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

ARTICLE *in* CURRENT OPINION IN INVESTIGATIONAL DRUGS (LONDON, ENGLAND: 2000) · FEBRUARY 2010

Impact Factor: 3.55 · Source: PubMed

THOMSON REUTERS

Current Opinion in Investigational Drugs 2010 **11**(2):165-174
 ISSN 2040-3429

REVIEW

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

Alessandro C Pasqualotto[1,2]*, Karoline O Thiele[3] & Luciano Z Goldani[1,4]

Addresses
[1]Universidade Federal do Rio Grande do Sul,
Rua Ramiro Barcelos 2400, 90035-003, Porto Alegre, Brazil

[2]Hospital Dom Vicente Scherer, Santa Casa-Complexo Hospitalar, Serviço de Controle de Infecção Hospitalar,
Avenida Independência 155, 90035-075, Porto Alegre, Brazil
Email: acpasqualotto@hotmail.com

[3]Centro Universitário Feevale, Rodovia RS-239,
93352-000, Novo Hamburgo, Brazil

[4]Hospital de Clinicas de Porto Alegre, Rua Ramiro Barcelos 2350,
90035-903, Porto Alegre, Brazil

*To whom correspondence should be addressed

Azoles are important compounds for the treatment of fungal infections. This review focuses on three azoles: isavuconazole, ravuconazole and albaconazole (Stiefel). These drugs exhibit a broad spectrum of activity in vitro, including activity against several fungal isolates that are resistant to other azoles. However, poor or limited activity of these compounds has been demonstrated against species of Fusarium and Scedosporium, as well as against Zygomycetes. As isavuconazole and ravuconazole have been developed both as intravenous and oral formulations, these compounds are suitable candidates for the treatment of various invasive fungal diseases. Most clinical trials with albaconazole have targeted mucocutaneous fungal infections. Although all of these agents appear to be well tolerated, cross-resistance is a concern in the azole family of compounds.

Keywords Albaconazole, antifungal agent, azole, isavuconazole, ravuconazole

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 voriconzaole 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

Figure 1. The structure of albaconazole.

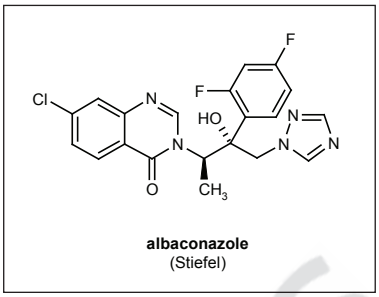
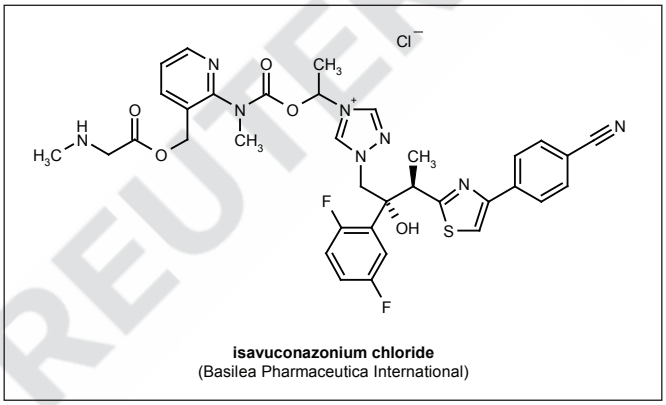


Figure 2. The structure of isavuconazonium chloride.



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: C_{max} values were reached in 2 to 4 h, and the drug was widely distributed throughout body fluids [26].

