Novel triazole antifungal drugs: Focus on isavuconazole, ravuconazole and albaconazole
**Introduction**

Azoles are important antifungal compounds, and all drugs in this class inhibit ergosterol synthesis by blocking the 14-α-demethylase enzyme, resulting in the accumulation of toxic methylsterols that may culminate in fungal death [1]. Although azoles demonstrate equivalent mechanisms of action, these compounds vary in chemical structure, as well as in pharmacokinetic (PK), pharmacodynamic (PD), drug interaction and safety profiles.

Currently available triazoles

Fluconazole was the first triazole to be licensed, and is available both as oral and intravenous formulations. This drug has been widely used in clinical practice, particularly for the treatment of candidosis and cryptococcosis. Itraconazole, another triazole, demonstrates a broader spectrum of activity than fluconazole, and is active against most filamentous fungi. While itraconazole capsules are associated with irregular absorption, the cyclodextrin contained in the itraconazole solution confers better absorption, but at the cost of increased gastrointestinal toxicity [2]. Drug interactions are a particular problem for itraconazole, and the intravenous preparation is no longer commercially available.

Voriconazole and posaconazole are second-generation triazoles that have activity against a wide range of pathogens, including *Aspergillus* species [3] and Zygomycetes (posaconazole only). However, concerns associated with the use of voriconazole include drug interactions and unpredictable metabolism [4]. The intravenous formulation of voriconazole also contains cyclodextrin [5], and therefore should be used with caution in patients with advanced renal failure. While the structure of posaconazole is similar to that of itraconazole, gastric acidity does not affect posaconazole absorption to the same extent as the absorption of itraconazole [6]. Posaconazole is less prone to drug interactions than itraconazole and voriconazole, and is usually well tolerated. As posaconazole is available only as an oral solution, the main use for this compound is in antifungal prophylaxis [7,8]. An additional limitation for the use of both voriconazole and posaconazole, particularly in developing countries, is the high cost of these drugs. For example, daily expenses for a 70-kg patient...
taking oral voriconazole or posaconazole are equivalent to US $245 and US $85 to 114, respectively [9].

**Novel triazoles**

Isavuconazole (BAL-4815), ravuconazole (BMS-207147, ER-30346) and albaconazole (UR-9825; Stiefel) (Figure 1) are extended-spectrum triazoles that have demonstrated promise in the treatment of fungal diseases. Most studies have been conducted with isavuconazole, which can be administered both orally and intravenously. Isavuconazonium chloride (BAL-8557; Basilea Pharmaceutica International Ltd; Figure 2), the prodrug of isavuconazole, is under development for the treatment of fungal diseases (for simplification purposes, isavuconazonium chloride is herein referred to as isavuconazole). Isavuconazole is water-soluble, thus eliminating the need for cyclodextrin [10]. Ravuconazole is structurally similar to isavuconazole [11]; an intravenous prodrug of ravuconazole, BMS-379224 [12], similarly does not accumulate in the presence of renal failure. However, the development of BMS-379224 has ceased following the reacquisition of the worldwide rights to ravuconazole by Eisai Co Ltd [13]. E-1224 (Eisai Co Ltd/Drugs for Neglected Diseases initiative), a ravuconazole prodrug, is under development as a potential treatment for fungal infections. This review discusses the data that have been generated with ravuconazole as well as BMS-379224. Both isavuconazole and ravuconazole have a long elimination half-life and a large volume of distribution, and demonstrate high levels of protein binding. Albaconazole, an oral agent that has demonstrated high levels of bioavailability and potent antifungal activity [14,15], is under development for the treatment of onychomycosis. Table 1 highlights the development status of isavuconazole, ravuconazole and albaconazole for various fungal infections.

