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Current and future antifungal therapy: new targets for antifungal agents

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Invasive fungal infections are a major problem in immunocompromised patients. The recent expansion of antifungal drug research has occurred because there is a critical need for new antifungal agents to treat these life-threatening invasive infections. The overview of the development of antifungal therapy which is provided herein reflects the increased interest in this very special area of infectious diseases. Although we have newer, less toxic, antifungal agents that are available for clinical use, their clinical efficacy in some invasive fungal infections, such as aspergillosis and fusariosis, is not optimal. Thus, intense efforts in antifungal drug discovery are still needed to develop more promising and effective antifungal agents for use in the clinical arena.

Introduction

Invasive fungal infections, particularly in immunosuppressed patients, have continued to increase in incidence during the past 20 years and are now significant causes of morbidity and mortality. This is particularly true in patients with haematological malignancies undergoing induction or consolidation chemotherapy (especially during the nadir of their granulocytopenia), in immunosuppressed organ transplant recipients, and in patients with acquired immunodeficiency secondary to infection by human immunodeficiency viruses. These infections also occur in some iatrogenic or nosocomial clinical settings.[1,2] Autopsy data indicate that more than half of the patients who die with malignancies are infected with *Candida* spp., approximately one-third with *Aspergillus* spp., and increasing numbers with *Cryptococcus* spp. or other fungi such as *Fusarium* spp.[1,6]

Major factors which predispose patients to invasive fungal disease include: prolonged neutropenia (chemotherapy induced); defective T-lymphocyte function (associated with organ transplantation and HIV infection); impaired macrophage function, particularly of pulmonary macrophages (associated with high doses and prolonged administration of corticosteroids); and barrier defects (associated with invasive medical procedures, vascular catheters, parenteral nutrition and haemodialysis and peritoneal dialysis) in compromised patients.[1–3, 7–11]

Although invasive fungal diseases are now more frequent than during the first half of the century, they are still difficult to diagnose clinically. During the latter half of the century, particularly during the past two decades, a number of different classes of antifungal agents have been discovered. Although, since the discovery of amphotericin B, there has been much progress in this field, there is still a critical need for new antifungal agents to treat life-threatening invasive mycoses.[1,2,7,11–14]

This review will briefly discuss currently available antifungal agents, as well as novel targets for some compounds currently under evaluation. In this review, the antifungal agents which have been or are currently being evaluated for use in treating invasive mycoses are classified by their site of action in fungal cells. These classes include: the polyenes; nucleoside analogues (fluorinated pyrimidines); azoles; pneumocandins–echinocandins; pradimicins– benanomycins; nikkomycins; allylamines and thiocarbamates; sordarins; and others.

The antifungal agents currently available for the treatment of systemic fungal infections are: amphotericin B and lipid formulations of amphotericin B; 5-fluorocytosine; and the azoles, miconazole, ketoconazole, fluconazole and itraconazole. Currently, the optimal properties sought in a new antifungal drug candidate include: inhibition of fungal cell wall biosynthesis; potency comparable with that of amphotericin B; safety comparable with that of fluconazole; and fungicidal activity both *in vitro* and *in vivo*.

Polyenes

The polyene antifungal agents form complexes with ergosterol and disrupt the fungal plasma membrane, resulting in increased membrane permeability, leakage of the cytoplasmic contents and death of the fungal cell. Thus, the polyenes are fungicidal and have the broadest spectrum of antifungal activity of any of the clinically available agents. They are also somewhat less toxic to mammalian cells because the affinity of the polyenes for ergosterol in fungal cells is higher than the affinity for cholesterol in mammalian cells.[1,7,11,15,16]

Nystatin

Brown & Hazen[17–18] discovered nystatin in 1949 in a soil sample, obtained from a farm in Virginia, USA, containing a strain of *Streptomyces noursei*. Nystatin, named after New York State, was not absorbable after oral administration and could not be given parenterally, but was effective topically in the treatment of oropharyngeal candidosis. It was licensed for use in 1951 for superficial (mucosal) candida infections of the oropharynx, oesophagus and intestinal tract.[19]

