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REVIEW ARTICLE

Pharmacokinetics and Pharmacodynamics of Ibrexafungerp

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Abstract
On 2 June, 2021, the US Food and Drug Administration approved ibrexafungerp (formerly MK-3118 and SCY-078) for the treatment of vulvovaginal candidiasis, also known as vaginal yeast infection. Ibrexafungerp is the first drug approved in a novel antifungal class in more than two decades, and the Food and Drug Administration's decision was based on positive results from two pivotal phase III studies in which oral ibrexafungerp proved both safe and effective in patients with vulvovaginal candidiasis. The decision was also based on substantial preclinical and clinical work in both the pharmacokinetics and pharmacodynamics of ibrexafungerp. This paper reviews that research and looks ahead to explore how this novel antifungal agent may be used in the future to address the expanding problem of drug-resistant mycotic infections.

Key Points

Ibrexafungerp is the first drug approved in a novel antifungal class in more than 20 years.

Ibrexafungerp is now approved for the treatment of vulvovaginal candidiasis.

Ibrexafungerp has activity against a variety of multidrug-resistant fungi, including *Candida auris*.

Ibrexafungerp is under investigation for a variety of invasive conditions, including fungemia, to be used alone or in combination with other antimicrobial agents.

1 Introduction

The rapid emergence of drug-resistant fungal pathogens poses an expanding threat to public health. Treatment strategies are limited and new drugs are urgently needed. Ibrexafungerp (originally known as MK-3118) is a semi-synthetic, orally bioavailable antifungal derivative of the echinocandin enfumafungin [1, 2]. Echinocandins are fungicidal against yeast and fungistatic against molds and serve as first-line agents for treating many severe invasive mycotic infections [3–5]. This class of drugs alters the integrity of the fungal cell wall via the inhibition of the synthesis of (1→3)-β-D-glucan [6, 7]. However, US Food and Drug Administration (FDA)-approved echinocandins are only available in intravenous formulations, which limits their use in the treatment of less severe fungal infections, such as vulovaginal candidiasis, or as step-down agents [8].

Ibrexafungerp is a first-in-class triterpenoid antifungal agent that is available in an oral formulation. Similar to echinocandins, ibrexafungerp inhibits (1→3)-β-D-glucan synthase, a key component of the fungal cell wall, and has both in vitro and in vivo activity against a variety of clinically relevant fungal species, including the yeast *Candida* and the mold *Aspergillus* [9, 10]. However, the full spectrum of activity of ibrexafungerp is not yet known, especially against invasive mold infections such as mucormycosis, scedosporiosis, and fusariosis.

Although there are a number of novel antifungal agents in development, ibrexafungerp received attention in the early stages of clinical development because the drug is in a distinct class of antifungal agents and retains in vitro activity

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against both echinocandin-resistant and triazole-resistant strains of pathogenic fungi, making it an attractive agent to address the escalating problem of drug-resistant invasive fungal infections [11–13].

2 Pharmacokinetics and Pharmacodynamics

2.1 Preclinical Studies

Pfaller and colleagues evaluated the activity of ibrexafungerp against more than 100 clinical isolates of *Candida* spp., including *C. albicans*, *C. glabrata*, and *C. kruseii*, using CLSI and EUCAST broth microdilution methods. Ibrexafungerp was active against all species tested in vitro and demonstrated similar efficacy to caspofungin, a widely used antifungal drug [14]. Importantly, the drug also showed efficacy against strains of *Candida* that were inherently resistant to echinocandins and triazoles. The difference between caspofungin and ibrexafungerp was most pronounced in strains of *Candida* harboring *FKS1* and *FKS2* mutations.

Lepak et al. subsequently performed an initial pharmacodynamic evaluation of ibrexafungerp in a neutropenic murine model of invasive candidiasis [15]. Mean free area under the concentration–time curve (AUC)/minimum inhibitory concentration (MIC) values associated with a 1-log kill endpoint against *Candida albicans*, *Candida glabrata*, and *Candida parapsilosis* were not statistically different between species but were lower than those observed for echinocandins.

Building on this work, Wring and colleagues performed single-dose pharmacokinetic studies in rats, mice, and dogs to characterize bioavailability and potential dosing regimens [16]. The drug was well absorbed across species, demonstrating good oral bioavailability in mice (> 51%), rats (45%), and dogs (35%). Ibrexafungerp also revealed a low level of clearance in rodents representing approximately 10–15% of hepatic blood flow; estimates for the terminal elimination-phase half-life ranged from 5.5 to 8.7 h in rodents to ~ 9.3 h in dogs, suggesting once-daily dosing would be appropriate in humans.