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

Drug	Fungal disease	Development status	Reference
Isavuconazole	Candidosis	Phase III	[NCT00444366]
	Aspergillosis	Phase III	[NCT00412893]
	Zygomycosis	Preclinical	[58,81-84,91,92]
	Fusariosis	Preclinical	[84,91-93]
	Cryptococosis	Preclinical	[103,104]
	Histoplasmosis	Preclinical	[92]
	Dermatophytes	Preclinical	[91,123]
	Scedosporiosis	Preclinical	[84,91,92]
Ravuconazole*	Candidosis	Preclinical	[34-36,38,44,45,64]
	Aspergillosis	Preclinical	[45,55,59-64,68]
	Zygomycosis	Preclinical	[59,63,85,92]
	Fusariosis	Preclinical	[59,63,85,92-94]
	Cryptococosis	Preclinical	[34,38,45,64,99-101,105]
	Histoplasmosis	Preclinical	[92,120,121]
	Dermatophytes	Preclinical	[64,126]
	Scedosporiosis	Preclinical	[63,85,92,126]
Albaconazole	Candidosis	Phase II	[33]
	Aspergillosis	Preclinical	[14,65]
	Zygomycosis	No data available	–
	Fusariosis	Preclinical	[65,94]
	Cryptococosis	Preclinical	[99,102,106]
	Histoplasmosis	No data available	–
	Dermatophytes	Phase I/II	[127]
	Scedosporiosis	Preclinical	[113,114]

*The development of ravuconazole has been superseded by the prodrug E-1224.

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].

Alves *et al* demonstrated that cross-resistance may occur among several azoles for *Candida glabrata* isolates; the minimum inhibitory concentration (MIC) for ravuconazole and albaconazole 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 (MIC_{50} = 0.004, 0.5, 0.008, 0.03, 0.125 and 8 μg/ml, respectively), and has lower MIC_{50} 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]. Albaconazole is also more active *in vitro* than fluconazole and itraconazole against *Candida* species, with MIC_{90} values ranging from ≤ 0.0002 to 0.12 μg/ml [15]. Most isolates of *Candida albicans* and *C glabrata* are susceptible to treatment with albaconazole (MIC_{90} = 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 to 98% 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, albaconazole demonstrated similar efficacy to fluconazole in the treatment of non-complicated *Candida* vulvovaginitis; a single dose of albaconazole (≥ 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 [7,8]. 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]. Albaconazole 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, albaconazole 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 (MIC_{90} > 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 aganist *Absidia corymbifera*, *Cunninghamella* spp, *Rhizopus* spp, *Rhizomucor* spp and *Mucor* spp were 2, 2, 1, 0.5 and > 16 μg/ml; 2, 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 MIC_{50} 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 MIC_{50}/MIC_{90} 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 MIC_{90} 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* (MIC_{90} = 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-flucytosinem) 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 apiospermum,* the latter being the anamorph of *Pseudallescheria boydii* [107,108]. Scedosporiosis is histopatologically 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 apiospermum* 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 MIC_{90} values of > 16 μg/ml against *Scedosporium* spp [84]. Ravuconazole also demonstrated inactivity against *S prolificans*, while only one-third of *S apiospermum* 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* (MIC_{90} = 2 and 4 μg/ml, respectively) than isavuconazole and ravuconazole [92]. Additionally, albaconazole demonstrated efficacy in a rabbit model of *S prolificans* 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 ravuconazole; 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 vitro,* 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* (MIC_{90} = 0.5 μg/ml) [92,124]. Posaconazole, ravuconazole and isavuconazole demonstrated similar activity against *Paecilomyces lilacinus* (MIC_{90} = 2 μg/ml), while voriconazole exhibited a higher MIC_{90} value (4 μg/ml) [92]. In the same study, *Coccidioides posadasii* isolates were susceptible to all of the azoles tested, except fluconazole, and both isavuconazole and ravuconazole demonstrated activity against *Alternaria alternata* (MIC_{90} = 1 μg/ml). *Curvalaria lunata* displayed lower susceptibility to isavuconazole and ravuconazole (MIC_{90} = 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* (MIC_{90} = 0.125 μg/ml) and *Chaetomium* (MIC_{90} = 2 μg/ml) [65]. Moreover, albaconazole demonstrated greater activity than amphotericin B against most pathogenic fungi, except *F solani* and *Scytalidium* 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 onycomycosis 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

1. Zonios DI, Bennett JE: **Update on azole antifungals.** *Semin Respir Crit Care Med* (2008) **29**(2):198-210.

2. Stevens D: **Itraconazole in cyclodextrin solution.** *Pharmacotherapy* (1999) **19**(5):603-611.

3. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R *et al*: **Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis.** *N Engl J Med* (2002) **347**(6):408-415.

