Current and Emerging Antifungal Agents in Japan

Hideyo Yamaguchi

Teikyo University Institute of Medical Mycology, Tokyo, Japan

Currently available antifungal agents for the treatment of systemic fungal infections in Japan are smaller in number than those in the United States and Europe and probably in Korea. Therefore, the development of novel antifungal drugs for clinical use, including new formulations of approved agents, with advantages over and/or complimentary to existing agents is particularly needed in Japan. In this review, I have described historical perspectives of existing systemic antifungal agents and provided a brief overview of the current status of clinical development of several different categories of new drugs as follows: (1) liposomal amphotericin B; (2) itraconazole-hydroxypropyl-β-cyclodextrin complexes; (3) phosphatyl fluconazole (phosfluconazole); (4) voriconazole; and (5) micafungin (FK463). At this moment, micafungin, a member of echinocandins attracts the greatest attention of Japanese medical mycologists because it has just been introduced into the clinic and has unique chemical and biological characteristics distinct from any other existing class of antifungal drugs. Micafungin, as well as other new drugs under clinical development, should constitute effective new options for the management of a variety of systemic fungal infections. **[Kor J Med Mycol 2003; 8(2): 35-42]**

Key Words: Antifungal agents, Amphotericin B lipid formulations, Itraconazole-hydroxypropyl-β-cyclodextrin complex, New generation antifungal triazoles, Echinocandins

During the last few decades, the incidence of deep-seated fungal infections has continued to increase in immunologically or physiologically compromised patients[1]. In particular, invasive infections caused by *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans* and other opportunistic fungi are now becoming a major threat to many hospitalized patients, especially those compromised by severe underlying diseases, such as leukemia and other malignancies, who are often further compromised by increasing use of antineoplastic drugs, immunosuppressive agents, bone marrow transplantation and other modern aggressive medical cares.

In those patients who become highly compromised, invasive mycoses are among the most frequent causes of formidable morbidity and mortality. Those fungal infections are difficult to diagnose during lifetime, particularly at the early stage of infection and, when diagnosed, often refractory to treatment with existing antifungal therapy. Our current therapeutic armamentarium against invasive mycoses is limited to a paucity of compounds that are often ineffective and/or toxic. There can be, therefore, no doubt that the development of new antifungal agents, which should be ideally be superior or at least complimentary to existing therapies. This paper is a review of the current and developing antifungal drugs for the treatment of deep-seated mycoses, particularly those in Japan (Table 1).

The field of antifungal chemotherapy is pre-

†Correspondence author: Hideyo Yamaguchi, Teikyo University Institute of Medical Mycology, 359 Otsuka, Hachioji-shi, Tokyo 192-0395, Japan
Phone: +81-426-76-3003, Fax: +81-426-74-9190
e-mail: timm@main.teikyo-u.ac.jp

*This is the revised article of the lecture presented in the 4th Symposium of the Korean Society for Medical Mycology Society held on October 26, 2001 in Seoul.

Table 1. Drugs approved for treatment of systemic fungal diseases in Japan (As of December 2002)

Class	Generic name	Brand name	Available form	Year initially approved
Polyene	Amphotericin B	Fungizone®	Intravenous	1962
Pyrimidine	Flucytosine	Ancotil®	Oral tablet	1979
Azole (imidazole)	Miconazole	Florid F®	Intravenous	1986
Azole (triazole)	Fluconazole	Diflucan®	Intravenous, oral capsule	1989
Azole (triazole)	Itraconazole	Itrizole®	Oral capsule	1993
Candin	Micafungin	Funguard®	Intravenous	2002

sently rapidly moving. It began in 1903, with the successful use of a saturated solution of potassium iodide (SSKI) in therapy of lymphocutaneous sporotrichosis. Unfortunately, progress for 50 years, when in 1951 Brown and Hazen introduced nystatin (then called fungicidin), the first of the useful polyene macrolides. Amphotericin B was first isolated and described by Gold et al. in 1956[2]. Four and 11 years later, it was clinically introduced as a deoxycholate complex preparation for parenteral administration in the United States and Japan, respectively. Since then, only four antifungal drugs of two or three different classes have been successfully developed for medical use in the last 30 years of the 20th Century in Japan: (i) flucytosine (pyrimidine class); (ii) miconazole (imidazole or azole class); and (iii) fluconazole and itraconazole (triazole or azole class) as listed in Table 1. However, even after the advent of these newer drugs, amphotericin B is still the historical and "gold" standard of systemic antifungals for the treatment of severe invasive mycoses. One of main reasons for such a slow progress is that, like mammalian (human) cells, fungi are enkaryotic, and thus, there may be very few selective targets for antifungal action.

