128]

Mucorales

Mucorales, even more than the other presented fungal pathogens, boasts high mortality rates, limited treatment options and complicated clinical courses.[129] Because of these factors, combination therapy against Mucorales, including several common *Mucor* species and *Rhizopus* species, has been studied a fair amount because the advent of the newest triazole antifungals. These data are described in detail elsewhere.[126,129–131] Despite a relatively larger amount of data for Mucorales, there is still not a universally accepted combination for these difficult-to-treat infections, though the guidelines from the European Confederation of Medical Mycology provide helpful insight.[132]

Pipeline agents

With rising fungal resistance, especially *Candida* spp., the demand for novel antifungal therapies has exponentially increased over the last decade.[133] Despite advances in coverage of non-*Candida* pathogens with newer azole agents, clinical scenarios involving multidrug-resistant fungal pathogens continue to arise in practice, and data for combination therapy has been limited outside cryptococcal disease.[134,135]

Below, new antifungal agents will be further explored. Specifically, focus will be placed on pharmacokinetics and pharmacodynamics (PK/PD) and relevant data from clinical trials that have either been completed or are in the process of being completed. A brief summation of all agents can be found in Table 2. Of note, opelconazole and oteseconazole are not discussed in detail below, and we direct the reader to the following articles for further information on these agents.[136–141]

Fosmanogepix

Mechanism and spectrum

Fosmanogepix (APX001) is a prodrug with a novel mechanism that is rapidly converted to the active moiety manogepix.[137] Once converted, manogepix targets the enzyme Gwt1, which is a protein involved in the catalysation of inositol acylation and ultimately trafficking and anchoring of mannoproteins. Blockade of the Gwt1 leads to an interruption in the synthesis of glycosylphosphatidylinositol-anchored mannoproteins, which causes dis-

Table 2. Comparison of new and upcoming antifungal agents.

	Fosmanogepix	Ibrexafungerp	Olorofim	Rezafungin
Mechanism of action	Disruptions to cell wall via interruption in synthesis of mannoproteins	Inhibition of biosynthesis of β-(1,3)-D-glucan through a binding site unique from the other echinocandins	Inhibition of cell wall synthesis via inhibition of uridine-50-monophosphate and uridine-50-triphosphate	Inhibition of β-(1,3)-D-glucan
Spectrum of activity	Yeasts and moulds, including those with resistance to echinocandins and azoles	*Candida*, *Aspergillus*, *Pneumocystis*	Moulds and dimorphic fungi	*Candida*, some *Aspergillus* species
Penetration sites	Excellent tissue penetration, including brain tissue and eyes	Excellent tissue penetration outside the central nervous system and eyes	Excellent tissue penetration, including brain tissue	Excellent tissue penetration outside the central nervous system, eyes, urine
Common dosing	1000 mg twice × 1 day, then 600 or 700 mg daily IV or orally	300 mg twice daily orally	150 mg twice daily × 1 day followed by 90 mg twice daily IV and orally	400 mg × 1, then 200 mg weekly IV
Renally adjusted	No	No	Unknown, currently being studied	No
Adverse effects	Headache	Gastrointestinal, headache	Infusion-related, dizziness, gastrointestinal	Pyrexia, hypokalaemia
FDA approval indication and date	NA	Vulvovaginal candidiasis; 2021	NA	Candidaemia and invasive candidiasis; 2023

IV, intravenously; NA, not available.

ruptions in the integrity of the cell wall. Additionally, mannoproteins are necessary for both adhesion to host cells as well as evasion of the host immune response, and disruption of mannoprotein maturation and localization has numerous downstream physiological effects.[142]

Activity of fosmanogepix encompasses many fungal pathogens, including both yeasts and moulds. Specifically, fosmanogepix has shown *in vitro* activity against *Candida* spp. (including *C. auris*), *Cryptococcus neoformans*, *Coccidioides* spp., *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp. and other moulds. Furthermore, fosmanogepix retains *in vitro* activity against isolates of *C. albicans*, *C. auris* and *C. glabrata* that are resistant to both azoles and echinocandins and against azole-resistant *A. fumigatus*.[137,142] However, fosmanogepix has poor *in vitro* activity against *C. krusei* and some of the Mucorales, including *Mucor* and some *Rhizopus* spp.[137,142]

