Clinical efficacy of new antifungal agents

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Several new options are now available for treating serious fungal infections. All three echinocandin agents currently available have been shown in randomized, blinded clinical trials to be efficacious in treating candidemia and invasive candidiasis. By contrast, the demonstrated efficacy of the echinocandins for the treatment of invasive aspergillosis has been based on historically controlled salvage treatment trials in patients failing or intolerant of other therapies. The new triazole agents, voriconazole and posaconazole, have a broad spectrum of antifungal activity. Voriconazole has become the agent of choice for invasive aspergillosis. On the basis of compassionate treatment data, posaconazole appears to be effective for treatment of zygomycosis. These agents have also been shown to be effective in the treatment of non-*Aspergillus* mould infections, several of the endemic mycoses and serious *Candida* infections.

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Introduction

The increasing burden of fungal infections, especially in markedly immunosuppressed patients and patients in the intensive care unit with multiple diseases, has created an urgent need for new antifungal agents. The past few years have seen the introduction of several new agents and the anticipated approval of yet one more this year. The new agents are members of two major drug classes, the azoles and the echinocandins. This review focuses on new agents in these two classes and the studies with these agents from the past few years, with the most emphasis placed on studies from the last two years. Because several of these agents have recently been approved, or are yet to be approved, the next five years will better define their role in the antifungal armamentarium.

Echinocandin agents

Candida infections

The echinocandins (for a summary see Table 1) are cidal agents for all *Candida* species and their greatest use will probably be in the treatment of candidemia and invasive candidiasis. All three echinocandins are effective in the treatment of candidal esophagitis. However, this disease — previously commonly seen in AIDS (acquired immune deficiency syndrome) patients — is now rarely seen in the United States and Europe. More importantly, all three agents have proven efficacy in treating candidemia and invasive candidiasis [1–3]. The most experience has been gained with caspofungin following the report in 2002 of its efficacy for candidiasis [1]. With reports of the isolation of greater numbers of fluconazole-resistant *Candida* species, especially *Candida glabrata*, physicians are increasingly using caspofungin as a first-line agent for the treatment of candidemia and invasive *Candida* infections. Experience with the other echinocandins is limited because FDA (Food and Drug Administration) approval was only recently granted for anidulafungin and is still pending for micafungin for this indication.

A multi-center randomized blinded treatment trial that compared anidulafungin with fluconazole for the treatment of candidemia and invasive candidiasis has been reported, but not yet published [2]. These data not only showed the efficacy of anidulafungin for treating candidemia but also showed for the first time that an echinocandin was superior to an azole. The response rates at the end of treatment were 76% for anidulafungin and 60% for fluconazole, $p = .01$, and at two weeks post-treatment were 65% and 49%, respectively, $p = .01$.

Preliminary results of a multi-center, randomized, blinded treatment trial that compared micafungin with liposomal amphotericin B for candidemia and invasive candidiasis treatment have been reported but not yet published [3]. Micafungin appeared to be equally efficacious as liposomal amphotericin B with success rates of 74% and 70%, respectively, at the end of therapy.

The potential for resistance of *Candida* species to the echinocandins has been realized since their introduction into general use. Resistance has now been described in *Candida parapsilosis*, *C. glabrata*, and *Candida albicans* isolates [4–6]. Increasing resistance over time in one strain was documented for each of these species. The *C. glabrata* strain became resistant to amphotericin B as well as caspofungin [6], and the *C. parapsilosis* strain developed resistance to both echinocandins (caspofungin and

Table 1

Clinical uses of echinocandin antifungal agents.

Fungal Infection	Comments	References
Caspofungin		
Candidemia and invasive candidiasis	As efficacious as AmB (RCT)	[1]
Candida esophagitis	As efficacious as fluconazole (RCT)	
Aspergillosis	Efficacious as salvage therapy	
	Use as second-line agent (salvage trial)	[7]
Empiric treatment of fever in neutropenic patients	Shown to be effective (RCT)	[10]
Micafungin		
Candidemia and invasive candidiasis	As efficacious as L-AmB	[3]
Candida esophagitis	As efficacious as fluconazole (RCT)	
Aspergillosis	Appears to be efficacious, but most patients on several drugs (salvage trial)	[9]
Prophylaxis of patients at high risk for invasive fungal infection	Effective in stem cell transplant patients prior to engraftment (RCT)	[11]
Anidulafungin		
Candidemia and invasive candidiasis	More effective than fluconazole (RCT)	[2]
Candida esophagitis	As efficacious as fluconazole (RCT)	
Aspergillosis	No trials reported	

AmB, amphotericin B; L-AmB, liposomal amphotericin B; RCT, randomized controlled trial.

micafungin) and azoles (fluconazole and voriconazole) [4]. Whether these reports are a harbinger of problems to come, or whether they will remain isolated events will be known only as use of these agents increases over the next several years.