The decades of 1970s saw the addition of a fluorinated pyrimidine analog flucytosine. It has a relatively narrow antifungal spectrum limited to *Candida* species and *Cryptococcus neoformans* and is usually used with amphotericin B to prevent emergence of resistance to flucytosine and augment the activity of amphotericin B[3].

With this exception, there was little further progress Until the 1970s when a series of imidazole antifungals was developed. These drugs had broad-spectrum activity against dermatophytes, *Candida* and other fungal infections. A number of these drugs came into use as topical agents and are still used today. Miconazole was the first imidazole derivative of this series of antifungal agents for systemic use and approved for the treatment of deep-seated mycoses in 1986 in Japan. Although response rates with miconazole in some-deep mycoses were favorable, the need to give the drug intravenously and its short half-life, requiring multiple administrations per day, made it logistically difficult to give long courses of therapy. The inability to eradicate or suppress residual disease undoubtedly contribute to the unsatisfactory relapse rate.

In a few years, the second systemic imidazole ketoconazole followed as the first relatively non-toxic orally administered antifungal drug with a broad-spectrum of activity[4]. Ketoconazole is characterized largely by the modification of azole drugs, bringing agents which can be given orally and have increasing potency, decreasing toxicity, and broad-spectrum of activity. The following azole era is actually opened by ketoconazole. Unfortunately, clinical development of ketoconazole failed and this drug did not come into medical use in Japan because of the potential of toxicity.

Significant advances in antifungal therapy have occurred in the last two decades. Most of these advances have been tied to the introduction of the two oral triazoles, fluconazole and itraconazole. Their clinical usefulness for the treatment of many deep-seated mycoses has been dramatic. Fluconazole is now routinely used for systemic candidiasis, and occasionally for cryptococcosis and other yeastlike fungal infections, became of its several advantages as follows; (i) both oral and intravenous preparations available; (ii) low toxicity; and (iii) favorable pharmacokinetics[4,5]. On the other hand, itraconazole is generally more potent than ketoconazole or fluconazole, has a broader spectrum covering almost all pathogenic yeastlike and filamentous fungi and much better tolerated than ketoconazole[4]. Although itraconazole is mainly indicated for the treatment of subacute to chronic infections with the endemic pathogenic fungi, such as coccidioidomycosis and histoplasmosis, it is also useful to treat infections with *Aspergillus* spp. and other opportunistic filamentous fungi[4,6].

Such a rapid expansion of our antifungal armamentarium is timely because deep-seated mycoses are on the rise in the 1990s. This is related to more aggressive immunosuppression for a variety of conditions, more intensive antineoplastic chemotherapy and enhanced survival of patients in the immunosuppressed state, increased use of transplantation (bone marrow, solid organs), vascular catheters, parenteral nutrition and hemodialysis, use of more powerful and broad-spectrum antibacterials, and the modern plague of AIDS.

However, clinical usefulness of these triazoles is limited by drawbacks associated with their in sufficient efficacy in severely illed patients. Thus, in spite of introduction of the two triazoles, amphotericin B is continuing to have an important role for many fungal infections, particularly for those which are severe and life-threatening, irrespective of its relatively high toxicity. Currently amphotericin B alone or in conjunction with flucytosine has been considered as the first-line drug and fluconazole or itraconazole as the second-line drug for the management of most of acute and severe deep-seated mycoses due to *Candida* spp., *Aspergillus* spp., *Cr. neoformans*, zygomycetes, and several emerging fugal pathogens, such as *Trichosporon* spp., *Fusarium* spp. and *P. boydii*[7].