Amphotericin B

Amphotericin B was isolated from a strain of *Streptomyces nodosus* recovered from a soil sample obtained at Tembladora on the Orinoco River in Venezuela by Gold and colleagues.[20,21] It has broad-spectrum antifungal activity, is fungicidal and has excellent in-vitro activity against *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Sporotrichium* spp. and *Torulopsis* (*Candida*) *glabrata*. It also has excellent activity against *Candida albicans* and most other *Candida* spp., except for *Candida lusitaniae*. It has variable activity against *Aspergillus* spp. and zygomycetes (e.g. *Mucor* spp.), whereas *Fusarium* and *Trichosporon* spp. and *Pseudoallescheria boydii* are often resistant.[1,7,13] Although this drug is not well absorbed after oral administration,[22] an oral preparation is available for treatment of oral mucosal candidosis. Topical preparations are also available. Intravenous amphotericin B has been the mainstay of effective therapy for invasive fungal infections.[1,12,13,21,23,24] It is recommended by most clinical mycologists as the drug of choice for severe blastomycosis, coccidioidomycosis (pulmonary, meningeal and disseminated), paracoccidioidomycosis, histoplasmosis, fusariosis, severe and moderate cryptococcal meningitis, candidosis (including candidaemia, disseminated candidosis, endophthalmitis, endocarditis, peritonitis and candida infections of the central nervous system) and for all forms of invasive aspergillosis and mucormycosis.[1,13,23–25]

Nephrotoxicity is the most serious side effect of amphotericin B therapy. Almost every patient develops some abnormality in renal function.[1,12,21] A number of methods have been used to attempt to reduce this serious side effect, most notably, the use of liposomal preparations of this drug.[26]

Lipid formulations of amphotericin B. Liposomal preparations of amphotericin B have been used to reduce the nephrotoxiciy of conventional amphotericin B.[1,2,26] Amphotericin B in lipid complexes or liposomes has antifungal activity comparable with that of standard amphotericin B, but differs in its pharmacological and toxicological properties.[1,12] Specifically, with liposomal preparations the interaction of amphotericin B with mammalian cell membranes is modified and the organ distribution is altered because liposomes are preferentially taken up by spleen, lung, liver, lymph node, kidney, bone marrow and heart.[1] Lipid formulations in use clinically include: amphotericin B lipid complex (ABLC, Abelcet, The Liposome Co., Princeton, NJ, USA), an assembly of ribbon-like structures of a bilayered membrane formed by combining a 7:3 molar ratio of L-α-dimyristoylphosphatidylcholine (DMPC) and L-α-dimyristoylphosphatidylglycerol (DMPG) with amphotericin B with a drug:lipid ratio of 1:1; amphotericin B cholesteryl sulphate complex, a colloidal dispersion (ABCD, Amphotec, Sequus Pharmaceuticals, Menlo Park, CA, USA) composed of disc-like structures of cholesteryl sulphate complexed with amphotericin B in a 1:1 molar ratio; and a true liposomal amphotericin B preparation (L-AmB, Ambisome, Nexstar, San Dimas, CA, USA) which consists of small unilamellar liposomes made up of a bilayer membrane of hydrogenated soya phosphatidylcholine and distearoylphosphatidylglycerol stabilized with cholesterol and combined with amphotericin B in a 2:0.8:1:0.4 ratio.[1,2,12,26–32] Although the nephrotoxicity associated with each of these three lipid preparations is lower than with conventional amphotericin B, the rates of acute infusion-related reactions (which differ among the three lipid formulations)[33] do not differ substantially from those observed with conventional amphotericin B[1,26,29,32,34] except that they are more frequent with ABCD.[33]