Early trials

Multiple studies have evaluated the PK/PD of fosmanogepix in animal models. In 2017, Mansbach et al. evaluated the PK/PD of a single oral or intravenous dose of fosmanogepix in both rat and monkey models.[143] Results from this study demonstrated the excellent tissue penetration of fosmanogepix, including to lung, brain and eyes in both animal models regardless of the route of administration. In 2020, Alkhazraji et al. evaluated the *in vivo* activity of fosmanogepix in immunosuppressed murine models with haematogeneously disseminated fusariosis and pulmonary scedosporiosis.[144] For scedosporiosis, treatment of mice with 78 mg/kg and 104 mg/kg of body weight fosmanogepix, along with 1-aminobenzotriazole significantly increased median survival time *versus* placebo from 7 days to 13 and 11 days, respectively. For fusariosis, 78 mg/kg and 104 mg/kg fosmanogepix plus 1-aminobenzotriazole enhanced median survival time from 7 days to 12 and 10 days, respectively. Reductions in kidney and brain conidial burden were also seen with both scedosporiosis and fusariosis models, especially with higher dosing. The authors concluded that these results mirror those seen with high-dose liposomal amphotericin B (10–15 mg/kg).[144] Additional animal studies (mainly murine) have tested, either *in vitro*, *in vivo* or

both, fosmanogepix against disseminated *C. auris*,[145], neutropenic disseminated candidiasis (including *C. auris*),[146] cryptococcal meningitis,[147] and invasive pulmonary aspergillosis caused by *A. fumigatus*,[148] with positive results in terms of survival and clearance of pathogen.

Numerous phase I studies have been completed evaluating the PK/PD data in human participants for fosmanogepix, along with the safety and tolerability profile of the medication.[149,150] In 2017, Hodges et al. evaluated the safety, tolerability and PK of both a single dose and multiple doses of fosmanogepix.[149] Results from this study indicated that fosmanogepix has linear PK/PD up to oral doses of 1000 mg, oral bioavailability >90% and, after 14 days of dosing at 500 and 1000 mg, AUC_{0-24} values of 192 and 325 µg/mL, respectively. Additionally, absorption was not affected under fed conditions and was well tolerated across all doses. Another study by Hodges et al. in 2017 evaluated single ascending dose and multiple ascending dose-escalation strategies of fosmanogepix.[150] Here, the authors demonstrated that doses as high as 600 mg a day for 14 days were well tolerated and led to no dose-limiting toxicities, although the maximum dose was never determined. In 2018, a phase Ib PK trial in patients with acute myeloid leukaemia was performed, but the results are not currently available (clinicaltrials.gov: NCT03333005). In 2022, a phase I clinical trial was initiated to determine how fosmanogepix is processed in people with varying degrees of liver dysfunction. Results for this study are also pending with an estimated completion date of December 2023 (NCT05582187). Additional phase I studies have also been performed to date (NCT04166669, NCT04804059).

Phase II and III trials

Phase II and III trials for fosmanogepix, though limited, are listed in Table 3. In 2020, Pappas et al. evaluated safety and efficacy of fosmanogepix for first-line treatment of candidaemia in a multicentre, open-label, single-arm phase II trial.[151] Patients were included if they had positive blood culture for *Candida* spp. within 96 hours before study entry, with ≤2 days of prior antifungal treatment. At end of study treatment, 80% (16/20) of patients met the primary outcome of treatment success. Additionally, 30-day survival was 85% (17/20), and there were no serious adverse effects reported. Another multicentre study (APEX Trial), which is currently unpublished, evaluated the efficacy and safety of fosmanogepix for infections caused by *C. auris* (ClinicalTrials.gov; NCT04148287). Nine adult patients were included in the study, and all patients received fosmanogepix for up to 42 days. At end of study treatment, 89% (8/9) of patients met the primary outcome of treatment success. Additionally, 30-day all-cause mortality was low (2/9; 22%), but serious adverse effects reported were higher than seen in the trial from Pappas et al. The AEGIS trial was terminated early in anticipation of a phase III trial, but the trial start date has yet to be announced (NCT04240886).