•• *Presents data from the largest randomized clinical trial of invasive aspergillosis, demonstrating the superiority of voriconazole compared with amphotericin B*.

4. Pasqualotto AC, Xavier MO, Andreolla HF, Linden R: **Voriconazole therapeutic drug monitoring: focus on safety.** *Expert Opin Drug Saf* (2010) **9**(1):125-137.

5. Johnson LB, Kauffman CA: **Voriconazole: A new triazole antifungal agent.** *Clin Infect Dis* (2003) **36**(5):630-637.

6. Courtney R, Radwanski E, Lim J, Laughlin M: **Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men.** *Antimicrob Agents Chemother* (2004) **48**(3):804-808.

7. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M *et al*: **Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia.** *N Engl J Med* (2007) **356**(4):348-359.

•• *Demonstrated that posaconazole prevented invasive fungal diseases more effectively than fluconazole/itraconazole, improving overall survival*.

8. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais De Azevedo W, Reddy V, Boparai N, Pedicone L *et al*: **Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease.** *N Engl J Med* (2007) **356**(4):335-347.

•• *Demonstrated that posaconazole was superior to fluconazole in preventing invasive aspergillosis and in reducing the rate of death related to fungal infection in patients with GvHD*.

9. PDR staff (Ed): *2006 Redbook: Pharmacy's Fundamental Reference*. Thomson PDR, Montvale, NJ, USA (2006).

10. Seifert H, Aurbach U, Stefanik D, Cornely O: ***In vitro* activities of isavuconazole and other antifungal agents against *Candida* bloodstream isolates.** *Antimicrob Agents Chemother* (2007) **51**(5):1818-1821.

11. Pasqualotto AC, Denning DW: **New and emerging treatments for fungal infections.** *J Antimicrob Chemother* (2008) **61** (Suppl 1):i19-i30.

• *Reviews newer and emerging antifungal drugs, including ravuconazole, albaconazole and isavuconazole*.

12. Ueda Y, Barbour N, Bronson JJ, Connolly TP, Dali M, Gao Q, Golik J, Huang S, Hudyma TW, Kang S, Knipe J *et al*: **BMS-379224, a water-soluble prodrug of ravuconazole.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2002) **42**:Abs F-817.

13. Eisai Co Ltd: **Eisai and DNDi enter collaboration and license agreement to develop new drug for Chagas disease.** *Press Release* (2009): September 29.

14. Bartroli J, Turmo E, Algueró M, Boncompte E, Vericat ML, Conte L, Ramis J, Merlos M, García-Rafanell J, Forn J: **New azole antifungals. 3. Synthesis and antifungal activity of 3-substituted-4(3*H*)-quinazolinones.** *J Med Chem* (1998) **41**(11):1869-1882.

15. Ramos G, Cuenca-Estrella M, Monzón A, Rodriguez-Tudela JL: ***In vitro* comparative activity of UR-9825, itraconazole and fluconazole against clinical isolates of *Candida* spp.** *J Antimicrob Chemother* (1999) **44**(2):283-286.

16. Schmitt-Hoffmann A, Roos B, Heep M, Schleimer M, Weidekamm E, Brown T, Roehrle M, Beglinger C: **Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams) and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers.** *Antimicrob Agents Chemother* (2006) **50**(1):279-285.

• *Presents data from a single-ascending-dose clinical trial evaluating the PKs of isavuconazole and its prodrug, BAL-8557.*

17. Schmitt-Hoffmann A, Roos B, Maares J, Heep M, Spickerman J, Weidekamm E, Brown T, Roehrle M: **Multiple-dose pharmacokinetics and safety of the new antifungal triazole BAL4815 after intravenous infusion and oral administration of its prodrug, BAL8557, in healthy volunteers.** *Antimicrob Agents Chemother* (2006) **50**(1):286-293.

• *Clinical trial assessing the safety and PKs of isavuconazole and its prodrug, BAL-4815, in healthy volunteers assigned to four treatment cohorts*.

18. Warn PA, Sharp A, Parmar A, Majithiya J, Denning DW, Hope WW: **Pharmacokinetics and pharmacodynamics of a novel triazole, isavuconazole: Mathematical modeling, importance of tissue concentrations, and impact of immune status on antifungal effect.** *Antimicrob Agents Chemother* (2009) **53**(8):3453-3461.