Aspergillus infections

The echinocandins are best described as static for species of *Aspergillus*. They destroy the cell wall at the growing hyphal tips and branch points along the hyphae. Caspofungin is the only echinocandin that has received FDA approval for the treatment of invasive aspergillosis. Approval was based on data from a salvage study, in which patients were enrolled if their aspergillosis was refractory to other therapy or they were intolerant of other therapy [7]. For the 83 patients who were treated on this protocol, most of whom had prior treatment with amphotericin B, the overall complete and partial response rate was 45%, a result similar to that shown in historical controls. Similar results using micafungin for salvage therapy of invasive aspergillosis have been reported [8••]. In one study, 36% of patients were deemed to have a partial or a complete response [9]. These data are hard to interpret because most patients in this compassionate trial received other antifungal agents in combination with micafungin [9]. There have been no prospective, comparative trials of any echinocandin as primary therapy for invasive aspergillosis. For this reason, the echinocandins are generally used as secondary therapy after an initial response to voriconazole or amphotericin B or in combination with these other agents.

Other indications

Other situations in which echinocandins have been shown to be efficacious include empiric treatment of fever in neutropenic patients and prophylaxis in stem cell transplant patients [10,11]. In a blinded trial that compared caspofungin with liposomal amphotericin B for empirical use in febrile neutropenic patients, it was shown that caspofungin was better tolerated, with many fewer side effects, was as efficacious as liposomal amphotericin B in preventing breakthrough fungal infections and was superior to liposomal amphotericin B in treating baseline fungal infections that were present at the time of enrollment [10].

In a blinded comparative trial that compared micafungin with fluconazole given for prophylaxis until engraftment occurred in stem cell transplant recipients, micafungin was shown to be more effective than fluconazole at preventing fungal infections; a successful outcome was noted in 80% of those receiving micafungin versus 73% in those receiving fluconazole, $p = .03$. There were fewer *Aspergillus* infections in the micafungin arm (one infection) than the fluconazole arm (seven infections) [11].

The echinocandins are not active against the endemic mycoses *in vitro*, and this has been borne out in limited studies in animal models. They should not be used to treat infections caused by *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis*.

Side effects

As a class, the echinocandins have proved to be extremely safe in comparison with the other classes of antifungal agents [8••]. Safety analyses have been reported in adults and children for anidulafungin [12,13] and micafungin [9,14], and just in adults for caspofungin [7,10]. The most common adverse effects reported with echinocandin use are infusion reactions that manifest as flushing, urticaria

and pruritus, rash, thrombophlebitis at the infusion site and elevations of the levels of liver enzymes.

Given what appears to be similar efficacy and safety among the echinocandins, the choice of agent will probably, and appropriately, be determined by costs to hospitals for each of these agents.

Triazole agents

Both of the new triazole agents (for a summary of the azole agents see Table 2) have broad-spectrum activity against many fungi. They are fungicidal for moulds and static for *Candida* and other yeasts [15,16••]. Voriconazole has been available for use since 2002, and posaconazole is available in Europe and will probably be available in the United States late in 2006. In comparison to the similar features among the echinocandins, there are major differences in pharmacokinetics, drug interactions and effectiveness against some moulds between these two triazoles.

Aspergillus infections

Voriconazole has become the drug of choice for the treatment of invasive aspergillosis. The change from amphotericin B to voriconazole for primary therapy of aspergillosis followed the publication of a large multinational randomized trial that compared amphotericin B with voriconazole in 277 patients with proven or probable invasive aspergillosis [17]. At week 12, complete or partial responses were noted in 53% of the voriconazole group and 32% of the amphotericin B group. Patient survival was 71% in the voriconazole group and 58% in the amphotericin B group, p = .02. These results showed voriconazole to be more effective than amphotericin B as initial therapy for patients with invasive aspergillosis. Subsequent reports have shown the effectiveness of voriconazole for central nervous system and osteoarticular aspergillosis [18,19]. Voriconazole is the agent of choice for the treatment of infections caused by *Aspergillus terreus*, an organism that has intrinsic resistance to amphotericin B and that is increasingly seen as a pathogen in immunocompromised hosts [20].