**Pharmacokinetic data**

In a phase I, single-ascending-dose clinical trial of isavuconazole, the mean elimination half-life was 56 to 77 h and 76 to 104 h following oral and intravenous administration, respectively [16]. Accordingly, the volume of distribution was large and the systemic clearance was low [16]. A phase I, multiple-dose trial that assessed the safety and pharmacokinetics of isavuconazole, through the administration of multiple ascending oral and intravenous doses of isavuconazole, demonstrated that plasma concentrations of isavuconazole reached a peak at 2.0 to 3.5 h following drug intake and 0.7 to 1.0 h following the start of intravenous infusion [17]. In all treatment groups, the serum levels of isavuconazole were dose-proportional, with no indication of induction or inhibition of its own metabolism. The concentration of isavuconazole was demonstrated to be approximately 6-fold greater in the kidneys than in the plasma, with an *in vivo* post-antifungal effect that lasted for 8.4 h in mouse models [18]. A trial in healthy volunteers demonstrated the bioavailability of isavuconazole (po) [19]. In contrast to other azoles, the PK/PD parameters of isavuconazole are affected minimally by food intake [20]. The PK values of isavuconazole in patients with neutropenia were within the range predicted for healthy volunteers [21]; however, in patients with mild-to-moderate hepatic impairment, a 2-fold increase in half-life and AUC values was observed (p < 0.05) [22]. No data are available for isavuconazole in patients with more advanced liver disease.

In an ascending-dose clinical trial of ravuconazole (50, 100, 200, 400, 600 and 800 mg po), an approximately dose-proportional increase in drug plasma levels was observed, and a 2- to 4-fold increase in bioavailability occurred when the drug was administered with a high-fat meal [23]. In another trial, the administration of ravuconazole (50, 100, 200 or 400 mg qd po) for 14 days resulted in a 10-fold accumulation in the plasma [24], in accordance with the half-life of the drug (4 to 8 days) [23,24]. A trial of BMS-379224 (25 to 600 mg, administered parenterally) demonstrated that single doses of the drug resulted in linear plasma PK data [25]. No clinical data on the ravuconazole prodrug E-1224 are available.

A phase I, first-in-human clinical trial of albaconazole (5, 10, 20, 40, 80, 160, 240, 320 and 400 mg) in healthy volunteers demonstrated rapid absorption of the drug: Cmax values were reached in 2 to 4 h, and the drug was widely distributed throughout body fluids [26].
Drug interactions

Isavuconazole appears to cause fewer drug interactions than itraconazole or voriconazole [11]. Isavuconazole is mainly inactivated by slow, cytochrome P450 (CYP)3A4-mediated metabolic clearance, for which the drug is a moderate inhibitor and inductor, and is eliminated from the body in the feces. In several phase I clinical trials, the administration of isavuconazole had no significant effect on the exposure of both warfarin [27,28] and cyclosporine [29], while the coadministration of isavuconazole and rifampicin resulted in a 35-fold increase in the clearance of isavuconazole [30].

Limited data are available regarding the drug interactions of ravuconazole, and no data are available for E-1224. In a similar manner to isavuconazole, ravuconazole demonstrates a lower potential for drug interactions compared with the licensed triazoles; ravuconazole is a less potent inhibitor of CYP3A4 [31]. No information is available on drug interactions with other CYP enzymes, such as CYP2C9 or CYP2C19, with which voriconazole interacts.

No published data are available regarding the metabolism of albaconazole.

Safety profiles

Isavuconazole appears to be a safe drug, with toxicity profiles that are comparable to those of the licensed azoles [16,17,32]. In the multiple-dose clinical trial, the most frequently reported adverse events included headache, nasopharyngitis and rhinitis; however, no relevant changes in vital signs or ECG parameters were observed in the volunteers in the trial [19]. In the BMS-379224 trial, single doses of the drug were well tolerated, with dizziness and nausea being the most common adverse events (each with an incidence of 6%) [25]. No serious adverse effects occurred in the studies involving albaconazole [26,33].

The use of novel azoles for the treatment of fungal diseases

Candidosis

Although candidosis is caused mostly by fluconazole-susceptible fungal strains, the occurrence of fluconazole resistance may limit the therapeutic options available to treat this disease. For example, in results from 2003 from the SENTRY study, fluconazole, voriconazole and ravuconazole displayed up to 2-fold less activity compared with activity during the period from 1997 to 1999 [34].

Table 1. The development status for novel azoles in the treatment of fungal diseases.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fungal disease</th>
<th>Development status</th>
<th>Reference</th>
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<td></td>
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<td>[84,91-93]</td>
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<td>Cryptococcosis</td>
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<td></td>
<td>Histoplasmosis</td>
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<td>Dermatophytes</td>
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<td>[91,123]</td>
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<td>Scedosporiosis</td>
<td>Preclinical</td>
<td>[84,91,92]</td>
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<td>Ravuconazole*</td>
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<td>[113,114]</td>
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*The development of ravuconazole has been superseded by the prodrug E-1224.
Alves et al demonstrated that cross-resistance may occur among several azoles for Candida glabrata isolates; the minimum inhibitory concentration (MIC) for ravuconazole and albacoazole was as high as 8 µg/ml [35]. Resistance to ravuconazole can be predicted for C glabrata when a high level of resistance to fluconazole is present (ie, MIC values of ≥ 64 µg/ml) [36].