19. Schmitt-Hoffmann A, Ross B, Heep M, Brown T: **Steady-state bioavailability of oral isavuconazole in healthy volunteers.** *European Congress of Clinical Microbiology and Infectious Diseases, Munich, Germany* (2007) **17**:Abs P987.

20. Schmitt-Hoffmann A, Roos B, Spickermann J, Heep M, Roehrle M, Schoetzau A, Simmens U: **No relevant food effect in man on isavuconazole oral pharmacokinetics preliminary data.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2008) **48**:Abs A-008.

21. Cornely O, Böhme A, Heep M, Schmitt-Hoffmann A, Ullmann A: **Pharmacokinetics, safety and tolerability results of a dose escalation study of isavuconazole in neutropenic patients.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2008) **48**:Abs M-2137.

22. Schmitt-Hoffmann A, Roos B, Spickermann J, Heep M, Peterfaí E, Edwards DJ, Stoeckel K: **Effect of mild and moderate liver disease on the pharmacokinetics of isavuconazole after intravenous and oral administration of a single dose of the prodrug BAL8557.** *Antimicrob Agents Chemother* (2009) **53**(11):4885-4890.

23. Olsen SJ, Mummaneni V, Rolan P, Norton J, Grasela DM: **Ravuconazole single ascending oral dose study in healthy subjects.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2000) **40**:Abs A-838.

24. Grasela DM, Olsen SJ, Mummaneni V, Rolan P, Christopher L, Norton J, Hadjilambris OW, Marino MR: **Ravuconazole: Multiple ascending oral dose study in healthy subjects.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2000) **40**:Abs A-839.

25. Bello A, Russo R, Grasela D, Salahudeen I: **Pharmacokinetics of intravenous BMS-379224 (pro-drug of ravuconazole) in healthy male subjects.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2003) **43**:Abs A-1567.

26. Izquierdo I, Lurigados C, Perez I, Tumo E, Ramis J: **First administration into man of UR-9825: A new triazole class of antifungal agent.** *European Confederation of Medical Mycology Congress, Barcelona, Spain* (2000) **6**:Abs P2-004.

27. Schmitt-Hoffmann A, Roos B, Sauer J, Maares J, Brown T, Spickermann J, Allison M, Heep M: **Effect of BAL8557, a water-soluble azole pro-drug, on the pharmacokinetics of S- and R-warfarin.** *Congress of the International Society for Human and Animal Mycology, Paris, France* (2006) **16**:Abs P-0321.

28. Schmitt-Hoffmann A, Roos B, Allison M, Heep M: **Effect of isavuconazole on the pharmacokinetics and the pharmacodynamics of warfarin.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2007) **47**:Abs A-776.

29. Schmitt-Hoffmann A, Roos B, Sauer J, Maares J, Brown T, Spickermann J, Roehrle M, Heep M: **Effect of BAL8557, a water-soluble azole pro-drug, on the pharmacokinetics of cyclosporine.** *Congress of the International Society for Human and Animal Mycology, Paris, France* (2006) **16**:Abs P-0136.

30. Schmitt-Hoffmann A, Roos B, Sauer J, Maares J, Spickermann J, Iersel MP, Heep M: **Effect of rifampicin on the pharmacokinetics of BAL4815 at steady state after multiple oral doses of BAL8557 and rifampicin.** *Congress of the International Society for Human and Animal Mycology, Paris, France* (2006) **16**:Abs P-0319.

31. Mummaneni V, Geraldes M, Hadjilambris OW, Ouyang Z, Uderman H, Marino MR: **Effect of ravuconazole on the pharmacokinetics of simvastatin in healthy subjects.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2000) **40**:Abs A-841.

32. Viljoen JJ, Mitha I, Heep M, Ghannoum M: **Efficacy, safety, and tolerability of three different dosing regimens of BAL8557 vs fluconazole in a double-blind, randomized, multicenter trial for the treatment of esophageal candidiasis in immunocompromised adults.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2005) **45**:Abs LB2-32.