Clinical responses in patients with invasive aspergillosis appear slightly better in the lipid formulation-treated groups compared with retrospective case control groups treated with conventional amphotericin B.[1,34] In contrast, clinical trials with lipid formulations used empirically in neutropenic cancer patients suggest that there is less nephrotoxicity but that clinical efficacy is similar to that of conventional amphotericin B.[1,34] Also, a recent multi centre, open-label non-comparative study of ABLC in patients with aspergillosis, disseminated candidosis, zygomycoses and fusariosis, who were refractory to or intolerant of conventional antifungal therapy, demonstrated that ABLC had reasonable efficacy in these infections.[35]

Some important questions about the use of amphotericin B lipid preparations remain unanswered. Are there differ-

ences in the clinical efficacy and/or toxicities of the preparations and what is their exact mechanism of action? Do they have long-term toxicity? Is there an optimal dose schedule and what is the most cost-effective way to use them? Unfortunately, although amphotericin B lipid preparations have reduced nephrotoxicity they have not produced substantial improvements in efficacy in many of the clinical settings in which they have been evaluated.[1,2,34]

Some physicians have used a locally prepared variant of lipid-associated amphotericin B made by mixing conventional amphotericin B with Intralipid, Kabi Pharmacia, Saint-Quentin-en-Yvelines, France, for intravenous infusion.[1,36] However, this preparation has not reduced nephrotoxicity, has not been standardized and has not been licensed for use, so it should not be used. Licensed preparations of lipid formulations of amphotericin B should be considered in patients with invasive fungal infections who have dose-limiting renal insufficiency, in patients intolerant of amphotericin B and for specific fungal infections that are progressive despite treatment with amphotericin B.[1,2]

Investigational polyenes

A liposomal preparation of nystatin has been studied in neutropenic animals with invasive pulmonary aspergillosis (rabbits) and disseminated aspergillosis (mice). Liposomal nystatin improved survival and reduced the tissue burden of aspergillus in these neutropenic animals.[37,38]

A new polyene, SPA-S-843, has been studied *in vitro* against strains of *Candida*, *Cryptococcus* and *Saccharo - myces* spp. and has better activity *in vitro* than conventional amphotericin B.[39] We have also studied this compound in an animal model of invasive aspergillosis and observed that, although SPA-S-843 was less toxic than conventional amphotericin B, it was also less effective in sterilizing organ tissues (unpublished observations).

Nucleoside analogues

Flucytosine

5-Fluorocytosine (flucytosine, 5-FC) is a fluorinated pyrimidine that was synthesized in 1957 as a cytosine analogue for the treatment of leukaemia; however, it was ineffective because it had no cytotoxic activity. The antifungal activity of 5-fluorocytosine was discovered later and was reported in 1963 in a murine model of candidosis.[40] It inhibits pyrimidine metabolism by interfering with RNA and protein synthesis in the fungal cell.[1,2,7,12,13,41] Flucytosine enters fungal cells via cytosine permease and is deaminated to 5-fluorouracil, which is incorporated into RNA. Uridine 5-monophosphate pyrophosphorylase then converts 5-fluorouracil into fluorodeoxyuridine monophosphate, which inhibits thymidylate synthetase and interferes with DNA synthesis.[1,2,7,12,13] This drug is selectively toxic to fungi because mammalian cells lack cytosine permease and do not convert large amounts of flucytosine to 5-fluorouracil.

Although flucytosine is active *in vitro* against *Candida* spp. (including *C. glabrata*), *C. neoformans* and *Aspergillus* spp., clinical studies have used flucytosine only in candidosis and cryptococcosis.[1,13] Flucytosine, when used alone, has weak therapeutic activity and fungal resistance develops rapidly in candida and cryptococcal organisms. Bone marow toxicity occurs with high blood levels (>100 mg/L) and most hospital laboratories are unable to measure blood levels of flucytosine. Although flucytosine, primarily in combination with amphotericin B, is used by some clinicians in the treatment of candida endophthalmitis and meningitis, cryptococcal meningitis and in trichosporonosis,[1,12,13] the development of newer, more effective and less toxic antifungal agents is likely to decrease flucytosine use in the future.[1,12,13,19,24]

Azoles

The initial azole compounds were the imidazoles (clotrimazole, miconazole and ketoconazole), which were then followed by the triazoles, fluconazole and itraconazole.