The potent in vitro activity of the novel azoles against Candida species was demonstrated in several studies. Isavuconazole is more active than amphotericin B, itraconazole, voriconazole, 5-flucytosine and fluconazole (MIC₉₀ = 0.004, 0.5, 0.008, 0.03, 0.125 and 8 µg/ml, respectively), and has lower MIC₉₀ values compared with voriconazole in the majority of Candida species [37]. However, C glabrata isolates demonstrating high MIC values for isavuconazole (2 to 4 µg/ml) have also been reported [10]. Ravuconazole demonstrated activity against fluconazole-resistant Candida isolates [38]. However, higher MIC values for ravuconazole have been reported for Candida isolates that display resistance to fluconazole compared with more susceptible isolates [38]. Albacoazole is also more active in vitro than fluconazole and itraconazole against Candida species, with MIC₉₀ values ranging from ≤ 0.0002 to 0.12 µg/ml [15]. Most isolates of Candida albicans and C glabrata are susceptible to treatment with albacoazole (MIC₉₀ = 0.5 and 2 µg/ml, respectively) [39].

In animal models of candidosis, the AUC/MIC ratio of the novel azoles appears to provide the best correlation between isavuconazole exposure and effect [18,40-42]. In a neutropenic murine model of Candida infection, isavuconazole significantly reduced fungal burden and was at least as effective as voriconazole [43]. The available data also suggest that the AUC/MIC ratio is the critical PK/PD parameter in terms of predicting the efficacy of ravuconazole, although the ratio of the peak serum level to MIC also may be important [44]. Both isavuconazole and ravuconazole undergo extensive distribution to target tissues [18,45-47].

Isavuconazole has been investigated in a few phase II/III clinical trials of candidosis. A phase II trial compared isavuconazole (50 and 100 mg/day, and 400 mg/week) with fluconazole (100 mg/day) for the treatment of esophageal candidosis [32]. An endoscopically confirmed clinical cure was achieved in 95% of patients treated with isavuconazole (all three doses) and in 95% of patients in the fluconazole arm [32]. A phase III, randomized, double-blind trial is ongoing to evaluate the efficacy of isavuconazole versus caspofungin followed by voriconazole for the treatment of invasive candidosis (ClinicalTrials.gov identifier: NCT00444366). A phase I/II, open-label, dose-escalation trial evaluating the effectiveness of ravuconazole (po) in preventing fungal infections in patients undergoing allogeneic hematological stem cell transplantation (NCT00064311) was initiated in June 2003; however, no further information related to this trial is available. In a phase II trial, albacoazole demonstrated similar efficacy to fluconazole in the treatment of non-complicated Candida vulvovaginitis; a single dose of albacoazole (≥ 40 mg) was more efficacious than fluconazole (150 mg) [14].

Aspergillosis
Azoles are generally used for both the treatment and prophylaxis of invasive aspergillosis (IA). For example, voriconazole is considered a first-line therapy for IA [3], itraconazole is a suitable treatment for the chronic forms of aspergillosis [48], and posaconazole has demonstrated high efficacy in preventing IA [78]. Itraconazole resistance has been reported in Aspergillus strains [49], and cross-resistance among the azoles is a concern [50-53]. In a large study evaluating 519 Aspergillus fumigatus isolates, the frequency of itraconazole resistance before 2004 was 1%, but had increased to 8% since 2004 [54]. Of the itraconazole-resistant isolates, 58 and 66% were cross-resistant to voriconazole and posaconazole, respectively [54].

The novel azoles demonstrated potent in vitro activity against Aspergillus species [34,55-65]. In a study evaluating 118 Aspergillus isolates (including 16 itraconazole-resistant isolates), the geometric mean (GM) MIC value of isavuconazole was 0.62 µg/ml [57]. Several studies also demonstrated the potent activity of ravuconazole against Aspergillus species [59-64]. In one study, the GM MIC values for ravuconazole ranged from 0.3 (Aspergillus nidulans) to 1 µg/ml (Aspergillus flavus) [63]. Albacoazole also demonstrated potent in vitro activity against Aspergillus species (MIC = 0.06 to 0.5 µg/ml) [65].