Place in therapy

These results indicate that fosmanogepix is promising in patients with candidaemia. Although a small patient population, these results suggest fosmanogepix may be a treatment option in patients with *C. auris* infections. Additionally, fosmanogepix demonstrates broad *in vitro* and *in vivo* mould coverage. Although not discussed in detail, multiple case reports have demonstrated positive clinical results with combination therapy of fosmanogepix plus either an azole and/or liposomal amphotericin B.[152,153] Further studies comparing fosmanogepix to standard of care in these infections are needed.

Ibrexafungerp

Ibrexafungerp is a triterpenoid that shares many similarities to echinocandins but has enhanced PK/PD properties, allowing for oral administration. The mechanism of action of ibrexafungerp resembles that of echinocandins (inhibits biosynthesis of β-(1,3)-D-glucan within the fungal cell wall, leading to increased cell permeability and ultimately cell lysis), but the binding site for ibrexafungerp is novel, limiting cross-resistance seen between ibrexafungerp and echinocandins.[137,154,155] With limited cross-resistance, ibrexafungerp offers a potential agent with retained activity to *Candida* spp. that is resistant to echinocandins. Furthermore, ibrexafungerp demonstrates *in vitro* and/or *in vivo* activity against *C. auris*, azole-resistant *Candida* spp., *FKS*-producing yeast, *Aspergillus* spp. and the ascus form of *Pneumocystis* spp.[154]

Early trials/PK/PD

In 2017, Borroto-Esoda et al. tested ibrexafungerp against two azole-resistant *A. fumigatus* isolates.[156] Mice receiving orally administered ibrexafungerp 15 mg/kg or 20 mg/kg followed by BID maintenance doses of 7.5 or 10 mg/kg, respectively, were compared with mice receiving caspofungin and amphotericin B daily by intraperitoneal injection at doses of 5 mg/kg and 10 mg/kg, respectively. Ibrexafungerp significantly increased mean survival in all strains ($p \leq 0.003$). Moreover, fungal kidney burden was significantly reduced ($p < 0.05$), and all doses were well tolerated. Collective data indicate that ibrexafungerp has excellent tissue penetration outside the central nervous system and lens of eyes with both intravenous and oral administration.[157–159]

Numerous phase I human trials have taken place evaluating the efficacy, safety and PK/PD of ibrexafungerp (SCY-078-101 through SCY-078-109).[159] Ibrexafungerp is primarily eliminated in the faeces, has a half-life of ~20 hours, is >99% plasma protein bound, is well absorbed orally without regard for food, is well tolerated with a

Table 3. Fosmanogepix phase II and III clinical trials.

Trial name/NCT number	Phase	Population	Intervention	Primary outcome	Primary result	Other demographics/ results
NCT05421858	III	Adults with proven candidaemia and/or invasive candidaemia	Fosmanogepix IV with option to switch to PO *vs* Caspofungin with option to switch to PO fluconazole	Response to treatment up to 42 days and proportion of patients alive	Pending	Randomized trial with estimated 450 participants 2:1 ratio of fosmanogepix *vs* comparator
NCT03604705	II	Adults with proven candidaemia who were non-neutropenic	1000 mg IV BID on day 1, 600 mg IV QD for at least days 2 and 3, followed by either 600 mg IV QD or 700 mg PO QD for 14 days total	Clearance of *Candida* from blood cultures with no additional antifungal treatment and survival at EOST	16/20 (80%) patients in mITT meet primary outcome	Average time to first negative blood culture was 2.4 days All-cause mortality was 5/21 (23%) Serious AE in 9/21 (42%)
NCT04148287 (APEX Trial)	II	Adults with candidaemia and/or invasive candidiasis caused by *Candida auris*	1000 mg IV BID on day 1, 600 mg IV QD for at least days 2 and 3, followed by either 600 mg IV QD or 800 mg PO QD for up to 42 days total	Percentage of participants with treatment success at EOST	8/9 (89%) patients in mITT meet primary outcome	Average time to first negative blood culture was 6 days All-cause mortality was 2/9 (22%) Serious AE in 2/9 (22%)
NCT04240886 (AEGIS Trial)	II	Adults with invasive mould infections caused by *Aspergillus* spp. or rare moulds	Fosmanogepic IV or PO	All-cause mortality at day 42	Terminated	*Scedosporium* spp., *Fusarium* spp., *Mucor* spp. and *Rhizopus* spp. included Non-randomized, multicentre trial with 21 participants enrolled

