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UNVEILING TOMORROW'S ANTIFUNGALS: A COMPREHENSIVE REVIEW OF RECENT PIPELINE ADVANCEMENTS

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Abstract:

The treatment of invasive fungal infections is limited to a range of drugs from five recognized classes of antifungal therapy and is linked to considerable morbidity and death. In reality, dose-limiting toxicities, medication interactions, and delivery methods frequently place restrictions on the use of currently available antifungal medications. The need for the discovery of new antifungals, especially those with unique modes of action, has arisen from the increased incidence of invasive fungal infections, rising resistance rates, and the practical limits of current treatments. An overview of antifungal drugs at different phases of clinical development is provided in this article. We'll talk about the latest additions to the current family of antifungal medications, which includes the highly bioavailable azole SUBA-itraconazole, the oral amphotericin B cochleate, and the long-acting echinocandin rezafungin, which can be used once a week. We will also evaluate new first-in-class drugs including olorofim, an oral pyrimidine synthesis inhibitor with a broad range of action and an oral formulation, and ibrexafungerp, an oral glucan synthase inhibitor with effectiveness against a variety of resistant fungal isolates. We will also look at several other novel antifungal drugs and classes, such as MGCD290, tetrazoles, and fosmanogepix.

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INTRODUCTION:

Polyenes (amphotericin B), azoles (fluconazole, itraconazole, posaconazole, voriconazole, and isavuconazole), echinocandins (caspofungin, micafungin, and anidulafungin), allylamines (terbinafine), and antimetabolites (flucytosine) are the current five classes of antifungal agents used in the treatment of systemic mycoses.

By binding ergosterol in the cell membrane, polyenes provide a fungicidal effect by increasing permeability and allowing internal components to seep out, ultimately causing cell death.[1,2] The most clinically significant polyene for invasive fungal infections is amphotericin B, which has a wide range of fungicidal action against yeasts, molds, and dimorphic fungi. Lack of an oral formulation, infusion responses, and severe dose-limiting toxicities such as nephrotoxicity restrict its practical usage. While patient acceptability has increased because of the introduction of many lipid-based formulations and their co-administration with normal saline, toxicities have not entirely disappeared. Amphotericin B is consistently used in clinical practice as an empirical treatment for invasive fungal infections despite these disadvantages, at least until a more acceptable formulation or therapy is found.

Azole compounds, like polyenes, work by targeting ergosterol to provide fungicidal effects.[2,3] By blocking the enzyme lanosterol 14-demethylase, they particularly prevent the formation of ergosterol. Since they have a wide range of coverage and strong fungicidal action, azoles are now first-line therapy for the management of many invasive fungal infections, as well as for prevention. Many azoles are easily obtained in intravenous and oral formulations; nevertheless, nonlinear pharmacokinetics and irregular absorption (oral suspension formulations) might make it challenging to determine the drug exposure of particular azoles, necessitating therapeutic drug monitoring. Azole enzyme inhibition is not just seen in fungal cells; in some situations, the class is linked to cytochrome P450 inhibition, which can result in harmful drug-drug interactions and "off-target" adverse effects. [4-7] Additionally, the class is limited by a broad several serious toxicities, including hepatotoxicity, QTc prolongation, and hallucinations.[8] Recent increases in primary and acquired resistance among several fungus species have also had an impact on the usage of azole.

Apart from ergosterol, 1,3-d-glucan, a crucial constituent of fungal cell walls, is also a very effective antifungal target. Echinocandins cause cell lysis by preventing the production of 1,3-d-glucan, which weakens the walls of fungal cells. Echinocandins are still one of the best treatments for invasive candidiasis, including candidemia, even though their coverage is mostly restricted to yeasts and molds and they have minimal effect on endemic mycoses. Notably, echinocandins have few side effects and few medication interactions due to their high tolerance. Instead, the lack of oral formulations limits use, as all echinocandins currently on the market are only accessible as intravenous infusions once daily.

