



REVIEW

Advances in anti-fungal therapies

Grant Waterer

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Abstract Anti-fungal therapies remain sub-optimal, and resistant pathogens are increasing. New therapies are desperately needed, especially options that are less toxic than most of the currently available selection. In this review, I will discuss anti-fungal therapies that are in at least phase I human trials. These include VT-1161 and VT-1598, modified azoles with a tetrazole metal-binding group; the echinocandin rezafugin; the novel β -1,3-d-glucan synthase inhibitor ibrexafungerp; fosmanogepix, a novel anti-fungal targeting Gwt1; the arylamidine T-2307; the dihydroorotate inhibitor olorofim; and the cyclic hexapeptide ASP2397. The available data including spectrum of activity, toxicity and stage of clinical development will be discussed for each of these so clinicians are aware of promising anti-fungal agents with a strong likelihood of clinical availability in the next 5–7 years.

Keywords Anti-fungal · Phase II · Phase III · Development

Introduction

COVID-19 has exposed our paltry supply of effective anti-viral therapies. However, the truth is that anti-infectives generally have vastly increased in the past two decades, and this is equally and perhaps especially true of anti-fungal therapies.

Existing anti-fungal agents have a variety of limitations, from toxicity to rising levels of resistance in common fungal pathogens, significant drug interactions and sub-optimal efficacy. The rising proportion of the community in western countries with induced immune deficiencies from immunomodulatory therapies and their expanding indications is gradually increasing the burden of fungal disease. Equally, unlike anti-bacterial therapies which have exceptionally good response rates in sensitive pathogens, anti-fungal therapies are not as efficacious, probably due to a mixture of poor host immunity, innate fungal properties and dosing limitations due to toxicity. There is no question that new anti-fungal agents would be welcomed by clinicians and patients routinely dealing with these infections.

In this review, I will focus on promising anti-fungal therapies with at least phase I human data in the public domain (clinicaltrials.gov, PubMed and web search). While there are many agents not yet at this stage of development, their time frame for clinical use (if successful) is unlikely to be within the next decade.

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G. Waterer (✉)
University of Western Australia, Royal Perth Hospital,
Level 3 Executive Corridor, Wellington St, Perth 6000,
Australia
e-mail: grant.waterer@uwa.edu.au

VT-1161 and VT-1598

These two related compounds (and a third so far less advanced VT-1129) from the same company are modifications of the azoles with replacement of the triazole metal-binding group with a tetrazole and other structural changes to reduce the affinity for mammalian CYP 450 enzymes but maintain activity against fungal Cyp51 [1]. These changes are hoped will lead to less toxicity and less drug interactions.

VT-1161 has in vitro activity against *C. glabrata* and *C. krusei* isolates resistant to azoles and echinocandins [2], *Trichophyton spp.* [3], *Coccidioides immitis* and *Coccidioides posadasii* [4]. VT-1161 appears to have superior in vitro activity to VT-1120 for *Candida* and in interleukin-17 deficient mice was highly effective against fluconazole-susceptible and fluconazole-resistant oropharyngeal candidiasis [5]. Against *C. posadasii* in a murine model, VT-1161 had at least equivalent efficacy to fluconazole [4], and prophylactic administration was more effective than posaconazole in preventing *Rhizopus arrhizus* infection in neutropenic mice [6]. In an open-label study of naturally occurring coccidioidomycosis in dogs, VT-1161 was well tolerated and an apparent 83% successful response to therapy [7]. Other evidence of excellent anti-fungal activity of VT-1161 includes dermatophytosis in a guinea pig model [8].

In a phase II study of VT-1161 in recurrent vulvovaginal candidiasis, 215 women were randomized to one of five regimes i) 150 mg once daily for 7 days followed by 150 mg once weekly for 11 weeks; ii) 300 mg once daily for 7 days followed by 300 mg once weekly for 11 weeks; iii) 150 mg once daily for 7 days followed by 150 mg once weekly for 23 weeks; iv) 300 mg once daily for 7 days followed by 300 mg once weekly for 23 weeks; v) a matching placebo regime. On an intention to treat basis all VT-1161 arms substantially reduced the number of candidiasis episodes compared to placebo (0–7% vs 52%). No safety concerns arose during the trial with no effect on liver function observed. The basis for undertaking the phase II study was earlier work showing efficacy of VT-1161 in a murine model of vaginal candidiasis [9]. A second phase 2 study in vulvovaginal candidiasis compared 300 mg once daily for 3 days, 600 mg once daily for 3 days, 600 mg twice daily for 3 days or a single dose of 150 mg of fluconazole. No significant differences were observed

between the VT-1161 and fluconazole treated groups, nor were there significant differences in response rates between the VT-1161 groups. A trend to higher recurrence rates at 3 and 6 months was observed in the fluconazole arm (0% at 3 and 6 months for VT-1161 groups vs 28.5% and 46.1% for fluconazole) [10]. Two identical phase 3 studies (as required by the Federal Drug Administration for registration) of VT-1161 in recurrent vaginal candidiasis are currently listed as active on clinicaltrials.gov (NCT03562156 and NCT03561701) with estimated study completion dates in mid-2021.