AE, adverse events; BID, twice daily; EOST, end of study treatment; IV, intravenously; mITT, modified intent-to-treat; PO, by mouth; QD, once daily.

maximally tolerated single dose of 1600 mg, and is a substrate for both CYP3A4 and P-glycoprotein (P-gp). Ibrexafungerp is a substrate of 3A4 and P-gp but, to date, no dose reductions of potentially interacting medications have been warranted (ClinicalTrials.gov NCT04092725, NCT04092751).[157,158] In 2020, Scynexis Inc. submitted their ibrexafungerp New Drug Application for the treatment of vulvovaginal candidiasis in women (VVC).[158]

Phase II and III trials

Ten phase II and III trials evaluating ibrexafungerp are completed or ongoing (Table 4). In VANISH 303 and VAN-

Table 4. Ibrexafungerp phase II and III clinical trials.

Trial name/ NCT number	Phase	Population	Intervention	Primary outcome	Primary result	Other demographics/ results
NCT03363841 (CARES Trial)	III	Adult patients with infections caused by *Candida auris*	Single-arm IBX up to 90 days	Global success at EOT	Pending	42 and 84 days survival Percentage of patients with AE 30 participants
NCT04029116 (CANDLE Trial)	III	Adults with recurrent VVC	3 days of fluconazole followed by IBX or placebo given BID q4 weeks for six total dosing days	Clinical success at week 24	Submitted February 8th, 2023	Week 24 and 36 recurrence Discontinuation due to AEs 440 participants
NCT03059992 (FURI Trial)	III	Adults with fungal disease that is refractory to SOC or SOC is not tolerated	Single-arm IBX up to 180 days	Global response at day 180	Pending	Day 42 and 84 survival Recurrence up to 42 days post IBX treatment 200 participants
NCT03987620 (VANISH 306 Trial)	III	≥12 years of age with acute VVC	300 mg IBX BID for 1 day *vs* placebo	Clinical cure at TOC (mITT)	63% IBX (n=188) *vs* 44% placebo (n=84) p=0.007	Mycological eradication at TOC in mITT: 59% IBX (n=188) *vs* 29% placebo (n=84) p=0.022 All-cause mortality: 0% IBX (n=298) *vs* 0% placebo (n=151) 455 participants
NCT03734991 (VANISH 303 Trial)	III	≥12 years of age with acute VVC	300 mg IBX BID for 1 day *vs* placebo	Clinical cure at TOC (mITT)	51% IBX (n=188) *vs* 29% placebo (n=98) p=0.001	Mycological eradication at TOC in mITT: 50% IBX (n=188) *vs* 19% placebo (n=98) p<0.001 All-cause mortality: 0% IBX (n=247) *vs* 0% placebo (n=124) 376 participants
NCT05178862 (MARIO Trial)	III	Adults with invasive candidiasis	Echinocandin followed by either PO fluconazole or IBX	30-day all-cause mortality	Pending	14 days global response 220 participants

(*Continued*)

Table 4. (Continued)

NCT03672292 (SCYNERGIA Trial)	II	Adults with invasive pulmonary aspergillosis	Voriconazole plus IBX 500 mg BID days 1–2 then 500 mg daily *vs* voriconazole alone	AE, DC or death at study completion (~19 weeks)	Pending	Days 42 and 84 survival Days 42 and 84 global response 60 participants
NCT03253094 (DOVE Trial)	II	Adults with acute VVC	Fluconazole 150 mg day 1 IBX 750 mg day 1 IBX 300 mg BID day 1 IBX 450 mg BID day 1 IBX 150 mg BID days 1–3 IBX 300 mg BID days 1–3	Clinical cure at TOC (mITT)	58% fluconazole 150 mg (*n*=24) 35% IBX 750 mg (*n*=26) 52% IBX 300 mg BID (*n*=27) 62% IBX 450 mg BID (*n*=21) 48% IBX 150 mg BID (*n*=29) 58% IBX 300 mg BID (*n*=26)	All-cause mortality was 0% in all treatment groups Serious AEs were not reported in any of the treatment groups 186 participants
NCT02679456	II	Adults with VVC	PO fluconazole IBX dosing regimen 1 IBX dosing regimen 2	Therapeutic cure at TOC	None posted	4-month recurrence 96 participants
NCT02244606	II	Adults with invasive candidiasis	All participants received IV echinocandin initially then switched to PO fluconazole 400 mg per day or micafungin 100 mg per day PO IBX 1000 mg day 1 followed by 500 mg per day Po IBX 1,250 mg day 1 followed by 750 mg per day	Safety and tolerability and IBX dose that achieves target drug exposure	Submitted February 8th, 2023	2 and 6 week relapse after EOT 27 participants