Allylamines, like terbinafine, prevent squalene epoxidase from functioning, which hinders the formation of ergosterol. Terbinafine is frequently used as a topical drug; however, because of the effectiveness and more acceptable side effect profile of other antifungal medications, it is only employed in the salvage context to treat dermatophytes and molds.[9]

The last clinically significant agent is flucytosine, a pyrimidine analog that acts by specifically interfering with the production of fungal nucleic acids.[3] It may be taken orally, and the main side effects are restricted to bone marrow suppression. It is primarily used as a component of combination therapy for the treatment of cryptococcal meningitis, urinary candidiasis, or chromoblastomycosis; however, its use as monotherapy is uncommon due to the quick development of resistance.

Even after taking into consideration spectra, toxicities, and formulations, the current antifungal choices still have gaps in treatment and provide a lot of room for the creation of novel drugs. New agents within the current classes (rezafungin) and enhanced formulations of previously authorized drugs (SUBA-itraconazole, Amphotericin B cochleate) have been the subject of some development. Antifungal novel classes are also being actively developed. While many other agents in development (olorofim, MGCD290, Fosmanogepix, VL-2397, T-2307) aim to establish entirely novel targets of antifungal activity, ibrexafungerp and the tetrazoles act on similar fungal biosynthesis pathways previously targeted by existing classes (1,3-d-glucan and ergosterol synthesis).

1. SUBA-ITRACONAZOLE:

Even though a lot of work has gone into finding new antifungal compounds and classes, there has also been advancement in the optimization of the agents already in the antifungal armory. Although it is a broad-spectrum triazole, it has very little bioavailability, which has hindered its clinical use.[10,11] The bioavailability of conventional oral

itraconazole capsules is around 55% when taken with meals; however, this varies greatly across people and is decreased in those with a raised stomach pH (i.e., those on acid suppression treatment). The creation of super-bioavailability-itraconazole (SUBA-itraconazole; Mayne Pharmaceuticals) has been prompted by this. The itraconazole solid dispersion in a pH-dependent polymer matrix is used in this oral capsule formulation to improve absorption and dissolution. Compared to conventional oral formulation, it has been demonstrated to dramatically reduce interpatient variability and boost oral bioavailability (173%).[11] Furthermore, this unique formulation has little effect on bioavailability due to food or acid, which is a considerable improvement over standard itraconazole.[12]

To control endemic mycosis, SUBA-itraconazole was compared to traditional itraconazole therapy in phase III research (NCT03572049). In comparison to a previous cohort of patients receiving traditional itraconazole, research assessing its use as prophylaxis in patients undergoing stem cell transplantation discovered that the SUBA-itraconazole formulation had much greater therapeutic levels and better gastrointestinal tolerability.[13] Following this, the FDA authorized SUBA-itraconazole for the treatment of blastomycosis, histoplasmosis, and aspergillosis (in patients who were resistant to or intolerant to amphotericin B therapy). It is now offered as a 65 mg oral capsule. For the first three days, a loading dosage of 130 mg three times a day may be necessary, after which a maintenance dose of 130 mg once a day with meals is advised.

2. REZAFUNGIN:

Rezafungin (CD101; Cidara Therapeutics) is a next-generation echinocandin in development that functions similarly to previous members of its class [2] in that it inhibits the production of 1,3-d-glucan. It is a structural analog of anidulafungin that has been modified to improve solubility and stability. It is widely disseminated in tissues and has a pharmacokinetic advantage due to its much longer half-life (~133 h) when compared to other echinocandins. It has been shown that dose-proportional pharmacokinetics have a good safety profile and minimal interpatient variability.[14]

In the treatment of candidemia/invasive candidiasis (STRIVE; NCT02734862), two loading doses of rezafungin were compared to caspofungin in a recently finished two-part phase II research.[2,15] An oral fluconazole step-down may thereafter be necessary. The most effective dose regimen was found to be rezafungin 400 mg during the first week, followed by 200 mg once weekly. This regimen is now being studied in the ongoing phase III invasive candidiasis trial (ReSTORE; NCT03667690).