The in vivo activity of isavuconazole was demonstrated in neutropenic murine models of disseminated Aspergillus infection [66,67]. Warn et al demonstrated that isavuconazole was effective even in a strain that exhibited an MIC value of 4 µg/ml, and which demonstrated in vivo resistance to itraconazole [67]. The administration of ravuconazole (po) significantly delayed mortality in both murine [45] and guinea pig [68] neutropenic models of IA. Additionally, albacoazole administered prophylactically protected rats infected with A fumigatus conidia in a dose-related manner [14] – an effect that was similar to that of amphotericin B. No clinical data are available regarding the treatment of aspergillosis with newer azoles. However, a phase III, double-blind, randomized clinical trial is ongoing to investigate isavuconazole, in comparison with voriconazole, as a first-line therapy for patients with invasive mold diseases (NCT00412893).

Zygomycosis
Zygomycosis mostly affects patients with neutropenia or diabetes mellitus and is frequently lethal [69]. Most human cases of the disease have been associated with fungi belonging to the genera Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia [70]. Zygomycosis
is an emerging problem and appears to be associated with the increasing use of voriconazole (a drug with no activity against Zygomycetes) [71]. Accordingly, cases of breakthrough zygomycosis have been described in patients taking voriconazole [72-77]. The treatment of zygomycosis is complicated, as the fungi causing this disease are resistant to multiple drugs; treatment usually requires a combination of surgical debridement and the use of high doses of amphotericin B. Posaconazole is an attractive alternative for treatment; data from two open-label, non-randomized, compassionate clinical trials demonstrated efficacy with this drug [78,79]. The combination of polyenes with caspofungin also might improve the outcome of patients with severe zygomycosis [80].

Isavuconazole demonstrated variable in vitro activity against Zygomycetes [81,82]. Verweij et al. tested 100 isolates of Zygomycetes against several antifungal compounds [83]. Amphotericin B demonstrated the lowest median MIC against Rhizopus spp, followed by posaconazole and itraconazole (MIC = 0.25, 0.5 and 0.5 µg/ml, respectively). Isavuconazole was also active, with a median MIC of 1 µg/ml (range = 0.25 to 32 µg/ml) [83]. More recently, Perkhofer et al. confirmed the variable activity of isavuconazole against Zygomycetes, obtaining MIC values ranging from 1 to > 8 µg/ml [58]. In a study evaluating 45 isolates of Zygomycetes, isavuconazole performed as poorly as voriconazole (MIC90 > 16 µg/ml) [84]. Another study demonstrated that itraconazole, ravuconazole and voriconazole did not display in vitro activity against Mucor spp (MIC > 16 µg/ml for all three compounds) [85]. The median MIC values against Absidia corymbifera, Cunninghamella spp, Rhizopus spp, Rhizomucor spp and Mucor spp were 2, 2, 1, 0.5 and > 16 µg/ml; 2, 2, 1 and > 16 µg/ml; and 1, 4, 1, 0.5 and 1 µg/ml for ravuconazole, itraconazole and amphotericin B, respectively [85].

**Fusariosis**

Most cases of fusariosis are associated with Fusarium solani (~ 50%), followed by Fusarium oxysporum (~ 20%) and Fusarium verticillioides (~ 10%) [86]. While patients with localized fusariosis may benefit from surgical debridement, systemic antifungal therapy is the mainstream treatment for individuals with disseminated infections. Fungi belonging to the Fusarium genus have demonstrated high resistance to antifungal drugs [87]. Amphotericin B has been the most commonly used drug for the treatment of fusariosis; however, based on single case reports and a small open salvage study [88], clinicians have also been inclined to recommend the use of voriconazole for the treatment of systemic fusariosis. As most studies have demonstrated MIC90 values of > 8 µg/ml for itraconazole, voriconazole and posaconazole [49,89,90], antifungal susceptibility testing has been recommended.

Based on the available in vitro data, the novel antifungal azoles do not appear to provide additional benefit for the treatment of fusariosis. Isavuconazole and ravuconazole demonstrated limited activity against isolates of Fusarium spp (MIC = 1 to 16 µg/ml) [85,91-93]. A study investigating isavuconazole and voriconazole demonstrated MIC50/MIC90 values of 16/16 and 4/4 µg/ml, respectively [84]. Additionally, Cuenca-Estrella et al. demonstrated that only 9.3% of Fusarium isolates were susceptible to ravuconazole [63]. Despite the limited activity of ravuconazole against Fusarium spp, in one study, the compound exhibited synergy against 6 of the 11 isolates tested when combined with amphotericin B [94]. No in vivo data exist for the treatment of fusariosis with the newer azoles.