Posaconazole has not been studied in a controlled prospective treatment trial in patients who have aspergillosis, and there are few clinical reports of its efficacy because it is currently available only for compassionate use in individual patients. Preliminary results from an historically controlled study of salvage therapy for patients whose aspergillosis had failed to respond to standard therapy, showed that posaconazole was more efficacious (42% complete or partial response) compared with other agents (26% complete or partial response) [21].

Other mould infections

Both voriconazole and posaconazole have been used for refractory infections caused by *Scedosporium apiospermum* (the anamorph of *Pseudallescheria boydii*), *Fusarium* and other angioinvasive fungi [22,23•,24•]. Treatment of fusariosis has been especially problematic. Perfect *et al.* [22] reported a 45% response rate (complete and partial response plus stable disease) in 11 patients treated with voriconazole, and Raad [24•] noted a complete or partial response in 10 of 21 (48%) patients who were treated with posaconazole. Not unexpectedly, those patients whose

Table 2

Clinical uses of new azole antifungal agents.

Fungal Infection	Comments	References
Voriconazole		
Candidemia and invasive candidiasis	As efficacious as amphotericin B followed by fluconazole (RCT)	[32•]
Candida esophagitis	As efficacious as fluconazole (RCT)	[15]
Aspergillosis	Has become drug of choice (RCT)	[17]
Zygomycosis	Not effective	
Other moulds	Approved for *Scedosporium* and *Fusarium* infections (case reports and salvage trials)	[22,23•]
Endemic mycoses	Perhaps effective for coccidioidomycosis, blastomycosis and histoplasmosis (case reports)	[34–39]
Empiric treatment of fever in neutropenic patients	Commonly used for this indication although failed to gain FDA approval	[44]
Posaconazole		
Candidemia	No trials reported	
Oropharyngeal candidiasis	As efficacious as fluconazole (RCT)	[33]
Aspergillosis	Appears to be effective (salvage trial)	[21]
Zygomycosis	Appears to be effective (salvage trial)	[29,30••]
Other moulds	Appears to be effective for fusariosis (salvage trial)	[24•]
Endemic mycoses	Perhaps effective for coccidioidomycosis and histoplasmosis (case reports)	[41,42,43•]
Prophylaxis in patients at high risk for invasive fungal infection	Shown to be effective in patients with acute leukemia and in stem cell transplant recipients who have severe graft versus host disease (RCT)	[46,47]

RCT, randomized controlled trial.

neutrophil counts returned to normal levels had a 65% response rate compared with a 20% response rate in those patients who remained neutropenic. Results with both agents are comparable or slightly better than the response rate to lipid formulations of amphotericin B, which had been considered the treatment of choice before the advent of the new triazoles [25,26].

A major difference between posaconazole and voriconazole is that posaconazole has activity against the Zygomycetes, such as *Mucor* and *Rhizopus*, and voriconazole has no activity against this class of fungi. In fact, voriconazole use for prophylaxis in stem cell transplant units has been associated with the emergence of zygomycosis as a major pathogen in these units [27,28•]. Posaconazole is the first non-amphotericin B antifungal agent to prove effective for treating zygomycosis. Success rates of 60% have been reported in patients who had failed or were intolerant of standard therapy, predominantly lipid formulation amphotericin B, for zygomycosis [29,30••]. These response rates compare favorably with those noted over the years for amphotericin B and for those noted specifically with amphotericin B lipid complex [25,31••].

Candida infections

Many clinical trials and much anecdotal evidence have accumulated on the treatment of mould infections with the new triazoles, but these agents also have broad activity against all *Candida* species and have been shown efficacious for treating infections with these organisms. A large multi-center randomized trial compared a regimen of voriconazole alone with that of amphotericin B for the first four to seven days followed by fluconazole for treating candidemia [32•]. At the end of therapy, both regimens showed equivalent efficacy, 65% for the voriconazole arm and 71% for the amphotericin B and fluconazole arm. There are no randomized clinical trials that have reported on the use of posaconazole for candidemia or invasive candidiasis. There is one study showing equivalent efficacy of posaconazole when compared with fluconazole for treating oropharyngeal candidiasis in patients with AIDS [33].