Considering the limitation in both number and usefulness of antifungal agents currently available to treat systemic fungal infections, there is un urgent need to discover and develop new antifungal drugs with advantages over and/or complimentary to existing drugs. For this purpose, the following five categories of new drugs have currently been the major target of study and development: (1) liposomal amphotericin B as a lipid formulation of amphotericin B; (2) itraconazole-hydroxypropyl-β-cyclodextrin complexes as a soluble preparation of itraconazole; (3) phosphatylfluconazole (phosfluconazole) as a prodrug of fluconazole; (4) voriconazole as a new generation triazole; and (5) micafungin (FK463) as a member of candins, a new class of antifungals.

Liposomal amphotericin B (Table 2). Although amphotericin B remains the "golden standard" for the treatment of many invasive mycoses, there is a need for less toxic alternatives Lipid formulations of amphotericin B was expected to meet this criterion and actually proved to be less nephrotoxic than conventional amphotericin B (Fungizone®) in many clinical studies, allowing the use of higher doses[8]. Currently, three commercial formulations are available in Europe and the United States: AmBisome® (liposomal amphotericin B); Abelcet® (amphotericin B lipid complex); and Amphocil® (amphotericin B colloidal dispersion). These three formulations differ significantly in their composition and pharmacokinetics and the rate of acute reactions associated with these formulations also differ considerably[8,9]. However, all of these formu-

Table 2. New formulations anad prodrug of approved compounds and their clinical development status in Japan (As of December, 2002)

Compound (Class)	Formulation or chemical modification	Form	Development status
Amphotericin B (Polyene)	Monolayered liposome [SM-26000[a)]]	IV	P-III
	Lipid complex	IV	– [b)]
	Colloidal dispersion	IV	– [b)]
Itraconazole (Triazole)	Hydroxypropyl-β-cyclodextrin oral solution [JK1211[a)]]	Oral	P-III
	Hydroxypropyl-β-cyclodextrin solution [ITR-Iv [a)]]	IV	P-III
Fluconazole (Triazole)	Phosphatyl fluconazole (Phosfluconazole) [UK-292, 663[a)]]	IV	Registered

[a)] Development code in Japan, [b)] not entered into clinical studies

lations appear to reduce the toxicity of the conventional amphotericin B; most importantly, nephrotoxicity has been diminished markedly. An important issue remains to be answered is what doses are necessary to achieve a clinical response equal to, or if possible better than, conventional amphotericin B[9]. So far as concerned with AmBisome®, recent clinical studies conducted in the United States demonstrated that this liposomal amphotericin B at dosages as high as 15 mg/kg/day is well tolerated and can provide effective therapy for aspergillosis and other filamentous fungal infections including fusariosis and zygomycosis[10]. At this time, the major drawback to the use of the lipid formulations of amphotericin B is the high acquisition cost. If the costs are decreased it is likely that these drugs will ultimately replace the conventional amphotericin B for the treatment of various fungal infections.

In Japan, none of these lipid formulations of amphotericin B is commercially available. Only a liposomal formulation equivalent to AmBisome® has been undergoing clinical trials.

Itraconazole-hydroxypropyl-β-cyclodextrin complex (Table 2). Itraconazole, available only as oral capsule, has been used successfully for many years for the treatment of superficial and subcutaneous fungal infections, as well as more serious endemic and opportunistic deep-seated mycoses. However, the absorption of itraconazole from the capsules is variable in patients, particularly immunocompromised patients with AIDS or bone marrow transplant, who have gastrointestinal abnormalities or reduced gastric acidity[11,12]. Moreover, patients with systemic fungal infections may be unable to tolerate solid-phase formulations, such as itraconazole capsule, and, even if they can, absorption may be reduced by low oral food intake, frequent vomiting or difficulty in swallowing the capsule[13].