In a similarly designed phase II study of VT-1161 in onychomycosis patients were randomized to 300 mg daily for 2 weeks followed by once weekly 300 mg dose for either 10 or 22 weeks or 600 mg daily for 2 weeks followed by 600 mg once weekly for 10 or 22 weeks or a matching placebo arm. Cure rates ranged from 32%–42% in the active arms compared to 0% in placebo. Again no significant adverse side effects were observed [11].

VT-1598 has been less well studied but also has activity against fluconazole-susceptible and fluconazole-resistant *C. albicans* [12], a variety of *Candida* and *Cryptococcus spp.*, *Aspergillus spp.* and *Rhizopus arrhizus* [13]. VT-1598 also appears to have good efficacy in murine models of central nervous system coccidioidomycosis [14], cryptococcal meningitis [15] and invasive aspergillosis [16]. A phase I study of VT-1598 (NCT04208321) is currently listed to complete in mid-2021.

Although VT-1161 and VT-1598 show promise, some caution needs to be stated in that mutations of Erg3 have been described in *C. albicans* which confer resistance to both agents [17]. Similarly, the common mechanisms for azole resistance in *C. glabrata*, mutations within the zinc cluster transcription factor Pdr1 [18], can reduce susceptibility to both VT-1161 and VT-1598 [19]. Given the wide-spread problems that have arisen with azole-resistant *C. glabrata* [20], it is likely that resistance will rapidly become a problem with this pathogen.

Rezafungin (CD101)

Rezafungin is an echinocandin, targeting β 1,3-D-glucan like caspofungin, micafungin and anidulafungin. The modifications incorporated into rezafungin

were designed to give it a longer half-life and therefore potentially less frequent administration than daily dosing required with other echinocandins [21]. Pharmacokinetic studies in mice, rats, dogs, monkeys and chimpanzees confirmed that may be suitable for weekly administration. Indeed, in the chimpanzees, the $t_{1/2}$ was 81 h compared to 30 h for anidulafungin [22].

Against a variety of fungal isolates in the SENTRY 2015 surveillance program rezafungin had equivalent efficacy to other echinocandins tested [23]. Similarly, rezafungin had equivalent efficacy to anidulafungin against a selection of Canadian clinical *Candida* spp. isolates, with both having potency against fluconazole-resistant isolates [24]. However, rezafungin did not maintain activity against a small number of anidulafungin-resistant isolates (5 *C. glabrata* and 2 *C. tropicalis*) [24]. The value of rezafungin is therefore in its longer half-life rather than increased spectrum of activity over existing echinocandins.

In a phase I study in 6 subjects, CD101 was tolerated at up to 400 mg as a weekly dose for 3 weeks. The $t_{1/2}$ was estimated at greater than 81 h in the 400 mg and 200 mg doses with minimal urinary clearance and no change observed in renal, hepatic or hematological blood tests [25].

In a randomized, head to head trial with a single dose of 150 mg of oral fluconazole, topical CD101 6% ointment (one dose) or 3% gel (daily dose for 2 days) was studied in 126 women with vulvovaginal candidiasis. While both preparations of topical CD101 were well tolerated, clinical cure rates were lower in the gel (35%) and ointment (30%) groups compared to fluconazole (52.6%) [26].

Thompson et al. [27] recently published a phase 2, randomized, double-blind study comparing rezafungin in one of two dosing regimes (400 mg weekly or 400 mg in the first week then 200 mg weekly) or caspofungin 70 mg for one day followed by 50 mg daily, in the setting of candidemia in 207 patients. There were no statistically significant differences between therapy arms, although there was a trend to lowest response in the 400 mg rezafungin arm (cure rate 60.5% in the 400 mg weekly, 76.1% in the 200 mg weekly and 67.2% in the caspofungin arm. Side effects were no different between groups.

Two current rezafungin studies are listed on clinicaltrials.gov. A phase 3 trial comparing rezafungin to fluconazole for the prevention of invasive

fungal disease in patients undergoing bone marrow transplantation is estimated to complete in 2022 (NCT04368559). A phase 3 comparison of rezafungin with caspofungin in the setting of candidemia is estimated to complete in mid-2021 (NCTNCT03667690). The dose chosen in the latter trial is the more efficacious arm of the rezafungin study by Thompson et al. of a 400 mg loading dose followed by 200 mg per week [27].