Endemic mycoses

In vitro studies with voriconazole and posaconazole have shown activity of these agents against *H. capsulatum*, *B. dermatitidis* and *C. immitis*, and a few animal studies have verified efficacy *in vivo* [15,16••]. No clinical trials have been successfully carried out, and the data available are only small case series and individual case reports. Voriconazole treatment was reported to be successful for three solid organ transplant recipients who had histoplasmosis and who had intolerance to other azoles [34]. Several patients with central nervous system blastomycosis were reported to have been cured with the use of voriconazole [35,36]. Similar results were noted in two patients with meningitis caused by *C. immitis* and also in another patient with disseminated coccidioidomycosis [37–39]. Posaconazole has been reported to be effective for histoplasmosis in a small number of patients. Six of seven patients, four of whom had disseminated infection, and all of whom had failed or were intolerant of other therapy were successfully treated with posaconazole [40]. One of these seven patients, who had meningitis, was also later reported as having been successfully treated with posaconazole [41]. One other patient who had disseminated histoplasmosis was also successfully treated with posaconazole [42]. In a small series, Anstead *et al.* [43•] noted success in five of six patients who were treated with posaconazole for pulmonary or disseminated coccidioidomycosis refractory to therapy with other agents, and another patient with meningitis has been reported to have been successfully treated with the drug [41].

Other indications

Other uses of the new triazoles include empirical therapy for febrile neutropenic patients and prophylaxis in patients at high risk for invasive fungal infections [44,45]. In a preliminary report, posaconazole was shown to be superior to fluconazole or itraconazole for prophylaxis in patients who had acute leukemia or myelodysplastic syndrome and who were neutropenic [46]. Allogeneic stem cell recipients with severe graft versus host disease were afforded increased protection from invasive fungal infection when given prophylaxis with posaconazole when compared with that when given fluconazole [47]. An ongoing randomized blinded trial of voriconazole versus fluconazole for prophylaxis during the first 100 days post stem cell transplantation should help define the risks and benefits of using this extended spectrum triazole in this high-risk population.

Side effects

The extended spectrum triazoles are relatively safe agents, but clearly have more adverse effects than the echinocandins. Drug interactions are a major drawback to the use of voriconazole; hepatotoxicity, rash and visual aberrations are not uncommon, and in some patients will limit the use of the drug [15,17,32•,44]. The availability of both an intravenous formulation and a well-absorbed oral formulation is a distinct advantage for voriconazole. In the limited experience to date with posaconazole, the major adverse effects appear to be gastrointestinal, including diarrhea, nausea and vomiting, and rashes [16••,24•]. Posaconazole has fewer drug interactions than voriconazole although there are some drug–drug interactions. The absorption of posaconazole is problematic, requiring high-fat meals for maximum absorption [45]. The lack of an intravenous formulation of posaconazole will remain a major disadvantage when treating seriously ill patients.

Conclusions

The echinocandins and the new expanded spectrum triazoles offer clinicians effective and safe alternatives

to amphotericin B for the treatment of most invasive fungal infections. All three echinocandin agents, caspofungin, micafungin and anidulafungin, are similar in their spectrum of activity, pharmacokinetics and efficacy. They will become standard therapy for the treatment of candidemia and invasive candidiasis, but will remain second-line therapy for invasive aspergillosis. They do not have a role in the treatment of other mould infections or the endemic mycoses. The new triazole agents, voriconazole and posaconazole, have a very broad spectrum of antifungal activity that includes *Candida* species, filamentous fungi and the dimorphic endemic mycoses. Voriconazole has become the agent of choice for invasive aspergillosis and is useful for non-*Aspergillus* mould infections. Posaconazole will probably become available for use in 2006 for prophylaxis in high-risk immunocompromised patients. This agent will assume an increasing role, probably in conjunction with lipid formulations of amphotericin B, in the treatment of zygomycosis, and will probably prove to be an important addition in the treatment of the endemic mycoses and non-*Aspergillus* mould infections.

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