Such limitations of the use of the capsule formulation for the management of systemic fungal infection in immunocompromised patients by the variable absorption of the drug prompted a development of new formulations of itraconazole with improved pharmacokinetics in patients with or at risk of systemic fungal infection. After intensive research to improve the absorption and bioavailability of itraconazole, two new formulations, containing the solubilizing excipient hydroxypropyl-β-cyclodextrin, an oral solution and IV formulation, have been developed[14]. It has been demonstrated that the itraconazole oral solution improved the absorption of the drug in not only healthy volunteers[15] but also various patient groups, including HIV-infected patients with or without AIDS[16,17], neutropenic patients with acute leukemia[18], bone marrow transplant recipients[19,20] and patients receiving omeprazole[21]. An IV formulation of itraconazole has also been introduced into the clinics in

Table 3. New generation triazoles and their clinical development status in Japan (As of December, 2002)

Compound	Form	Development status
Voriconazole [UK-109, 496[a)]]	Oral / IV	P-III (completed)
Posaconazole [SCH-56595[a)]]	Oral	P-I
Ravuconazole	Oral / IV	– [b)]

[a)] Development code in Japan, [b)] not entered into clinical studies

Table 4. Candins, a new class of anti-fungal agents, and their clinical development status in Japan and other countries (As of December, 2002)

Compound (Generic name)	Brand name	Form	Development Status in	
			Japan	Other countries
Micafungin [FK463[a)]]	Funguard®	IV	Launched	P-III, completed (US, EU)
Caspofungin	Cancidas®	IV	– [a)]	Launched (US)
Anidulafungin		IV	–	P-II, III (US)

[a)] Development code in Japan, [b)] not entered into clinical studies

the late 1990s in Europe and the United States. The favorable pharmacokinetics and safety of the IV formulation were confirmed by several studies in patients with advanced HIV infection or those in intensive care units[22]. The IV itraconazole formulation introduces more flexibility in the use of itraconazole and rapidly achieves high plasma drug concentrations when needed.

In Japan, both oral solution and IV formulation of itraconazole are under clinical trials and will be finished in 2003.

Phosfluconazole (Table 2). Parenteral fluconazole therapy has widely been indicated for the treatment of various clinical forms of candidiasis and cryptococcosis in severely ill patients by the intravenous infusion with an appropriate amount of infusion liquid usually at a drug concentration of 2 mg/ml. However, in some group of such patients the amount of infusion liquid to be given should be minimized to keep the general condition stable. Phosphatyl fluconazole (phosfluconazole) is a prodrug of fluconazole developed to administer sufficient doses of fluconazole by the intravenous bolus injection.

After administration into the human body, phosfluconazole is rapidly hydrolyzed by phosphatase to fluconazole and phosphate. As the water-solubility of phosfluconazole (>100 mg/ml) is much higher than fluconazole (4 mg/ml), fluconazole can be injected in a smaller dosing volume when phosfluconazole is used. Actually, the IV formulation of phosfluconazole for an intravenous bolus injection (100 mg/ml) has been developed. This formulation also has the merit of easiness of administration, storage and transportation.

Curiously, Japan is the sole country in the world where phosfluconazole has been clinically studied. In this country, the clinical trials of phosfluconazole IV formulation was completed in 2001 and it will be licensed imminently.

Voriconazole (Table 3). Three new generation triazole antifungal agents with brood-spectrum − voriconazole, posaconazole and ravuconazole − have recently been undergoing clinical trials in the United States and Europe. These drugs have an extended spectrum for various fungi causing systemic fungal infections. Among the three new triazoles only voriconazole is now licensed in the United

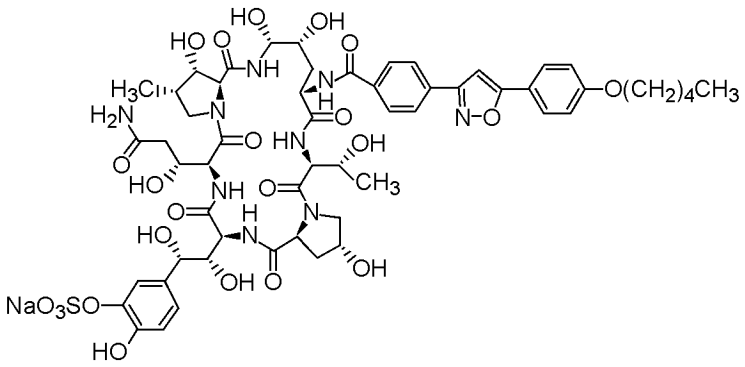

Fig. 1. Structure of micafungin (FK463).