**Cryptococcosis**

Cryptococcal disease is usually associated with HIV and solid-organ transplantation [95,96]; however, cryptococcosis is also identified increasingly in immunocompetent individuals following exposure to Cryptococcus gattii [97]. Amphotericin B, voriconazole and posaconazole have all demonstrated potent activity against Cryptococcus neoformans and C. gattii [98-101]. However, fluconazole resistance in Cryptococcus spp is increasing [100,102], with 46.6% of isolates displaying resistance to fluconazole in one study [100].

The potent in vitro activity of isavuconazole against both C. gattii and C. neoformans recently was demonstrated, with isavuconazole retaining activity against Cryptococcus spp isolates for which fluconazole demonstrated high MIC values [103,104].

Ravuconazole is active against Cryptococcus spp, with almost all isolates demonstrating MIC values of < 1 µg/ml [34,99-101]. In a study by Perkins et al., only 10 out of 317 C. neoformans isolates exhibited in vitro resistance to ravuconazole [100]. In another study, ravuconazole demonstrated MIC90 values of 1 and 4 µg/ml for isolates that had MIC values of 16 to 32 µg/ml and ≥ 64 µg/ml for fluconazole, respectively [105].

Albaconazole is also active against C. neoformans, including fluconazole-resistant isolates [106]. In one study, the MIC values for albaconazole were 0.002 to 0.2 µg/ml against the majority of cryptococcal isolates tested. Albaconazole also demonstrated potent activity against C. gattii (MIC90 = 0.125 µg/ml) [99], with in vitro activity that was greater than for voriconazole [102]. C. gattii is usually less susceptible to antifungal drugs (with the exception of amphotericin B and 5-flucytosine) than C. neoformans [98,99].

Limited in vivo data are available regarding the effect of the newer azoles in the treatment of cryptococcosis. In animal studies, ravuconazole was as efficacious as fluconazole against C. neoformans [106], and was more effective than itraconazole against systemic cryptococcosis [64], pulmonary cryptococcosis [45] and intracranial cryptococcosis [45]. However, clinical trials are lacking. Two variables might influence the clinical efficacy of the newer azoles in the treatment of
human cryptococcosis: the ability these agents to penetrate the CNS and the potential for drug interactions, in particular interactions with protease inhibitors and immunosuppressive drugs.

**Scedosporiosis**

Scedosporiosis is a mold infection caused by two species, *Scedosporium prolificans* and *Scedosporium apiospernum*, the latter being the anamorph of *Pseudallescheria boydii* [107,108]. Scedosporiosis is histopathologically and radiologically indistinguishable from other mold infections, such as aspergillosis and fusariosis [109]. Treatment of scedosporiosis is complicated by the high frequency of antifungal resistance: *S apiospernum* is resistant to amphotericin B, while voriconazole demonstrates greater activity than both itraconazole and posaconazole against this fungus [110-112]. *S prolificans* is resistant to all known antifungal drugs [109]. Therefore, combination antifungal therapy, in association with surgery, might be of benefit for these difficult-to-treat infections.

Voriconazole and isavuconazole demonstrated MIC₉₀ values of > 16 µg/ml against *Scedosporium* spp [84]. Ravuconazole also demonstrated inactivity against *S prolificans*, while only one-third of *S apiospernum* strains displayed susceptibility to the drug in one study [85]; poor activity has also been described against *P boydii* [113]. Voriconazole and posaconazole demonstrated greater activity against *P boydii* (MIC₉₀ = 2 and 4 µg/ml, respectively) than isavuconazole and ravuconazole [92]. Additionally, albaconazole demonstrated efficacy in a rabbit model of *S proliferans* infection [114].

**Pneumocystosis**

Despite the fungal nature of *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*), azoles have been ineffective against this pathogen [115]. Conversely, echinocandins, such as caspofungin, have been suggested to be effective against *P jirovecii* [116-118]. The inability to cultivate *P jirovecii* renders the evaluation of antifungal drugs against this pathogen impossible. As the lanosterol 14 α-demethylase protein is also present in *P jirovecii* [119], azoles might have a role in treating pneumocystosis. However, no data are available regarding the use of the newer azoles for the treatment of *P jirovecii* pneumonia.