Consistent with the other members of the echinocandin class, clinical studies conducted thus far have demonstrated a favorable safety profile.[2] It has been well tolerated, with few adverse events and no discernible differences between comparison groups and standard of treatment.

With strong coverage of several clinically significant Candida species, such as Candida albicans, Candida krusei, and Candida tropicalis, as well as some Aspergillus species, the effectiveness and range of action are similar to other echinocandins.[2] Rezafungin minimum inhibitory concentrations are impacted by FKS mutations that confer echinocandin resistance, however not in all isolates. Resafungin, caspofungin, and anidulafungin all show broad cross-resistance, although experiments using rezafungin's "front-loaded" dosing schedule are thought to slow the emergence of resistance.[16] Additionally, Rezafungin has been shown in vitro experiments to have strong anti-C. auris activity, outperforming both micafungin and caspofungin.[17] Additionally, in vivo experiments on animals have revealed that rezafungin, the only member of the class, could be able to stop Pneumocystis spp. infections.

Regarding antifungal prophylaxis against Candida, Aspergillus, and Pneumocystis, there is interest in the use of rezafungin due to its wide action. For this reason, patients undergoing blood or marrow transplantation will be randomly assigned to either rezafungin or standard of care (triazole with Trimethoprim/Sulfamethoxazole) in a phase III trial called ReSPECT (NCT number pending). Rezafungin's preferred once-weekly dosage schedule will be followed in all trials.

3. IBREXAFUNGERP:

Using a well-known mode of action, Ibrexafungerp (SCY-078; Scynexis, Inc.) is another first-in-class medication that is an antifungal terpenoid.[18] Similar to echinocandins, its antifungal effect is derived from inhibiting 1,3-d-glucan production. Ibrexafungerp, a triterpenoid Enfumafungin derivative, is structurally distinct from other members of the echinocandin family.[18,19]

Ibrexafungerp is an extremely bioavailable compound that may be given intravenously or orally.[18] Food improves the medication's stomach disintegration and systemic absorption. Oral ibrexafungerp is now being studied in phase III trials. The loading dosage is 750 mg PO BID for the first

two days, and then 750 mg PO daily for the remaining doses (NCT 03059992). Previous phase II trials used a once-loading dosage of 1250 mg PO. Studies have shown that it is generally well-tolerated and that its side effects are restricted to the gastrointestinal tract; many trials have found no appreciable difference when compared to placebo arms.[20]

Similar to echinocandins, a wide variety of therapeutically important Candida species, such as C. glabrata and C. auris, are included in the spectrum of action.[18] Ibrexafungerp continues to be active in vitro against strains of Candida that are resistant to echinocandin while having comparable modes of action. This suggests that the avidity of the target site is different. Furthermore, fungistatic efficacy against Aspergillus species, including azole-resistant strains, has been found through in vitro investigations.[21] Like echinocandins, Ibrexafungerp exhibits some action against traditionally difficult fungal species such as Paecilomyces variotii and Lomentospora prolificans, however, it is ineffective against mucormycosis agents.

Oral ibrexafungerp was evaluated as a treatment option in phase II trials for the treatment of moderate to severe vulvovaginal candidiasis, as well as an oral step-down therapy after echinocandin treatment.[18] It is presently being tested in a phase III study vs placebo in patients with recurrent vulvovaginal candidiasis (CANDLE; NCT04029116) and as a treatment for invasive fungal disease refractory or intolerant to standard-of-care therapy (FURI; NCT03059992). A preliminary examination of the research has revealed a clinical advantage in 17 out of the 20 assessed individuals.[20]

Ibrexafungerp has strong yeast activity and a desired safety profile, which seem to be functional commonalities with the echinocandin class. On the other hand, it provides a valuable oral formulation and greater antifungal coverage, including molds and echinocandin-resistant yeast, as a new structurally different class. The therapeutic purpose of ibrexafungerp will be further defined by ongoing research, however, development seems to be focused on treating resistant fungal infections or oral step-down therapy after echinocandin treatment.