States in both oral and parenteral formulations, primarily for the treatment of invasive aspergillosis and other systemic fungal infections.

Voriconazole is active against a wide range of pathogenic fungi including both fluconazole-susceptible and-resistant *Candida*, *Cryptococcus neoformans*, *Aspergillus*, *Fusarium*, *Pseudallescheria* and dimorphic fungi *in vitro*[23~25]. Recent clinical studies showed that voriconazole is clinically effective in mucosal candidiasis and invasive aspergillosis[26]. More recent studies presented at the 2001 and 2002 Interscience Conference on Antimicrobial Agents and Chemotherapy, also suggest voriconazole to be the drug of choice for the management of *Aspergillus* infections.

Micafungin (Table 4). The need for new antifungal agents with novel mechanisms of action to treat serious fungal infections continues despite the introduction of more effective and/or less toxic reformulations of amphotericin B and existing triazole agents as well as new generation triazoles as described above. The fungal cell wall is a unique structure that permits selective targeting distinct from that of mammalian cells. For this reason, out of the various antifungal compounds, the echinocandin-related compounds that interfere with the normal cell wall formation by inhibiting the synthesis of (1,3)β-D-glucan, an essential cell wall homopolysaccharide found in many pathogenic fungi, have been the most intensively developed in the United States and Japan. Compounds with this fungus-specific target referred to as echinocandins or candins have several attractive features: (i) absence of the target molecule (1,3)β-D-glucan synthase in mammalian cells; (ii) lack of target-associated toxicity; (iii) potential for fungicidal activity; and (iv) activity against species or strains with intrinsic or acquired resistance mechanisurs for existing antifungal agents, particularly triazoles. Candins are also referred to as lipopeptides because they are cyclic hexapeptides containing fatty acyl or other lipophilic acid chains. Three semiynthetic analogues of naturally occurring lipopeptides were considered as promising candidates for parenteral use in the treatment of systemic candidiasis and aspergillosis; they are MK 0991 (caspofungin), VER-002 (anidulafungin) and FK463 (micafungin). Clinical trials for the former two drugs were started in the United States and those for the latter in Japan in the late 1990's.

Micafungin is a lipopeptide compound synthesized by chemical modification of a product from the environmental mold *Coleophoma empedri* (Fig. 1)[27]. It has a markedly potent *in vitro* activity against *Candida* (including two azole-insusceptible species *C. glabrata* and *C. krusei*, and azole-resistant strains of *C. albicans*) and *Aspergillus*, but virtually no activity against *Cryptococcus neo-*

formans, *Trichosporon*, *Fusarium* and zygomycetes[27~29]. Caspofungin and anidulafungin are considered to be comparable with regard to spectrum of activity, although no direct comparison has been made to date.

In the phase 1 clinical study with the parenteral formulation of micafungin (sodium salt), it was shown to be well tolerated in intravenous doses ranging from 2.5 to 150 mg/day in healthy male volunteers. Based on these results, the multicenter, open-label clinical trial was conducted from May 1998 to November 2001 to evaluate the efficacy and safety of micafungin in patients with systemic candidiasis and aspergillosis. Patients were treated once daily with micafungin by the intravenous infusion in dose of 12.5 to 150 mg for up to 57 days. The results showed that the overall clinical response rates were 60.0% in aspergillosis and 78.6% in candidiasis, and that the incidence of adverse events related to micafungin was 31.3% without any dose-related occurrence[30]. Micafungin in daily doses of 50 to 300 mg was approved for the treatment of systemic aspergillosis and candidiasis in 2002 in Japan. In the same year, caspofungin was launched for clinical use in the United States.

It is true that our current therapeutic armamentarium against invasive fungal infections is steadily improving. However, there is a persisting need for the discovery and development of new antifungal agents. It is my hope that both Korean and Japanese medical mycologists could collaborate and jointly conduct the preclinical investigations as well as the clinical trials of promising candidates useful for the prophylaxis and treatment of intractable fungal infections.

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