33. Bartroli X, Uriach J: **A clinical multicenter study comparing efficacy and tolerability between five single oral doses of albaconazole and fluconazole 150 mg single dose in acute vulvovaginal candidiasis.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2005) **45**:Abs M-722.

34. Messer SA, Jones RN, Fritsche TR: **International surveillance of *Candida* spp. and *Aspergillus* spp.: Report from the SENTRY Antimicrobial Surveillance Program.** *J Clin Microbiol* (2003) **44**(5):1782-1787.

35. Alves SH, Da Matta DA, Azevedo AC, Loreto ES, Boff E, Santurio JM, Guarro J: ***In vitro* activities of new and conventional antimycotics against fluconazole-susceptible and non-susceptible Brazilian *Candida* spp. isolates.** *Mycoses* (2006) **49**(3):220-225.

36. Pfaller MA, Messer SA, Boyken L, Rice C, Tendolkar S, Hollis RJ, Diekema DJ: **Cross-resistance between fluconazole and ravuconazole and the use of fluconazole as a surrogate marker to predict susceptibility and resistance to ravuconazole among 12,796 clinical isolates of *Candida* spp.** *J Clin Microbiol* (2004) **42**(7):3137-3141.
•• *Discusses the relevance of cross-resistance between azole antifungal drugs*.

37. Mouton JW, Verwij PE, Warn P, Denning D, Heep M, Isham N, Ghannoum M: ***In vitro* activity of a new triazole BAL4815 against *Candida* isolates with decreased fluconazole susceptibility.** *Trends in Medical Mycology, Berlin, Germany* (2005) **2**:Abs P021.

38. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Garcia-Effron G, Rodriguez-Tudela JL: ***In vitro* activities of ravuconazole and four other antifungal agents against fluconazole-resistant or susceptible clinical yeast isolates.** *Antimicrob Agents Chemother* (2004) **48**(8):3107-3111.
• *Demonstrated the potent antifungal activity of ravuconazole against yeasts in vitro*.

39. Arechavala AI, Bianchi MH, Robles AM, Santiso G, Negroni R: **Identification and susceptibility against fluconazole and albaconazole of 100 yeasts' strains isolated from vaginal discharge.** *Rev Iberoam Micol* (2007) **24**(4):305-308.

40. Warn PA, Sharp A, Denning DW: **Dose response curves and dose fractionation studies with BAL8557 in a murine model of disseminated candidiasis.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2005) **45**:Abs B-47.

41. Te Dorsthorst D, Verweij PE, Meis JF, Mouton JW: **Pharmacodynamics of BAL4815: A new azole antifungal in a mouse model of systemic infection.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2004) **44**:Abs A-1874.

42. Warn PA, Parmer M, Jayesh M, Denning DW, Hope WW: **Pharmacokinetics (PK) and pharmacodynamics (PD) of isavuconazole in a murine model of disseminated candidiasis (DC).** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2008) **48**:Abs M-2140.

43. Majithiya J, Sharp A, Parmar A, Denning DW, Warn PA: **Efficacy of isavuconazole, voriconazole and fluconazole in temporarily neutropenic murine models of disseminated *Candida tropicalis* and *Candida krusei*.** *J Antimicrob Chemother* (2009) **63**(1):161-166.

44. Andes D, Marchillo K, Stamstad T, Conklin R: ***In vivo* pharmacodynamics of a new triazole, ravuconazole, in a murine candidiasis model.** *Antimicrob Agents Chemother* (2003) **47**(4):1193-1199.

45. Hata K, Kimura J, Miki H, Toyosawa T, Moriyama M, Katsu K: **Efficacy of ER-30346, a novel oral triazole antifungal agent, in experimental models of aspergillosis, candidiasis, and cryptococcosis.** *Antimicrob Agents Chemother* (1996) **40**(10): 2243-2247.

46. Mikamo H, Yin XH, Hayasaki Y, Shimamura Y, Uesugi K, Fukayama N, Satoh M, Tamaya T: **Penetration of ravuconazole, a new triazole antifungal, into rat tissues.** *Chemotherapy* (2002) **48**(1):7-9.