Murine studies compared dose-dependent steady-state exposure in plasma and kidney tissue after twice-daily treatment for 1 week. These models that use the reduction in the fungal tissue burden of an intervention vs an untreated control as a measure of antifungal efficacy in vivo. The mean plasma ibrexafungerp steady-state AUC from 0 to 24 h required for efficacy in mice was 15.4 ± 2.21 μM·h (11.2 ± 1.61 μg/mL·h), and the corresponding total drug AUC/MIC ratio was 373 ± 54. Ibrexafungerp exposure in kidney tissue exceeded plasma by more than 20-fold for the AUC from 0 h to infinity and maximum concentration. The free AUC/MIC found in blood was actually lower than for echinocandins, possibly because of higher kidney/plasma exposures.

An in vivo pharmacodynamic evaluation with ibrexafungerp in a neutropenic murine model of invasive candidiasis has also been performed against *C. albicans*, *C. parapsilosis*, and *C. glabrata* [15]. Oral doses of 3.125–200 mg/kg of ibrexafungerp produced peak concentrations of 0.04–2.66 μg/mL, AUC from 0 to 24 h of 0.61–41.10 μg·h/mL, and AUC from 0 h to infinity values of 0.68–40.31 μg·h/mL. The pharmacodynamic index AUC/MIC was explored by using total AUC and free AUC drug concentrations; maximum responses were 4.0, 4.0, and 4.3 log10 colony-forming units/kidney reductions for *C. albicans, C. glabrata,* and *C. parapsilosis*. Taken together, these findings suggested that the drug would be suitable for trials in humans.

2.2 Phase I Trials

A single-center, open-label phase I study of healthy subjects was performed to assess the drug–drug interaction potential between ibrexafungerp and the immunomodulator tacrolimus, which is commonly used in renal transplant recipients, and may predispose patients to invasive fungal infection [17]. An important finding was that co-administration of tacrolimus and ibrexafungerp had no effect on the maximum blood concentrations of tacrolimus. There was also no change in the maximum concentration of tacrolimus in plasma and a 1.4-fold increase in total AUC, suggesting that a dose adjustment for tacrolimus may not be warranted when combined with ibrexafungerp.

Another phase I, open-label, crossover study of ibrexafungerp was performed to evaluate the pharmacokinetic parameters of rosiglitazone, a sensitive substrate of cytochrome P450 2C8 metabolism [18–20]. Subjects were randomized to a single oral rosiglitazone 4-mg dose alone on day 1 or a SCY-078 1250-mg loading dose on day 1 followed by a once-daily SCY-078 750-mg dose for an additional 7 days with co-administration of a single oral rosiglitazone 4-mg dose on day 3, before alternating following a ≥ 10-day washout. This study had an important finding: maximum concentration values for rosiglitazone and its metabolite, *N*-desmethylrosiglitazone, were unaffected by co-administration with ibrexafungerp, suggesting a low risk for interaction of ibrexafungerp with drugs metabolized via the cytochrome P450 family of enzymes. Given these encouraging findings, ibrexafungerp advanced to phase II studies.

2.3 Phase II Trials

A multicenter, open-label phase II study of patients with documented invasive candidiasis randomized subjects to receive step-down therapy in one of three treatment arms:

two dosing regimens of oral ibrexafungerp or standard of care following initial echinocandin therapy [21]. Twenty-seven subjects enrolled: seven people received ibrexafungerp 500 mg, seven received ibrexafungerp 750 mg, and eight received the standard of care following echinocandin therapy.

Satisfactory response rates were reported among all groups: 86% ($n = 6$) in the ibrexafungerp 750-mg arm vs 71% ($n = 5$) in both ibrexafungerp 500-mg and standard of care treatment arms. All treatment regimens were well tolerated. A population pharmacokinetic analysis revealed that the ibrexafungerp 750-mg regimen leads to target exposure in approximately 85% of the population, suggesting that this dosage would be appropriate for further investigation.

Building on this work, a phase II, randomized, double-blind, dose-finding study was done to compare ibrexafungerp to fluconazole in women with vulvovaginal candidiasis [22]. The clinical cure (52 vs 58%) and mycological eradication (63 vs 63%) rates were similar for both drugs. Importantly, 1 month after diagnosis, clinical cure rates (70 vs 50%) were higher for the ibrexafungerp group than the fluconazole group, setting the stage for pivotal phase III studies, which are reviewed below.

2.4 Phase III Trials

The FDA approved ibrexafungerp after two successful randomized, double-blind, placebo-controlled, phase clinical trials, VANISH 303 and VANISH 306 [23, 24]. In VANISH 303, clinical cure, mycological eradication, and clinical improvement at day 25 were 51 vs 29%, 50 vs 19%, and 64 vs 37% in the ibrexafungerp group compared with placebo [11, 25]. In VANISH 306, 188 patients with acute vulvovaginal candidiasis were randomized to receive ibrexafungerp or placebo in a 2:1 ratio [9]. The primary endpoint of the trial was clinical cure rate, defined as the complete resolution of all signs and symptoms at the test-of-cure visit on day 10. Clinical cure, mycological eradication, and clinical improvement were 63 vs 44%, 59 vs 30%, and 72 vs 55% in the ibrexafungerp group compared with placebo [26]. The FDA approval occurred 2 months after these results were reported.