The azoles inhibit fungal cytochrome P450 3A-dependent C14-α-demethylase which is responsible for the conversion of lanosterol to ergosterol. This leads to the depletion of ergosterol in the fungal cell membrane.[1,2,7,12,13] The in-vitro antifungal activity of the azoles varies with each compound, and the clinical efficacy of each compound may not coincide exactly with in-vitro activity. The azoles are primarily active against *C. albicans*, *C. neoformans*, *C. immitis*, *H. capsulatum*, *B. dermatitidis*, *P. brasiliensis*; *C. glabrata*, *Aspergillus* spp., and *Fusarium* spp. and zygomycetes are resistant to currently available azoles.[1,2]

Older azoles

Clotrimazole, discovered in 1969,[42] cannot be given parenterally, has poor oral absorption and is used for the treatment of oral and vaginal candidosis.[1,12,19,24] Miconazole was also discovered in 1969 and also has poor oral bioavailability. An intravenous preparation was marketed but this had suboptimal efficacy and it is now rarely used.[1] However, miconazole is a useful topical drug for the treatment of superficial mycoses.[1,12,13,19,24]

Ketoconazole

Ketoconazole was discovered in 1978, and has good oral absorption, a broad spectrum of activity and low toxicity, although it may be hepatotoxic and does produce endocrine abnormalities by suppression of testosterone and ACTH-stimulated cortisol synthesis.[1,13] There is no intravenous preparation. Oral ketoconazole is effective in patients with candidosis, coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis and cuta-

neous dermatophyte infections. Ketoconazole is highly protein bound, has poor CNS penetration and is not suitable for treating CNS infections.[1,13] It has been replaced by newer azoles for the treatment of many of these fungal infections.[1,2,12,13,19,24]

Fluconazole

Fluconazole was formulated in 1981. It is a novel bistriazole, is metabolically stable and water soluble and has low lipophilicity and plasma protein binding. It is active by both oral and intravenous routes which have identical pharmacokinetics, i.e. once-daily dosing, high blood levels and rapid equilibration of drug in the body with good tissue distribution, including penetration into the cerebrospinal fluid. Fluconazole is well tolerated and has a very low incidence of side effects and a broad spectrum of antifungal activity, except against *Aspergillus* spp.

Fluconazole is one of the most effective agents for the treatment of oropharyngeal and oesophageal candidosis, especially in patients with AIDS or cancer, and is extremely effective for the treatment of vaginal candidosis.[1,2,12,13,24] It is also effective in peritonitis or disseminated candidosis (including in neutropenic patients), and in hepatosplenic candidosis.[1,2,12,13,43,44] Fluconazole is as effective as amphotericin B in non-neutropenic patients with candidaemia[1,2,12,13,24,43,45] and is the preferred treatment of funguria and focal fungal urinary tract infections.[45] Long-term oral fluconazole has also been used in patients with candida endocarditis to prevent relapse after initial therapy with amphotericin B.[46] Fluconazole has been used successfully for pulmonary or disseminated cryptococcosis and for acute cryptococcal meningitis, particularly in AIDS patients.[1,2,13,47] Recent studies showed that amphotericin B (with or without flucytosine) for at least the first 2 weeks, followed by an 8 week consolidation course with fluconazole or itraconazole, had excellent outcomes.[2,48] Fluconazole is the current drug of choice for life-long maintenance therapy of cryptococcosis,[1,2,12,13,24] and low-dose fluconazole, given 200 mg three times weekly to HIV-infected patients with <100 CD4 cells, was effective as primary prophylaxis for cryptococcal infections.[49]

