New antifungals: Where do we stand?

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The landscape of fungal infections has progressively changed over the years with the emergence of antifungal resistance constituting a growing problem in clinical practice and compromising successful patient outcomes [1]. While significant progress has been achieved in the development of novel agents, the survival rates for certain fungal infections have not improved. Some fungal species remain neglected and lack effective therapeutic options and multiple drug related limitations persist.

Resistance occurs due to selective pressure from the increased usage of antifungal drugs in empiric therapy and involves a number of mechanisms depending on their action, such as gene mutations, drug target modification, efflux pumps etc. [1]. Yet another reason for the emergence of resistance is antifungal prophylaxis. Although prophylactic therapy is proven to effectively prevent invasive fungal infections and improve survival of high-risk populations [patients with hematologic malignancies and allogeneic hematopoietic stem cell transplantation (HSCT)], some of these patients may develop breakthrough infections. When such infections occur, they often involve difficult to treat drug resistant pathogens [2].

Antifungal drug resistance is not the sole concern when dealing with fungal infection treatment. There are other drug associated factors that complicate treatment and emphasize the need for improvement of existing medications. Currently, mostly utilized agents have an oral route of administration with multiple limitations, cause significant adverse effects and induce drug-drug interactions. Also, toxicity and unstable pharmacokinetic parameters that impact drug efficacy, necessitate mention.

And even though there are currently plenty of therapeutic options available for *Candida* infections, the management of other rising difficult to treat molds and yeasts such as *Mucorales, Fusarium, Lomenospora*, and *Scedosporium*, is far more complex. Of note, despite our advances, survival rates of *Aspergillus* infection have not risen beyond 70% through the last 20 years [3-5]. This underscores the presence of numerous unmet needs in the treatment of fungal infections. To address this barrier, multiple strategies are currently under investigation. Hopefully, the development of novel antifungal drugs in addition to repurposing or establishing new methods of delivery of existing agents will enhance the available treatment options and achieve more favorable patient outcomes.

To this end, a number of new agents in currently used classes are currently coming out of the clinical research pipeline. Otesoconazole is a novel oral agent that differs from other azoles because it contains a tetrazole moiety instead of triazole or imidazole. This modification produces better selectivity for fungal CYP51 with less interaction with off-target human CYPs and improves the safety profile [6]. Otesoconazole is FDA approved for the treatment of recurrent vulvovaginal candidiasis (VVC) and demonstrated efficacy for onychomycosis treatment compared to itraconazole [7].

Opelconazole is a novel inhaled triazole with a broad spectrum against yeasts and molds. The inhaled route of administration achieves high local concentrations in the lung, rendering it a promising agent for invasive aspergillosis treatment including COVID-19 associated pulmonary aspergillosis, allergic bronchopulmonary aspergillosis and chronic pulmonary aspergillosis. The topical use maximizes local activity while minimizing systemic toxicity and drug-drug interactions [1].

Rezafungin is a next generation echinocandin, derived from anidulafungin. It has echinocandin-expected in-vitro activity against *Candida* spp and has a chemical

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modification that confers high stability, a longer half-life, and allows for a once-a-week dosing regimen [8]. A completed trial (ReSTORE) examined the rezafungin 400-mg/200-mg once-weekly regimen for the treatment of candidemia and invasive candidiasis. The active comparator was intravenous caspofungin. Rezafungin was non-inferior to caspofungin for the primary endpoints of day-14 global cure and 30-day all-cause mortality. Compared with other echinocandins in phase 3, results showed improved efficacy and safety. An ongoing trial (ReSPECT) is designed to evaluate the drug's role as prophylaxis [9].

Ibrexafungerp is a novel triterpenoid antifungal that shares mechanism of action with echinocandins. After two successful trials, VANISH 303 and 306, the FDA approved ibrexafungerp for the treatment of vulvovaginal candidiasis [10]. Another ongoing study (FURI) evaluates the role of ibrexafungerp as treatment for patients who are either intolerant of standard antifungal therapy or have not responded to standard therapy. The study has already shown that oral ibrexafungerp provides a favorable therapeutic response in patients with challenging fungal disease and limited treatment options [11].