Ibrexafungerp (SCY-078)

Also targeting β -1,3-d-glucan synthase is a novel synthetic derivative of enfumafungin, ibrexafungerp that has the added advantage over the echinocandins of being orally bioavailable [28]. Initial studies in a murine model of candidiasis showed good activity against multiple *Candida* spp. including *C. albicans*, *C. glabrata* and *C. parapsilosis* [28]. In vitro data from clinical isolates [29] and animal models [30] also suggest reasonable activity against *C. auris*. However, like echinocandins, ibrexafungerp is poorly active against *Mucorales* and *Fusarium*, but was active against *Scediosporium profliicans* [31]. Against echinocandin-resistant strains of *Candida* including *C. glabrata*, ibrexafungerp generally maintained reasonable activity with MIC values increasing 2–eight-fold compared to 2–133-fold for anidulafungin, 4–66-fold for caspofungin and 1–66 fold for micafungin [32].

Ibrexafungerp alone or in combination with isavuconazole was studied in a neutropenic rabbit model of invasive aspergillosis [33]. The combination of both agents was clearly superior to monotherapy with either, with the higher dose of ibrexafungerp (7.5 mg/kg/day) combined with isavuconazole having the best survival, lowest pulmonary infarct scores and lowest fungal burden.

An open-label phase 2 study looked at the efficacy of ibrexafungerp following echinocandin therapy in 27 patients with invasive candidiasis. Seven subjects received ibrexafungerp 500 mg, another 7 received 750 mg and the remainder received fluconazole(7) or micafungin(1) as standard of care [34]. Clinical success rates were similar across all groups at the end of treatment, 2-week post and 6-week post-time points with no safety concerns identified. These findings are consistent with in vitro data suggesting ibrexafungerp is fungostatic against *A. fumigatus* and

that synergy exists with azoles and amphotericin B against *Aspergillus spp* [35].

A phase I study of ibrexafungerp in healthy males is listed as completed in clinicaltrials.gov (NCT04307082), but results are not yet published. A number of other currently active studies include a phase 3 study in recurrent vulvovaginal candidiasis (NCT04029116), an open-label phase 1 study in invasive candidiasis due to *C.auris* (CT03363841) and an open-label study in patients with fungal disease refractory to other options (NCT03059992). All of these studies are due to complete by end 2021.

Fosmanogepix (APX001)

Fosmanogepix is a novel anti-fungal targeting Gwt1, which is an early enzyme in the synthesis of glycosylphosphatidylinositol [36, 37]. Murine neutropenic models suggest fosmanogepix may be an effective treatment option for invasive *Scediorporium* and *Fusarium* [38], invasive candidiasis [39] and promisingly also for *Rhizopus arrhizus* [40]. Fosmanogepix also had efficacy in *C.albicans* endophthalmitis and meningoencephalitis in non-neutropenic rabbits [41] (Table 1)

Serial passage experiments in candida species demonstrated that mutations leading to resistance to fosmanogepix developed at about the same rate as with existing anti-fungal therapies [42].

Three of four phase I studies of fosmanogepix listed on clinicaltrials.gov have been completed but so far data have only been presented in poster format [37]. Based on the data presented fosmanogepix has high

bioavailability and there were no barriers identified raising concerns about moving to phase 2 trials. Current phase 2 trials on clinicaltrials.gov are targeting invasive disease by *Aspergillus* or rare molds (NTC04240886) and invasive candidiasis due to *C.auris* (NTC04148287).

T-2307

T-2307 is an arylamidine similar to pentamidine and targets fungal mitochondria[43] through uptake via the high-affinity spermine and spermidine carrier [44]. In vitro T-2307 is active against *Cryptococcus neoformans* [45] and *gattii* [46], *A. fumigatus* [45] as well as most species of *Candida* [45], including echinocandin-resistant *C. glabrata* [47]. In a murine ocular model of *C.albicans*, T-2307 showed equivalent efficacy to amphotericin and fluconazole [48]. A successful phase I trial of T-2307 was completed in 2015 (clinicaltrials.gov NCT02289599), and a phase II study is currently proposed for 2022 [49].