4. OLOROFIM (F901318):

With a unique mode of action, olorofim (F901318; F2G Ltd.), another drug in development, creates a new antifungal class known as the orotomides.[2] A crucial enzyme in the production of pyrimidines, dihydroorotate dehydrogenase, is inhibited by the class. The synthesis of fungal nucleic acid, cell walls, and phospholipids, as well as cell regulation and protein synthesis, are all adversely affected when pyrimidine production is inhibited. Olorofim has an antifungal activity that varies with time, and its pharmacodynamic effectiveness is presently measured by C_{min}/MIC.

Although most studies have focused primarily on the oral formulation, olorofim can also be given intravenously. Olofim is broadly disseminated throughout tissues, including brain tissue, but at lower levels, according to recent pharmacokinetic investigations. Because it is metabolized by the CYP450 system, namely CYP3A4, it is susceptible to medication interactions. Although it exhibits modest CYP3A4 inhibition, it is not a CYP450 inducer per se. Currently under study is an oral dosage regimen consisting of a loading dose of 4 mg/kg split into two or three doses on Day 1, a maintenance dose of 2.5 mg/kg split into two or three doses per day, and dose modifications depending on blood drug level. Based on in vivo pharmacodynamic experiments against Aspergillus spp., a Cmin target of 0.5 mg/mL has been established.[22] Although intravenous dosage was previously investigated to target the aforementioned serum target, it has not been extensively pursued because of clinical discomfort.[2,23]

Olorofim is effective against a wide range of molds, however, it seems to be especially effective against Aspergillus species.[2,24] Strong activity has been demonstrated against cryptic species (Aspergillus lentulus and A. calidoustus) that are historically difficult to treat and may be intrinsically resistant to many of the antifungal classes currently on the market, as well as common species (Aspergillus fumigatus, A. nidulans, A. terreus, and A. niger). Olorofim's unique method of action allowed it to be effective against strains of Aspergillus that were resistant to many drugs, suggesting a lack of cross-resistance. Furthermore, A. fumigatus samples did not seem to develop resistance to olorofim exposure quickly.[2] It has efficacy against rare molds, such as Scedosporium spp. and Lomentospora prolificans, for which there is presently no other effective treatment option.[2,24] It has also been shown to have both in vitro and in vivo action against endemic mycoses such as Coccidioides.[25] While olorofim is effective against the aforementioned fungal species, it appears to have little to no impact on Candida spp., Mucorales spp., and Cryptococcus neoformans, and its effects on Fusarium spp. are inconsistent and frequently species-specific.[2]

Phase IIb open-label research is now being conducted to assess olorofim's efficacy in treating invasive fungal infections in patients who have few other treatment choices (FORMULA; NCT03583164). This is consistent with olorofim's intended use in treatment for patients with invasive fungal infections for which there are no other effective treatments or for which the organism is innately resistant or historically challenging to treat. Because of its early success, olorofim has been given a breakthrough designation by the FDA, and other phase III trials are now being developed.

5. MGCD290:

An oral Hos2 fungal histone deacetylase (HDAC) inhibitor called MGCD290 (Mirati Therapeutics) also affects non-histone proteins including Hsp90.[3] A class of enzymes called HDACs and Hsp90 is involved in the regulation of genes and the management of cellular processes. While MGCD290 seems to have some inherent antifungal action, most studies have focused on how well it works in combination with other antifungal medications. The cellular stress response may be weakened by the inhibition of certain fungal proteins, which might enhance the fungicidal effect of substances that target the fungal cell wall or membrane. Low concentrations of MGCD290 were found to increase azole and echinocandin activity against strains of Aspergillus and Candida, lowering minimum inhibitory concentrations (MICs) and causing a significant number of samples to change from resistant to intermediate or susceptible.[26,27] The efficacy of MGCD290 in vivo has not yet been shown, despite encouraging in vitro studies.[3] Although it seems to be well-tolerated, a phase II trial assessing MGCD290 as an adjuvant treatment to fluconazole in severe vulvovaginal candidiasis did not find any advantages over fluconazole alone.[28] It is not unusual for in vitro experiments to fail to transfer effectively into human in vivo investigations, and this can be caused by several intricate reasons. Currently, nonetheless, no more research has examined the assessment of MGCD290's in vivo efficacy as a possible adjuvant antifungal treatment.