AE, adverse effects; BID, twice daily; DC, discontinuation; EOT, end of treatment; IBX, ibrexafungerp; mITT, modified intention-to-treat; PO, oral; q, every; SOC, standard of care; TOC, test-of-cure; VVC, vulvovaginal candidiasis.

ISH 306 ibrexafungerp was compared with placebo in a 2:1 fashion for the treatment of acute VVC in over 500 patients.[160,161] Baseline demographics were similar in both trials, and the predominant pathogen seen with VVC was *C. albicans*. The primary outcome for each study was clinical cure at test-of-cure (TOC) clinic visit on day 11–14. Clinical cure was defined as the complete resolution of signs and symptoms of vulvovaginal infection without need for further antifungal treatment along with a vulvovaginal signs and symptoms score (VSS) of zero at TOC visit. In the VANISH 303 trial, 51% of patients met the primary outcome *versus* 63% in the VANISH 306.[160,161] Both results were considered statistically significant when compared with placebo. Patients in both trials also had statistically significant higher percentages of mycological eradication and complete resolution of signs and symptoms at TOC when compared with placebo. Together, these results demonstrated the superiority of ibrexafungerp *versus* placebo for the treatment of acute VVC.

In 2021, Nyirjesy et al. compared ibrexafungerp with oral fluconazole in a randomized trial (DOVE) for the treatment of VVC in adults at least 18 years of age.[162] Although five dosing strategies of ibrexafungerp were compared with fluconazole, doses higher than 300 mg twice daily did not respond to increases in efficacy and were excluded from primary results. To qualify for inclusion, patients had to have a VSS of at least 7, which was higher than the baseline of four in the VANISH 303 and 306 trials.[160,161] Other baseline characteristics were similar between the dosing groups. The primary endpoint was the percentage of patients with a clinical cure (complete resolution of signs and symptoms; VSS, 0) at TOC. Clinical cure (ibrexafungerp 51.9% *versus* fluconazole 58.3%) and mycological eradication (ibrexafungerp 63.0% *versus* fluconazole 62.5%) rates at TOC were similar. Additionally, no serious adverse effects or deaths were reported with the use of ibrexafungerp for any treatment group, including those who received higher doses of ibrexafungerp. The authors concluded that ibrexafungerp is a novel antifungal with comparable efficacy to fluconazole in the treatment of moderate-to-severe VVC. Additional trials are also under way evaluating the role of ibrexafungerp in patients with infections involving *C. auris* (CARES), recurrent VVC (CANDLE), refractory fungal disease (FURI), invasive candidiasis (MARIO) and invasive pulmonary aspergillosis (SCYNERGIA), but full data are not available for these trials to date (ClinicalTrials.gov: NCT05178862; NCT03672292).[163–165]

Place in therapy

Ibrexafungerp was approved by the FDA for VVC in adults and postmenarchal paediatric patients in 2021.[155] To date, ibrexafungerp usage is restricted to VVC; however, its utility could be expanded in the future as results from multiple trials that are pending. Unfortunately, PK/PD do not support ibrexafungerp usage for infections involving the central nervous system, which could limit its usage in clinical practice. Nonetheless, invasive candidiasis involving *C. auris* remains a focal point of discussion, and ibrexafungerp may have utility in fungaemia involving *C. auris* in the future.