Fluconazole has emerged as the drug of choice for coccidioidal meningitis,[1,2,50] although it is no more effective than other azoles for disseminated non-meningeal coccidioidomycosis.[1,2,24] It is not as effective as other azoles for the treatment of blastomycosis, histoplasmosis or sporotrichosis.[45,51,52] Fluconazole is effective as prophylaxis for fungal infections in neutropenic patients, and in patients undergoing bone marrow transplantation,[1,12,53] and weekly fluconazole (200 mg orally) is effective in preventing oropharyngeal and vaginal candidosis in HIV-infected women.[54]

Itraconazole

Itraconazole, discovered in 1986, is another triazole antifungal agent with broad-spectrum antifungal activity, including activity against *Aspergillus* spp. It is very insoluble, is only available in oral form and may be given once daily. However, higher does (not to exceed a total daily dose of 400 mg) may be required in serious infections and should be given in two divided doses each day. Since its bioavailability after oral administration may be erratic, maximal absorption is optimal when itraconazole is given with meals.[1,12,13,24] Absorption of itraconazole is reduced in patients with acute leukaemia and AIDS and concentrations of itraconazole in cerebrospinal fluid, the eye and saliva are negligible.[1,12] Itraconazole has been useful in the treatment of non-meningeal, non-life-threatening pulmonary and extrapulmonary blastomycosis and histoplasmosis, including chronic cavitary pulmonary disease and disseminated non-meningeal histoplasmosis, and in pulmonary, osseous/articular and lymphocutaneous sporotrichosis in non-immunosuppressed patients.

Itraconazole has established efficacy as primary treatment and maintenance of mild-to-moderate, non-meningeal histoplasmosis in HIV-infected patients and for prevention of relapse in AIDS patients with disseminated histoplasmosis.[1,2,13,45,55] Amphotericin B remains the treatment of choice for CNS/meningeal and severe disseminated sporotrichosis[1,45,55] and for meningeal and life-threatening disseminated blastomycosis and histoplasmosis, as well as for histoplasma endocarditis.[1,13,45,55] Less well defined studies suggest that itraconazole may have some efficacy in aspergillosis, candidosis, chromomycosis, coccidioidomycosis and paracoccidioidomycosis.[1,13,24,55] Itraconazole is not as effective as fluconazole in acute cryptococcal infection or as maintenance therapy for cryptococcal meningitis in AIDS patients, and should be considered as second-line therapy for patients with cryptococcosis.[1,2] Side effects, though infrequent, are more common than those observed with fluconazole. Prolonged oral absorption, with slow attainment of steady-state drug levels, and the lack of an intravenous formulation are impediments to itraconazole treatment.[1]

Investigational azoles

A number of new azoles are in various stages of development, including: voriconazole (UK-109-496; Pfizer); Sch-56592 (Schering); BMS-207147/ER-30346 (Bristol–Myers Squibb/Eisai); TAK-187 (Takeda); UR-9746, UR-9751 and UR-9825 (Uriach); T-8581 (Toyama); SYN-2835, SYN-2869, SYN-2903 and SYN-2921 (SYNPhar/Taiho); and SSY-726 (SS Pharm. Yoshitomi).[1,2,56–67] Of these, voriconazole is furthest along in clinical development. It has a chemical structure similar to fluconazole and has broad antifungal activity including in-vitro and in-vivo activity against *Aspergillus* spp.[1,2,56,57] Voriconazole has both oral and intravenous formulations, is widely distributed into body tissues including brain and cerebrospinal fluid, is 60% protein bound and has a low incidence of adverse events. Phase III clinical trials are nearly completed.