47. Warn PA, Sharp A, Majithiya JB, Parmar A, Denning DW: ***In vitro* post antibiotic effect of isavuconazole, voriconazole and amphotericin B against a strain of *C. albicans* with concentration-dependent pharmacokinetics in a murine model and susceptibility of strains for murine kidneys post infection.** *European Conference on Clinical Microbiology and Infectious Diseases*, *Barcelona, Spain* (2008) **18**:Abs P2177.

48. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Segal BH, Steinbach WJ, Stevens DA, van Burik JA *et al*: **Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America.** *Clin Infect Dis* (2008) **46**(3):327-360.
•• *Presents the most recent guidelines from the Infectious Diseases Society of America for the treatment of aspergillosis*.

49. Denning DW, Venkateswarlu K, Oakley KL, Anderson MJ, Manning NJ, Stevens DA, Warnock DW, Kelly SL: **Itraconazole resistance in *Aspergillus fumigatus*.** *Antimicrob Agents Chemother* (1997) **41**(6):1364-1368.

50. Howard SJ, Webster I, Moore CB, Gardiner RE, Park S, Perlin DS, Denning DW: **Multi-azole resistance in *Aspergillus fumigatus*.** *Int J Antimicrob Agents* (2006) **28**(5):450-453.

51. Howard SJ, Moore CB, Denning DW: **Azole resistance in *Aspergillus niger*.** *Advances Against Aspergillosis, Athens, Greece* (2006) **2**:Abs P071.

52. Diekema DJ, Messer S, Hollis R, Boyken L, Tendolkar S, Kroeger J, Pfaller MA: **Patterns of triazole cross-resistance/susceptibility among a large collection of clinical isolates of *Aspergillus*.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2007) **47**:Abs M-523.

53. Verweij PE, Van Der Lee HAL, Kuijpers J, Snelders E, Rijs AJMM, Melchers WJG: **Epidemiology of multiple-triazole-resistant *Aspergillus fumigatus*.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2007) **47**:Abs M-2018.

54. Howard SJ, Cerar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, Laverdiere M, Arendrup MC, Perlin D, Denning DW: **Frequency and evolution of azole resistance in *Aspergillus fumigatus* associated with treatment failure.** *Emerg Infect Dis* (2009) **15**(7):1068-1076.
•• *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.*

55. Baddley JW, Kano R, Brandt ME, Marr KA, Kauffman CA, Andes DA, Moser AS, Pappas PG, Balajee SA: **Molecular characterization and antifungal susceptibilities of Aspergilli from the Transplant-Associated Infection Surveillance Network (TRANSNET).** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2007) **47**:Abs M-2019.

56. Guinea J, Jensen J, Peláez T, Torres-Narbona M, Bouza E: ***In vitro* activity of isavuconazole (BAL4815) and voriconazole against 443 isolates of *Aspergillus* spp.** *Trends in Medical Micology, Torino, Italy* (2007) **3**:Abs P026.

57. Warn PA, Sharp A, Denning DW: ***In vitro* activity of a new triazole BAL4815, the active component of BAL8557 (the water-soluble prodrug), against *Aspergillus* spp.** *J Antimicrob Chemother* (2006) **57**(1):135-138.

58. Perkhofer S, Lechner V, Lass-Florl C: ***In vitro* activity of isavuconazole against *Aspergillus* species and Zygomycetes according to the methodology of the European Committee on Antimicrobial Susceptibility Testing.** *Antimicrob Agents Chemother* (2009) **53**(4):1645-1647.

59. Diekema DJ, Messer SA, Hollis RJ, Jones RN, Pfaller MA: **Activities of caspofungin, itraconazole, posaconazole, ravuconazole, voriconazole, and amphotericin B against 448 recent clinical isolates of filamentous fungi.** *J Clin Microbiol* (2003) **41**(8):3623-3626.

60. Espinel-Ingroff A, Fothergill A, Peter J, Rinaldi MG, Walsh TJ: **Testing conditions for determination of minimum fungicidal concentrations of new and established antifungal agents for *Aspergillus* spp.: NCCLS collaborative study.** *J Clin Microbiol* (2002) **40**(9):3204-3208.