Olorofim

Olorofim (formerly F901318), an orotomide, is a novel class antifungal. Olorofim is a reversible inhibitor of dihydroorotate dehydrogenase (DHODH), an oxidoreductase that catalyses the fourth step in the de novo synthesis of pyrimidine, which results in inhibition of the formation of uridine-50-monophosphate and uridine-50-triphosphate, which are key for cell wall synthesis. Through this mechanism, cell lysis occurs.[166] Olorofim PKs have been assessed in healthy volunteers. Bioavailability is high, ranging up to 82%, and it has high protein binding (>99%) and a large volume of distribution, including plasma, lungs, kidneys and the central nervous system.[167] Unlike previously mentioned antifungals, olorofim lacks appreciable activity against yeasts.[167] Similarly, activity against Mucorales is not present.[168] Olorofim does have a spectrum of activity against various other moulds and dimorphic fungi. Olorofim displays high *in vitro* activity against *A. fumigatus* isolates (n=332), with MICs ranging from 0.008 to 0.125 mg/L, and was not impacted by the presence of resistance to other antifungals, including either azoles or amphotericin B.[169] Against 160 other invasive moulds, including *Microascus*/*Scopulariopsis*, *Rasamsonia*, *Penicillium* and *Talaromyces* species, olorofim activity was observed, again, irrespective of resistance to other antifungals.[170]

Phase II and III trials

Two olorofim studies are actively recruiting (ClinicalTrials.gov: NCT03583164; NCT05101187). An open-label, single-arm, phase II study (FORMULA-OLS) plans to assess olorofim for adult patients with invasive fungal infections caused by *Lomentospora prolificans*, *Scedosporium* spp., *Aspergillus* spp. and other resistant fungi with limited treatment options (NCT03583164). Patients included in this study will receive olorofim 30 mg tablets, with dosage adjustments based upon plasma concentrations, up to doses of 300 mg. The primary outcome for this study is overall response comprised of clinical, mycological and radiological response at day 42. The OASIS study, a phase III adjudicator-blinded, randomized trial, will assess the efficacy and safety of olorofim *versus* liposomal amphotericin B followed by standard of care in patients with invasive aspergillosis (NCT05101187). Patients will receive either olorofim 150 mg twice daily followed by 90 mg twice daily or liposomal amphotericin B 3 mg/kg daily followed by standard of care according

to guidelines. The primary outcome of this study is all-cause mortality. Secondary outcomes include adjudicated assessed outcomes and safety assessments.

Place in therapy

Olorofim has a potential place in therapy for invasive mould infections, particularly where resistance to currently approved agents is present. However, more data are needed, particularly from phase III studies.

Rezafungin

Rezafungin (formerly CD101) is a new-generation echinocandin that invokes its fungicidal activity via inhibiting cell wall synthesis, specifically 1,3-β-D-glucan.[171] Whilst it is structurally similar to anidulafungin, a modified choline anima ether replaces the hemiaminal region, ultimately increasing solubility and stability.[171] Similar to other echinocandins, rezafungin displays activity against *Candida spp*. In an *in vitro* susceptibility study of nearly 2000 *Candida* isolates, rezafungin inhibited 99.8% of *C. albicans*, 95.7% of *C. glabrata*, 97.4% of *C. tropicalis*, 100% of *C. krusei* and 100% of *C. dubliniensis* isolates.[172] Interestingly, rezafungin displayed the most potent activity against 19 strains of *C. auris*, with MICs ranging from 0.03 to 0.25 mg/L when compared with the other echinocandins.[173] However, limited activity is exhibited against *Cryptococcus* spp., with MIC_{50}/MIC_{90} values of >2/>4 mg/L.[174] Additionally, rezafungin activity was assessed against 186 *A. fumigatus* and 28 *Aspergillus* section *flavi* isolates.[174] Rezafungin inhibited all *A. fumigatus* isolates at an MEC_{90} value of 0.06 mg/L and *Aspergillus* section *flavi* isolates at an MEC_{90} value of 0.03 mg/L, which was comparable to other echinocandins. Low potential for resistance development was observed against rezafungin in *Candida* spp.[175]