6. AMPHOTERECIN B COCHLEATE:

Amphotericin B cochleate is a novel oral dose formulation in the polyene family (CAMB/MAT2203; Matinas BioPharma). Only intravenous injection administration is permitted for current polyene formulations, such as amphotericin B deoxycholate and several lipid formulations of amphotericin.[29] Amphotericin deoxycholate usage is restricted because of dose-dependent renal toxicity and responses linked to infusion.[30] The gastrointestinal (GI) tract cannot break down amphotericin B cochleate like it can current authorized polyene formulations. Phosphatidylserine and phospholipid-calcium precipitates combine to form cochleates. Their multilayered structure creates a spiral-shaped, solid, lipid bilayer without an interior aqueous gap.[31] After being taken orally, the cochleate is absorbed from the GI tract and enters circulation; as the cochleates' calcium concentrations drop, the spiral formation opens, allowing the medicine that has been encapsulated to be released into the cell. The cochleate formulation is used to administer a variety of formulations, including proteins, peptides, and anticancer medications including doxorubicin, fistein, and raloxifene.[32] Cochleate formulations have several drawbacks, such as precipitation during storage, stability loss at temperatures higher than 4°C, and high manufacturing costs.[32]

Santangelo et al. successfully administered amphotericin B cochleate orally in a murine mouse model. Mice were given C. albicans intravenously; the non-cochleate group died 100% after either intraperitoneal deoxycholate amphotericin or oral liposomal amphotericin. On Day 16 post-infection, the group that received oral amphotericin B cochleate showed 100% survival. In this mouse model, the amphotericin B cochleate dosage varied from 0.5 mg/kg/day to 20 mg/kg/day.[31] Oral amphotericin provides a feasible way to administer a broad-spectrum antifungal that was previously limited by infusion-related problems and needed intravenous infusion. Research is intended to investigate the safety and effectiveness of treating cryptococcal meningitis orally, and vulvovaginal candidiasis (NCT02971007).

7. TETRAZOLES (VT-1129, VT-1161 AND VT-1598):

Tetrazole antifungals are new azole-like substances that exhibit a greater affinity for fungal cell CYP51 than for CYP in humans. Due to their interaction with human CYP450 enzymes, currently marketed triazoles may have greater rates of side effects and drug-drug interactions.[33,34]

An oral antifungal called VT-1129 (Mycovia Pharmaceuticals) is under development. Wiederhold et al. assessed the anti-Crypococcus activity of VT-1129 in a mouse model. The half-life of VT-1129 is lengthy—roughly six days. as a loading and maintenance dosage was given, the results showed that the treatment group had better survival and a lower fungal burden as compared to the control group.[33]

VT-1598 has antifungal action against endemic fungi, molds, and yeasts. Once more, Wiederhold et al. used a mouse murine model to study VT-1598's efficacy against Coccidioides immitis and Cocci posadasii. As opposed to fluconazole's 16 mcg/mL, they discovered that the MICs were 0.5 and 1 mcg/mL, respectively. A decreased fungal load was associated with a higher survival rate in the VT-1598 group.