SCH-56592 is a potent antifungal triazole with excellent in-vitro activity against *Candida* spp., *Aspergillus* spp. and zygomycetes and potent efficacy in animal models of pulmonary blastomycocis, cerebral cryptococcosis, disseminated histoplasmosis, systemic coccidioidomycosis and systemic candidosis.[2] Clinical studies of efficacy, pharmacokinetics and toxicology have not been published.
BMS-207147 (ER-30346) is a very potent antifungal triazole with excellent in-vitro and in-vivo activity against *Candida* spp., *C. neoformans*, *Aspergillus fumigatus*, *Trichosporon beigelli* and *P. boydii*.[2,59–61] BMS-207147 was extremely potent (comparable with conventional amphotericin B) in an experimental model of invasive aspergillosis.[59] Clinical studies are planned.

Echinocandins

The echinocandins are cyclic lipopeptide fungicidal agents. They act by preventing cell wall synthesis by non-competitive inhibition of 1,3-β-D-glucan synthase, an enzyme which is absent in mammalian cells.[1,2,7,14] This inhibition is highly specific and brief exposure to these drugs leads to cell death.[1,14] The main limitation of the echinocandins is that they lack activity against cryptococci.

LY 303366

The echinocandin compound, LY 303366, is nearest to clinical development. It has excellent activity against *Candida* and *Aspergillus* spp. *in vitro* and in animal models.[1,14,68,69] However, in an experimental model of invasive aspergillosis, although LY 303366 improved survival and reduced the level of aspergillus antigenaemia, it did not sterilize organ tissues (unpublished observations). In clinical studies, LY 303366 is well tolerated and has linear kinetics and a long plasma half-life (30–40 h) so that once-daily dosing is anticipated.

Pneumocandins

The pneumocandins are echinocandin analogues (one of the classes of echinocandin lipopeptides). They are cyclic hexapeptides which inhibit 1,3-β-D-glucan synthase which synthesizes a critical structural cell wall component.[1,2,14,70–72] They were called pneumocandins because they possess activity against *Pneumocystis carinii*. They also have activity against *Candida* and *Aspergillus* spp.[1,70] Like other analogues of echinocandins, the pneumocandins lack activity against cryptococci.

MK-0991 (L-743872)

A few pneumocandin compounds have been developed but only MK-0991 (L-743872) has undergone substantial investigation.[1,71–75] It has excellent efficacy in animal models of invasive aspergillosis, candidosis and histoplasmosis.[1,71,72,74]

Pradimicins and benanomicins

The pradimicins and benanomicins are fungicidal compounds. They appear to bind, in a calcium-dependent manner, to cell wall mannoproteins and this causes osmotic lysis and leakage of intracellular contents, particularly potassium, ultimately leading to cell death. Calcium-dependent binding to mammalian cells has not been observed with this class of antifungal agents.[2] The pradimicins–benanomicins are fungicidal against a wide variety of fungi, including isolates that are resistant to other antifungal agents.[1,2,7]

Investigational compounds

BMS-181184 was shown to be effective, though less active than conventional amphotericin B, in animal models of aspergillosis, candidosis and cryptococcosis,[1,2,7,76,77] but clinical investigation with BMS-181184 has been discontinued because of hepatotoxicity in human volunteers.[2] Several other water-soluble compounds are in very early development.[1,2]

Nikkomycins

The nikkomycins are competitive inhibitors of fungal chitin synthase enzymes which are necessary for fungal cell wall synthesis. Chitin is a linear polymer of β-(1,4)-linked *N*-acetylglucosamine residues and is synthesized on the cytoplasmic surface of the plasma membrane.[1,2,7] Chitin synthase catalyses the polymerization of *N*-acetylglucosamine in the formation of chitin.[1,2,7]

Investigational compounds

Nikkomycin Z (SP-920704) is effective *in vitro* and *in vivo* against the chitinous, dimorphic fungi *C. immitis* and *B. dermatitidis*, but only modestly active *in vitro* against *C. albicans*, *C. neoformans* and *H. capsulatum*.[1,2] Synergic activity *in vitro* was observed when nikkomycin Z was combined with either fluconazole or itraconazole, and tested against strains of *Candida* spp., *C. neoformans* and *A. fumigatus*, and *in vivo* against *H. capsulatum*.[78–80] Even though there is the potential to simultaneously inhibit two separate antifungal targets when nikkomycins are combined with azoles, their clinical utility remains to be determined.[1]