Phase II and III trials

Rezafungin has undergone two phase II clinical trials.[176,177] In the first trial, 99 patients with VVC were included to assess both efficacy and safety.[176] Patients were randomized into three groups: rezafungin vaginal gel (3%), rezafungin vaginal ointment (6%) and oral fluconazole (150 mg). Clinical cure rates at day 7 were 37%, 40% and 47.45%, respectively. There were no differences in therapeutic cures when stratified by recurrent VVC or baseline severity. Most treatment-emergent adverse events were mild or moderate and unrelated to study drugs, and no serious events were reported in any group. The STRIVE trial, a phase II randomized, double-blind study, assessed rezafungin *versus* caspofungin for invasive candidiasis.[177] Included patients were randomized in a 1:1:1 ratio to receive rezafungin IV once weekly for 2–4 weeks at either 400 mg or 400 mg on week 1 followed by 200 mg on subsequent weeks, or caspofungin once daily (70 mg loading dose followed by 50 mg daily with an optional oral stepdown available after day 3). The primary efficacy outcome was overall response (with overall cure defined as resolution of clinical signs of candidaemia/invasive candidiasis plus mycological eradication) at day 14 (±1 day). Secondarily, overall, mycological and investigator-assessed clinical response at day 5 were compared. A total of 207 patients were randomized: 81 to rezafungin 400 mg, 57 to rezafungin 400 mg once, followed by 200 mg on subsequent weeks, and 69 to caspofungin daily. The majority of patients were White men with a mean age of ~60 years. Candidaemia accounted for nearly 80% of the diagnoses. The most common pathogen isolated was *C. albicans* (49.7%) followed by *C. glabrata* (20.2%). In the three groups, overall cure was observed in 60.5%, 76.1% and 67.2%, respectively. Drug-related serious adverse events were reported in 1.2%, 1.9% and 2.9% of patients.

In the ReSTORE trial, rezafungin was compared with caspofungin for the treatment of invasive candidiasis and candidaemia.[178] This multicentre, double-blind, double-dummy, phase III trial randomized patients in a 1:1 ratio to receive either intravenous rezafungin once a week (400 mg in week 1, followed by 200 mg weekly, for a total of two to four doses) or intravenous caspofungin (70 mg loading dose on day 1, followed by 50 mg) daily for no more than 4 weeks. A total of 199 participants were randomized: 100 to treatment with rezafungin and 99 to treatment with caspofungin. Most patients were White males ~60 years old diagnosed with candidaemia only. The most common pathogen identified was *C. albicans*, and susceptibility to both drugs was >99%. The FDA primary outcome of 30-day all-cause mortality occurred in 24% of rezafungin-treated patients compared with 21% of caspofungin-treated patients. Cure at day 14 was observed in 59% of rezafungin-treated patients and 61% of caspofungin-treated patients, respectively. The most common treatment-emergent adverse events were pyrexia (14%) and hypokalaemia (13%). Serious adverse events occurred in 56% and 53% of patients overall, and these were deemed to be related to the study drug in two patients *versus* three patients in the rezafungin and caspofungin groups, respectively.

A phase III clinical trial (NCT04368559) assessing the safety and efficacy of rezafungin compared with standard regimens to prevent invasive fungal disease in patients undergoing allogeneic blood and marrow transplant (ReSPECT) is currently recruiting. This multicentre, randomized, double-blind study has an anticipated enrolment of 462 patients. Patients in the rezafungin group will receive 400 mg loading dose in week 1, followed by 200 mg once weekly, for a total of 13 weeks. The comparator group will receive either fluconazole, posaconazole or trimethoprim/sulfamethoxazole. The primary outcome is non-inferior fungal-free survival at 90 days.

Place in therapy

Rezafungin was approved by the FDA for candidaemia and invasive candidiasis in adults in 2023.[179] In patients with access difficulties to healthcare facilities, people who inject drugs or those with a history of catheter-associated bloodstream infections, rezafungin could be an alternative therapy to avoid intravenous catheters.

Conclusion

With rising fungal resistance, especially in *Candida* spp., the demand for novel antifungal therapies has exponentially increased over the last decade. Newer antifungal agents have become an attractive option for patients needing long-term therapy for infections or those requiring antifungal prophylaxis. Despite advances in coverage of non-*Candida* pathogens with newer agents, clinical scenarios involving multidrug-resistant fungal pathogens continue to arise in practice. Combination antifungal therapy can theoretically lead to a host of side-effects, some of which can be drug-limiting. Additional antifungal therapies with enhanced fungal spectrum of activity and decreased rates of adverse effects are warranted. Fosmanogepix, ibrexafungerp, olorofim and rezafungin may help fill some of these gaps in the antifungal armamentarium.

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