**Other fungal diseases**

In a study of *Histoplasma capsulatum* isolates recovered from patients who failed fluconazole therapy, Wheat et al. observed no increase in the MIC values of posaconazole or voriconazole; however, the MIC values for voriconazole increased > 4-fold in 42% of the isolates [120]. In experimental histoplasmosis, ravuconazole and itraconazole were equally effective [121]. In *vivo*, ravuconazole demonstrated activity against *H capsulatum* that was approximately 4-fold greater than that of itraconazole (MIC = 0.02 and 0.1 µg/ml, respectively) [121]. Limited data are available regarding the use of the newer azoles for the treatment of fungal diseases other than those mentioned in the previous sections of this review. The potent *in vitro* activity of isavuconazole against *Trichosporon, Rhodotorula, Geotrichum, Saccharomyces* and *Pichia* spp has recently been demonstrated [122]. Isavuconazole also demonstrated activity against dermatophytes (mean MIC = 0.01 µg/ml) [123], but limited activity against *Sporothrix schenckii* (MIC = 2 to 8 µg/ml) [91]. Both isavuconazole and ravuconazole demonstrated activity against species of *Exophiala* (MIC₉₀ = 0.5 µg/ml) [92,124]. Posaconazole, ravuconazole and isavuconazole demonstrated similar activity against *Paecilomyces lilacinus* (MIC₉₀ = 2 µg/ml), while voriconazole exhibited a higher MIC₉₀ value (4 µg/ml) [92]. In the same study, *Coccidioides posadasi* isolates were susceptible to all of the azoles tested, except fluconazole, and both isavuconazole and ravuconazole demonstrated activity against *Alternaria alternata* (MIC₉₀ = 1 µg/ml). *Curvularia lunata* displayed lower susceptibility to isavuconazole and ravuconazole (MIC₉₀ = 4 µg/ml) [92]. Both ravuconazole and albaconazole demonstrated activity against *Chaetomium* spp (MIC = 0.06 to 1 µg/ml) [125], and albaconazole demonstrated activity against species of *Paecilomyces* (MIC₉₀ = 0.125 µg/ml) and *Chaetomium* (MIC₉₀ = 2 µg/ml) [65]. Moreover, albaconazole demonstrated greater activity than amphotericin B against most pathogenic fungi, except *F solani* and *Scytaeidium* spp (MIC for albaconazole = 4 to > 16 and 2 to > 16 µg/ml, respectively) [65]. Albaconazole was also active against *Malassezia* spp [126] and other dermatophytes [127] *in vitro*.

Albaconazole was evaluated in a phase I, randomized, placebo-controlled clinical trial in patients with tinea pedis (NCT00509275), but results of this trial are unavailable. A phase II, randomized, double-blind, placebo-controlled trial of albaconazole for the treatment of toenail onychomycosis is ongoing (NCT00730405).

**Conclusion**

Isavuconazole, albaconazole and E-1224, a prodrug of ravuconazole, are the three main azole antifungal agents currently under development. Despite displaying similarly potent and broad *in vitro* activity against the most important pathogenic fungi, these newer azoles have demonstrated poor or limited activity against emerging fungi, such as species of *Fusarium*, *Scedosporium* and *Zygomycetes*. However, isavuconazole and ravuconazole are suitable candidates for the treatment of invasive mycoses. The limited drug-interaction profile and long half-life exhibited by these drugs in comparison with the available antifungal azoles may be advantageous therapeutically. Based on the currently available data, albaconazole will likely be used as a dermatological agent, although there is a potential for use of this agent in antifungal prophylaxis. However, most data regarding the new azoles are available from conference abstracts only, and results from clinical trials are awaited. The main concern associated with the new
azoles is the possibility of developing cross-resistance in this drug class, a phenomenon that has been well described in vitro.

References

- of outstanding interest
- of special interest


49. Present the most recent guidelines from the Infectious Diseases Society of America for the treatment of aspergillosis.


56. Demonstrated that Aspergillus resistance to azoles has increased in recent years. Resistance to antifungal drugs in this study was particularly associated with chronic cavitary pulmonary aspergillosis, mainly in patients receiving long-term treatment with itraconazole who demonstrated low serum levels of the drug.