Olorofim (F901318)

Olorofim is currently in clinical development through a phase IIa trial in patients with invasive fungal infection lacking other treatment options (Clinicaltrials.gov NCT03583164) with an estimated study completion date of February 2021. Olorofim inhibits the enzyme dihydroorotate (DHOD), a key step in the synthesis of pyrimidines [50]. In vitro F910318 is highly active against azole-resistant *Aspergillus*

Table 1 Summary of novel anti-fungals under development

Agent	Site of Action	Company	Stage of Development
VT-1161 and VT-1598	Cyp51	Mycovia Pharmaceuticals	Phase III trials
Rezafungin (CD101)	β 1,3-D-glucan	Cidara Therapeutics	Phase III trials
Ibrexafungerp (SCY-078)	β 1,3-D-glucan	Scynexis	Phase III trials
Fosmanogepix (APX001)	Gwt1	Amplix Pharmaceuticals	Phase II trials
T-2307	Spermine/spermidine carrier	Toyama Chemical	Phase II trial planned
Olorofim (FP01318)	Dihydroorotate	F2G	Phase IIa trial
ASP2397	Unknown	Vical	Animal studies complete
PC945	CYP51	Pulmocide	Phase I complete
Pur1900	Egosterol	Pulmatrix	Phase IIb planned

fumigatus, *Scedosporium spp.* and *Fusarium spp.*, but has no activity against Mucorales and *Candida* [51–55]. In a neutropenic, *A. terreus*-infected murine model, twice daily olorofim administration at 10 mg/kg was more effective than amphotericin (0% 2-week survival vs 90% for oral F901318 and 100% for intravenous) [56]. In a phase I study of oral olorofim at 360 mg per day was well tolerated with no adverse events [57], which is not surprising given there is only approximately 20% homology between human and fungal DHOD [58].

ASP2397

ASP2397 is produced by *Acremonium persicinum* and is a cyclic hexapeptide similar to a number of characterized fungal siderophores although its exact target is unknown [59]. ASP2397 is transported into *A. fumigatus* by the Sit 1 siderophore transporter, inactivation of which conveys resistance to its actions [60]. In vitro ASP2397 has excellent activity against *A. fumigatus*, *A. terreus* and *A. flavus*, as well as *Cryptococcus*, but not *Candida*, *Scedosporium* or *Rhizopus* [61]. In vivo in a neutropenic mouse *A. fumigatus* model, those in the ASP2397 treatment group demonstrated greater survival than those treated with posaconazole, amphotericin or caspofungin [61]. There are currently no active trials for ASP2397 listed on clinicaltrials.gov with a phase II study and development program terminated by the sponsor in 2019.

PC945

PC945 is a novel triazole targeting CYP51, inhibiting ergosterol synthesis, and was designed for inhalation rather than systemic administration [62]. In vitro the inhibition of ergosterol by PC945 appears to be significantly greater than that of voriconazole or posaconazole [63]. Against 96 clinical isolates of *A. fumigatus* the potency of PC945 was assessed as superior to voriconazole and comparable to posaconazole [63]. As well as *Aspergillus spp.*, PC945 has activity against a broad range of fungi including *Candida spp.*, *Cryptococcus spp.* and *Rhizopus oryzae* [63].

In a phase I trial, PC945 was well tolerated in healthy controls and subjects with mild asthma [64].

No current trials for PC945 are listed on clinicaltrials.gov although a phase III trial is slated for 2021 in patients with refractory or resistant pulmonary fungal disease [65].

Inhaled itraconazole

Although itraconazole has been available for over two decades, a novel inhaled formulation is in clinical trials. For airways disease, such as allergic bronchopulmonary aspergillosis and for prophylaxis in immunocompromised patients an inhaled route may offer improved efficacy at much lower toxicity than systemic therapy. A phase 1 study demonstrated good tolerability of an inhaled itraconazole formulation, PUR1900, with 70-fold higher sputum concentrations than with systemic therapy and 66-fold lower systemic concentrations. A randomized, double-blind study of PUR1900 is, however, listed as terminated on clinicaltrials.gov, and no further trials are listed although the parent company lists a planned phase IIb study in development.

Summary

A number of anti-fungals are in or approaching phase III trials that promise to significantly increase the therapeutic options available to clinicians and patients. That these agents have collectively a wide range of activity including drug-resistant *Candida*, *Aspergillus* and Mucorales will be particularly welcome.

None of these new agents will be immune to the development of fungal resistance, particularly given the steadily increasing number of patients requiring anti-fungal therapy and/or prophylaxis. However, with greater bioavailability, less toxicity and different modes of action promised by the emerging anti-fungal therapies discussed above, the possibility of combination therapy to reduce the likelihood of resistance developing, as well as potentially increasing the efficacy of therapy, becomes a real possibility. While it is highly unlikely all the candidates discussed will pass the phase 3 testing ground and get to market, a significant number is likely to be our new tools in the decade ahead.

Declarations

Conflict of interest I have no conflicts of interest to declare.

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