The group that received fluconazole, or VT-1598, at a lower dosage, had a higher fungal burden.[35] In vitro testing of VT-1598, VT-1161, and the triazoles fluconazole, itraconazole, posaconazole, and voriconazole for strains of Candida albicans sensitive to and resistant to azoles yielded MICs. With MICs of around 8 mcg/mL, VT-1598 and VT-1161 demonstrated strong efficacy against the majority of isolates, several of which were known to be fluconazole-resistant. The C. albicans strains employed in this investigation exhibited a variety of resistance mechanisms. In this investigation, VT-1598 showed lower MIC50 and MIC90 values than VT-1589 and VT-1161.[36]

8. FOSMANOGEPIX (AXP001):

Prodrug fosmanogepix (APX001; Amplyx) is converted to manogepix (MGX, originally APX001A), also called E1210, the active form.[37] It targets the fungal-specific enzyme Gwt1, which is in charge of the first stage of the manufacture of glycosylphosphatidylinositol (GPI)-anchor.[38] This substance has been effective against a variety of molds, endemic mycoses, and yeasts.[39] Low minimum inhibitory concentrations (MICs) have been reported for the following pathogens: Aspergillus spp. (0.03 mcg/ml), Candida spp. (0.06 mcg/mL), Scedosporium spp. (0.015 to 0.06 mcg/mL), and Fusarium spp. (0.12 mcg/mL).[1] Alkhazraji et al. evaluated the in vitro efficacy of MGX in two immunosuppressed murine models using a mouse model. MGX was shown to increase survival and decrease fungal load.[38] SURGE, NCT03604705, is a phase 2 clinical trial that is currently assessing the safety and efficacy of treating candidemia.

9. VL-2397:

VL-2397, often referred to as ASP2397 (Vical Inc.), is an intravenous antifungal that was isolated from Acremonium species. It enters the cell via the particular siderophore iron transporter 1 (Sit1) and, via an unidentified mechanism, affects intracellular processes. Its structure is similar to that of fungal siderophores.[2] Since Sit1 is absent from mammalian cells, even at high concentrations of VL-2397 is believed to cause toxicity that is extremely selective for fungal cells.

Studies on animals, both in vitro and in vivo, have demonstrated the effectiveness of VL-2397 in the treatment of Aspergillus infections, with a particular emphasis on A. fumigatus.[40] In immunocompromised people with acute leukemia or recipients of allogeneic hematopoietic cell transplants, a phase II trial was started to assess VL-2397 as first-line therapy for invasive aspergillosis. However, Vical Inc. recently abandoned the experiment (NCT03327727).

10. T-2307:

The arylamidine chemical T-2307 (Toyama Chemical) has a unique mode of action.[3,41] Via a polyamine transporter, it is specifically delivered into fungal cells, where it inhibits mitochondrial activity to provide a fungicidal effect. Studies on animals, both in vitro and in vivo, have shown a wide range of action against pathogenic fungi, such as Aspergillus, Candida, and Cryptococcus species. In the treatment of invasive fungal infections, T-2307 may be more effective than azole and polyene therapy, according to some animal models, and the minimum inhibitory concentrations that have been found have been incredibly low.[3] T-2307 has not yet moved on to clinical trials since in vitro and animal model studies are still being conducted to further define the properties of the chemical. Nonetheless, research is being undertaken to assess the clinical effectiveness of treating cryptococcal meningitis.

11. MISCELLANEOUS:

Several additional antifungal medicines, such as the chitinase inhibitor nikkomycin and drugs repurposed when in vitro antifungal activity was revealed (tamoxifen, sertraline, and auranofin), are at varying stages of development.[42,46] Numerous early clinical trials and in vitro/in vivo investigations have been conducted on these later drugs; nevertheless, a clear way ahead for their development has not yet been shown.

CONCLUSIONS:

The rate of invasive fungal infections keeps rising in tandem with advancements in autoimmune, rheumatologic, and oncologic treatment. The increasing number of patients at risk for invasive mycoses has made medication treatment more difficult because of drug interactions and intolerance to the antifungal medications that are already on the market. The development of resistance, whether acquired or intrinsic, also continues to be a significant barrier to bettering patient outcomes and lowering morbidity and death rates. The antifungal arsenal would benefit from the inclusion of new

drugs and classes, and the outcomes of ongoing research trials are keenly anticipated.

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