Another approach in the battle against fungal infections is the development of new methods of delivery for established agents. Alternative AmB formulations are currently under investigation and contain cochleates, nanoparticles and umbrellas. The intended objective is to target delivery, minimize toxicity and improve efficacy. Among the aforementioned, an oral encochleated form of AmB (MAT2203) is the furthest along clinical development [7]. There is a completed study for VVC that resulted in lower cure rates and more adverse effects in comparison to fluconazole. Phase 1 and phase 2 studies on cryptococcal meningitis in HIV infected patients are ongoing [7]. Oral cAmB was well tolerated when given in 4-6 divided daily doses without the toxicities commonly seen with IV AmB [12].

Last, we have been happy to see new agents with a totally new mechanism of action arising from clinical trials**.** Olorofim is the first member of a novel antifungal class, orotomides. The mechanism of action was identified during genetic screening of *Aspergillus nidulans* and is based on inhibition of dihydroorotate dehydrogenase (DHODH), a key enzyme for pyrimidine biosynthesis. The agent has *in vitro* activity against difficult-to-treat *Aspergillus* spp. with intrinsic and acquired antifungal resistance [13]. It is active against *Lomentospora, Scedosporium, Coccidioides* and *Fusarium* spp but lacks activity against mucorales and yeasts [1]. Interim results of a phase-2b, open-label trial (study 32) suggest that olorofim, when compared to relevant historical controls or expected outcomes for highly active, uncontrolled invasive fungal infection, has a positive benefit-risk profile in a well-defined population of patients with limited or no treatment options [14].

Fosmanogepix is a prodrug of the antifungal manogepix which targets glycosylphosphatidylinositol-anchored protein maturation through inhibition of the fungal enzyme Gwt1. This impacts fungal cell integrity, growth, and virulence [1]. The drug showed potent activities against most *Candida* species., except for *Candida krusei*. Compared to fluconazole, itraconazole, voriconazole, amphotericin B, and micafungin, fosmanogepix showed equally potent activities against fluconazole-resistant and fluconazole-susceptible *Candida* strains. It also had potent activities against various filamentous fungi, including *Aspergillus fumigatus* and it was active against *Fusarium solani* and some black molds. Given its broad spectrum of activity, fosmanogepix is likely to be a promising agent for the treatment of invasive fungal infections [15].

Last repurposing other drugs as antifungals remained always an option. Sertraline, a commonly prescribed antidepressant, offers a promising treatment option for cryptococcosis, notably for cryptococcal meningitis. Sertraline's ability to accumulate in central nervous system is a valuable characteristic relatively to other antifungal drugs. Contrasted with fluconazole, sertraline showed narrower range of inhibitory concentrations against multiple cryptococcal isolates which translates into a lower probability of resistance occurrence. In addition, a synergistic fungicidal effect with fluconazole was observed in a mammalian model and could potentially mark the shortening of treatment duration and the reduction in resistance emergence [16]. The role of Tamoxifen derivatives and related agents have also been investigated for similar purposes. The research pointed out the structural requirements for antifungal activity of these agents [17]. Calcineurin inhibitors also serve as repositionable candidates. There is evidence that calcineurine is required for virulence based on research on many human fungal pathogens including *C. albicans* and *C. neoformans*. Calcineurin fulfills critical functions in fungal growth, transition between morphological states and stress response. Thus, fungal specific calcineurin inhibitors, which do not cross react with human calcineurin causing im-

munosuppression must be developed, so as to be used as combination therapy for fungal infections [18]. Lastly, ebselen and auranofin exhibit potential for drug repurposing. Both agents demonstrated antifungal and anti-biofilm activities and presented synergistic effects when combined with other antifungal agents, thus rendering them promising candidates for combination therapy [19, 20].

In conclusion, there has been an extraordinary surge in the development of novel antifungals, including meaningfully different formulations, distinct new agents in existing antifungal classes and drugs with completely novel mechanisms of action and potential for spectrum targeting in difficult to treat fungi. However, whether these drugs are to address all our unmet needs is to be seen, since difficult to treat infections including *Mucorales* remain neglected. But most importantly, within our departments of critical care and immunocompromised patients, we need to be able to determine early enough those at high risk of specific infections, so as to provide meaningful prophylaxis or therapy in order to ensure successful outcomes. Unfortunately, at the moment, our diagnostic armamentarium remains limited in terms of sensitivity and specificity hampering therapeutic efforts, and underlining the need for parallel development of both diagnostic and therapeutic tools.

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