3 Future Directions

The widespread use of immunosuppressants and immunomodulators in clinical practice has expanded the population of patients with immune impairment who are susceptible to invasive fungal infections [27, 28]. For the past two decades, there have only been three major classes of antifungal agents (polyenes, triazoles, and echinocandins) and their use has been diminished by the emergence of drug-resistant fungal species [29–31]. Better treatment options are urgently needed.

Ibrexafungerp is an orally bioavailable, first-in-class, structurally novel, triterpene antifungal with potent in vitro and in vivo activity against a variety of clinically relevant fungal pathogens including both yeasts and molds [17, 21, 32, 33]. The drug was recently approved for the treatment of vulvovaginal candidiasis and recent work suggests the agent may be useful to treat other mycotic diseases, including multidrug-resistant infections, endemic mycoses, and emerging fungal pathogens [34]. A unique property of this drug is its solubility at lower pH, which facilitates penetration into acidic environments, creating opportunities for novel treatment approaches [11, 34, 35]. An intravenous formulation is also in development.

Ibrexafungerp may also be useful in the treatment of organisms that have acquired resistance to existing fungal agents. *Candida auris* is an emerging pathogen that was discovered in Japan in 2008 and has rapidly spread around the world, and it has been described in the popular press as a fungal "superbug" because it may demonstrate resistance to all three major classes of antifungal agents [36, 37]. The in vitro activity and in vivo efficacy of ibrexafungerp against *C. auris* was recently tested by broth microdilution against more than 50 *C. auris* isolates [38]. Neutropenic mice were intravenously infected with this organism, and a 1-week treatment course was initiated with ibrexafungerp, caspofungin, or fluconazole. Pathogen burden was evaluated by renal colony counts on day 8 and on day 21. Throughout the study, ibrexafungerp demonstrated consistent activity with MICs between 0.25 and 2 μg/mL against all isolates of *C. auris*. Crucially, a survival difference was noted in mice treated with the elevated doses of ibrexafungerp as compared with other drugs.

The key finding in this study is that ibrexafungerp is effective in vivo against *C. auris* even when appropriate therapy is not initiated promptly. This matters because the diagnosis of human fungal pathogens is sometimes delayed owing to limitations in molecular diagnostics [27, 39]. Although preclinical comparison studies are limited, this study serves as a proof of principle that ibrexafungerp may be a useful treatment option in clinical practice for an emerging fungal pathogen that is often resistant to existing treatment options, although further studies in humans are needed [40].

Additional phase III studies of ibrexafungerp are ongoing. A multicenter, randomized, double-blind phase III study (NCT04029116) is currently underway to investigate the efficacy of ibrexafungerp in women with recurrent vulvovaginal candidiasis [11]. Another phase III, open-label, single-arm study (NCT03059992) is investigating the efficacy of ibrexafungerp in patients with invasive candidiasis and aspergillosis as well as endemic mycoses such as blastomycosis, coccidioidomycosis, and histoplasmosis [11].

Some drug-resistant fungi, such as aspergillosis, may require combination therapy. There may also be a role for ibrexafungerp in combination with other antifungal agents. Petraitis and colleagues investigated the in vitro activity and in vivo efficacy of ibrexafungerp in combination with isavuconazole against invasive pulmonary aspergillosis [41]. The combination of ibrexafungerp and isavuconazole in in vitro studies resulted in additive and synergistic interactions against *Aspergillus* spp., decreased pulmonary injury, reduced mycotic burden, lower GMI and (1→3)-β-D-glucan levels, and prolonged survival in comparison to antifungal monotherapy [42]. Other combinations may prove similarly effective [31, 43].

The oral bioavailability of ibrexafungerp presents yet another avenue for its potential use in clinical practice as a stepdown agent. Many patients with invasive fungal infections are treated with intravenous agents while hospitalized and may be transitioned to an oral agent upon discharge [44, 45]. Future studies will undoubtedly explore ibrexafungerp as an oral option for patients who have been partially treated for an invasive fungal infection with an intravenous agent and no longer require hospitalization. The remarkable bioavailability of the drug may give clinicians newfound flexibility.

In the future, ibrexafungerp may be used to treat a variety of fungal infections, including those attributed to resistant organisms, and it may be use alone or in combination with other drugs to treat a variety of invasive fungal pathogens [12, 46]. We do not yet know the full potential of this novel antifungal agent, but FDA approval in June 2021 serves as an important milestone. A new class of antifungal agents has finally arrived.

Declarations

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Conflict of interest Dr. McCarthy has nothing to declare and reports no conflicts of interests associated with this article.

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