Very recently, a new synthetic antifungal agent, L-lysyl-L-norvalyl-N^3-(4-methoxylfumaroyl)-L-2,3-diaminopropanoic acid (Lys-Nva-FMDP), which acts as an inhibitor of glucose-6-phosphate synthase (an enzyme which catalyses the first step in chitin biosynthesis), has

been shown to inhibit growth of *H. capsulatum in vitro* and *in vivo*.[81] Although Lys-Nva-FMDP appears to be non-toxic for mice, additional studies are necessary to determine its clinical usefulness.

Recombinant human chitinase was recently produced. It was found to have efficacy in animal models of candidosis and aspergillosis, but was found to have significantly better activity when combined with conventional amphotericin B.[82]

Allylamines and thiocarbamates

The allylamines and thiocarbamates are synthetic fungicidal agents that are reversible, non-competitive inhibitors of squalene epoxidase, an enzyme which, together with squalene cyclase, converts squalene to lanosterol. In fungal cells, if squalene is not converted to lanosterol, the conversion of lanosterol to ergosterol is prevented. The resulting ergosterol depletion affects fungal cell membrane structure and function.[1,2,7] There are two allylamine antifungal agents, naftifine and terbinafine, and one thiocarbamate, talnaftate. Naftifine is a topical preparation whereas terbinafine (Lamisil; SF86-327, Sandoz Pharmaceuticals) is an oral systemic agent. The allylamine, naftifine, is considered an effective topical agent for treatment of dermatophyte infections of the skin.[1,2]

Terbinafine

Terbinafine has good in-vitro activity against *Aspergillus* spp., *Fusarium* spp. and other filamentous fungi, but variable activity against yeasts.[2,83,84] It has not been very effective in animal models of invasive aspergillosis, systemic sporotrichosis, systemic candidosis or pulmonary cryptococcosis. However, terbinafine has been shown to be effective *in vitro* against some strains of *Aspergillus* spp., *Candida* spp., including triazole-resistant strains, and *P. boydii*, when combined with azoles or amphotericin B,[1,83–86] and in an animal model of aspergillosis when combined with amphotericin B.[87] Terbinafine has been used in a Phase II/III study in patients with cutaneous sporotrichosis with good results.[88] The ultimate role of allylamines and thiocarbamates in the treatment of invasive fungal infections remains to be determined.

Sordarins

The sordarins are a new class of potential antifungal agents. They inhibit protein synthesis in pathogenic fungi: the primary target for sordarin activity has been identified recently as elongation factor 2.[89]

Investigational compounds

A number of new sordarins are being evaluated, including GM-191519, GM-193663, GM-211676, GM-222712, GM-237354 and GR-135402.[90–98] Some of these compounds have in-vitro activity against *Candida* spp., *Apergillus* spp., *C. neoformans*, *P. carinii* and some filamentous fungi.[89–94,97,98] A synergic or additive effect was observed when GM-222712 or GM-237354 was combined with amphotericin B, itraconazole or voriconazole against *Aspergillus* spp. or *Scedosporium apiospermum*.[91] These preliminary observations suggest further studies are warranted.

Cationic peptides

Cationic peptides, both naturally occurring and synthetic derivatives, bind to ergosterol and cholesterol in fungal cell membranes, ultimately leading to cell lysis.[2,99–102] These peptides have antifungal activity against *Aspergillus* spp., *Candida* spp., *C. neoformans* and *Fusarium* spp.[99–102]

Naturally occurring cationic peptides include cecropins, dermaseptins, indolicin, histatins, bactericidal permeability-increasing factor (BPI), lactoferrin and defensins.[2,99–101] The synthetic cationic peptide dolastatin 10, which targets intracellular tubulin and inhibits microtubule assembly and tubulin-dependent GTP binding, has potent fungicidal activity against *C. neoformans*.[102] Future investigations will determine whether cationic peptides have clinical applicability.

Other antifungal targets

The search for new antifungal agents has been expanded as progress in molecular biology has led to a better understanding of important and essential pathways in fungal cell growth and multiplication. A number of new compounds, some with unidentified mechanisms of action, are under study.[1,2] One group includes dication-substituted carbazoles, furans and benzimidazoles, which are aromatic dicationic compounds with antimicrobial activity. Some are quite active *in vitro* against *Candida* spp. (including azole-resistant strains), *C. neoformans*, *A. fumigatus* and *Fusarium* spp.[103] Carbendazim, a benzimidazole derivative, was used as an agricultural fungicide but recently was shown to cure experimental histoplasmosis.[104] Glycyrrhizin, an extract from liquorice roots, has been shown to have antifungal activity against *C. albicans* in thermally injured mice.[105] Recently, BAY 10-8888, a cyclic β-amino acid related to cispentacin was observed to have potent anticandida activity both *in vitro* and in an experimental model of systemic candidosis.[106] This compound has a dual mode of action: it is actively accumulated by amino acid permeases and it is a low-affinity inhibitor of isoleucyl-tRNA synthetase, disrupting protein biosynthesis and cell growth.[106]

The discovery of new molecular targets in both yeasts and filamentous fungi that will render these organisms

susceptible to novel antifungal drugs is likely to continue in view of the major challenge by systemic fungal infections in clinical medicine today.

Also, we need to learn more about combination antifungal therapy, e.g. about the effects of sequential blockade at two or more sites, and about the combination of antifungal agents with cytokines in an attempt to augment the inflammatory and immune responses of patients.

This overview of new antifungal drug development reflects the increased interest in this field of infectious diseases and demonstrates that, although some progress has been made, further efforts are necessary to develop more promising agents against invasive fungal disease.

Treatment guidelines

Although new antifungal agents are being developed, therapeutic guidelines are suggested in the Table with the realization that these guidelines are likely to be adapted, based on new clinical investigation as well as the preferences of individuals.

References

1. Andriole, V. T. (1998). Current and future therapy of invasive fungal infections. In *Current Clinical Topics in Infectious Diseases*,

Table. Treatment guidelines (adapted from references 1, 13, 24 and 55)

Disease	Therapy
Candidosis	
candidaemia	amphotericin B or fluconazole
acute disseminated	amphotericin B or fluconazole
chronic disseminated (hepatosplenic)	fluconazole
Cryptococcosis	
pulmonary	amphotericin or fluconazole
disseminated	amphotericin or fluconazole
CNS/meningitis	amphotericin B ± 5-FC or fluconazole
maintenance therapy (AIDS)	fluconazole
Aspergillosis	standard or liposomal amphotericin B (itraconazle)[a]
Coccidioidomycosis	
mild/moderate	
pulmonary	fluconazole
disseminated	fluconazole
meningeal	fluconazole
severe	amphotericin or fluconazole
Blastomycosis	
pulmonary	itraconazole
extrapulmonary	itraconazole
severe acute	amphotericin B
CNS/meningitis	amphotericin B
Sporotrichosis	
lymphocutaneous	intraconazole
bone and joint	itraconazole
pulmonary	itraconazole
CNS/meningitis	amphotericin B
severe disseminated	amphotericin B
Trichosporonosis	fluconazole ± amphotericin B or amphoteicin B ± 5-FC
Fusariosis	standard [b] or liposomal amphotericin B
Zygomycosis (*Mucor* spp.)	amphotericin B
Paracoccidioidomycosis	
mild/moderate	intraconazole
severe	amphotericin B
Pseudoallescheriosis	ketoconazole or itraconazole (miconazole)[a]

[a]Second-line agent.
[b]Recovery dependent upon resolution of neutropenia.

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