61. Moore CB, Walls CM, Denning DW: ***In vitro* activity of the new triazole BMS-207147 against *Aspergillus* species in comparison with itraconazole and amphotericin B.** *Antimicrob Agents Chemother* (2000) **44**(2):441-443.

62. Pfaller MA, Messer SA, Hollis RJ, Jones RN: **Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi: Report from SENTRY Antimicrobial Surveillance Program, 2000.** *Antimicrob Agents Chemother* (2002) **46**(4):1032-1037.

63. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Garcia-Effron G, Monzon A, Rodriguez-Tudela JL: ***In vitro* activity of ravuconazole against 923 clinical isolates of nondermatophyte filamentous fungi.** *Antimicrob Agents Chemother* (2005) **49**(12):5136-5138.

64. Hata K, Kimura J, Miki H, Toyosawa T, Nakamura T, Katsu K: ***In vitro* and *in vivo* activities of ER-30346, a novel oral triazole with a broad antifungal spectrum.** *Antimicrob Agents Chemother* (1996) **40**(10):2237-2242.

65. Capilla J, Ortoneda M, Pastor FJ, Guarro J: ***In vitro* antifungal activities of the new triazole UR-9825 against clinically important filamentous fungi.** *Antimicrob Agents Chemother* (2001) **45**(9):2635-2637.

66. Warn PA, Mosquera J, Sharp A, Denning DW: ***In vivo* efficacy of the triazole BAL8557 (BAL) compared to voriconazole (VOR), itraconazole (ITC) and caspofungin (CAS) by a new qPCR and quantitative culture in neutropenic murine model of *Aspergillus flavus*.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2005) **45**:Abs B-48.

67. Warn PA, Parmar A, Sharp A, Denning DW: **Dose response in neutropenic mice with disseminated infection of multiple strains of *Aspergillus fumigatus* with widely varying MIC and MFC values treated with isavuconazole.** *European Conference of Clinical Microbiology and Infectious Diseases*, *Munich, Germany* (2007) **17**:Abs P-1951.

68. Kirkpatrick WR, Perea S, Coco BJ, Patterson TF: **Efficacy of ravuconazole (BMS-207147) in a guinea pig model of disseminated aspergillosis.** *J Antimicrob Chemother* (2002) **49**(2):353-357.

69. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP *et al*: **Epidemiology and outcome of zygomycosis: A review of 929 reported cases.** *Clin Infect Dis* (2005) **41**(5):634-653.
• *A comprehensive review of zygomycosis*.

70. Rogers TR: **Treatment of zygomycosis: Current and new options.** *J Antimicrob Chemother* (2008) **61**(Suppl 1):i35-i40.

71. Lass-Flörl C: **The changing face of epidemiology of invasive fungal disease in Europe.** *Mycoses* (2009) **52**(3):197-205.

72. Trifilio SM, Bennett CL, Yarnold PR, McKoy JM, Parada J, Mehta J, Chamilos G, Palella F, Kennedy L, Mullane K, Tallman MS *et al*: **Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy.** *Bone Marrow Transplant* (2007) **39**(7):425-429.

73. Pagano L, Gleissner B, Fianchi L: **Breakthrough zygomycosis and voriconazole.** *J Infect Dis* (2005) **192**(8):1496-1497.

74. Oren I: **Breakthrough zygomycosis during empirical voriconazole therapy in febrile patients with neutropenia.** *Clin Infect Dis* (2005) **40**(5):770-771.

75. Kobayashi K, Kami M, Murashige N, Kishi Y, Fujisaki G, Mitamura T: **Breakthrough zygomycosis during voriconazole treatment for invasive aspergillosis.** *Haematologica* (2004) **89**(11):ECR42.

76. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA: **Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole.** *Clin Infect Dis* (2004) **39**(5): 743-746.

77. Marty FM, Cosimi LA, Baden LR: **Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants.** *N Engl J Med* (2004) **350**(9):950-952.

78. Greenberg RN, Mullane K, van Burik JA, Raad I, Abzug MJ, Anstead G, Herbrecht R, Langston A, Marr KA, Schiller G, Schuster M *et al*: **Posaconazole as salvage therapy for zygomycosis.** *Antimicrob Agents Chemother* (2006) **50**(1):126-133.

79. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP: **Posaconazole is effective as salvage therapy in zygomycosis: A retrospective summary of 91 cases.** *Clin Infect Dis* (2006) **42**(7):e61-e65.

80. Reed C, Bryant R, Ibrahim AS, Edwards J Jr, Filler SG, Goldberg R, Spellberg B: **Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis.** *Clin Infect Dis* (2008) **47**(3):364-371.

81. Warn P, Sharp A, Denning D: ***In vitro* activity of BAL4815 against Zygomycetes.** *International Society for Human and Animal Mycology, Paris, France* (2006):Abs P-0158.

82. Verweij PE, González GM, Wiedrhold NP, Lass-Flörl C, Warn P, Heep M, Ghannoum MA, Guinea J: ***In vitro* antifungal activity of isavuconazole against 345 mucorales isolates collected at study centers in eight countries.** *J Chemother* (2009) **21**(3):272-281.

83. Verweij PE, Van der Lee HAL, Rijs AJMM: **Isavuconazole is active against Zygomycetes *in vitro*.** *Trends in Medical Mycology, Torino, Italy* (2007) **3**:Abs P051.

84. Guinea J, Pelaez T, Recio S, Torres-Narbona M, Bouza E: ***In vitro* antifungal activities of isavuconazole, voriconazole and fluconazole against 1007 isolates of Zygomycete, *Candida, Aspergillus, Fusarium,* and *Scedosporium* species.** *Antimicrob Agents Chemother* (2008) **52**(4):1396-1400.

85. Minassian B, Huczko E, Washo T, Bonner D, Fung-Tomc J: ***In vitro* activity of ravuconazole against Zygomycetes, *Scedosporium* and *Fusarium* isolates.** *Clin Microbiol Infect* (2003) **9**(12): 1250-1252.

86. Nucci M, Anaissie E: ***Fusarium* infections in immuno-compromised patients.** *Clin Microbiol Rev* (2007) **20**(4):695-704.

87. Sekhon AS, Padhye AA, Garg AK, Ahmad H, Moledina N: ***In vitro* sensitivity of medically significant *Fusarium* species to various antimycotics.** *Chemotherapy* (1994) **40**(4):239-244.

88. Perfect JR, Marr KA, Walsh TJ, Greenberg RN, DuPont B, de la Torre-Cisneros J, Just-Nübling G, Schlamm HT, Lutsar I, Espinel-Ingroff A, Johnson E: **Voriconazole treatment for less-common, emerging, or refractory fungal infections.** *Clin Infect Dis* (2003) **36**(9):1122-1131.

89. Szekely A, Johnson EM, Warnock DW: **Comparison of E-test and broth microdilution methods for antifungal drug susceptibility testing of molds.** *J Clin Microbiol* (1999) **37**(5):1480-1483.

90. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL: **Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi.** *Antimicrob Agents Chemother* (2006) **50**(3):917-921.

91. Ghannoum M, Isham N: **Antifungal activity of BAL4815, a novel azole against dermatophytes and emerging non-dermatophyte fungi including Zygomycetes.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2005) **45**: Abs M-1623.

92. González GM: ***In vitro* activities of isavuconazole against opportunistic filamentous and dimorphic fungi.** *Med Mycol* (2009) **47**(1):71-76.

93. Alastruey-Izquierdo A, Cuenca-Estrella M, Monzón A, Mellado E, Rodríguez-Tudela JL: **Antifungal susceptibility profile of clinical *Fusarium* spp. isolates identified by molecular methods.** *J Antimicrob Chemother* (2008) **61**(4):805-809.

94. Ortoneda M, Capilla J, Javier Pastor F, Pujol I, Guarro J: ***In vitro* interactions of licensed and novel antifungal drugs against *Fusarium* spp.** *Diagn Microbiol Infect Dis* (2004) **48**(1):69-71.

95. Pasqualotto AC, Bittar AE, de Quadros M, Severo LC: **Cryptococcal cellulitis in a renal transplant patient.** *Nephrol Dial Transplant* (2005) **20**(9):2007-2008.

96. Pasqualotto AC, Severo CB, Oliveira FM, Severo LC: **Cryptococcemia. An analysis of 28 cases with emphasis on the clinical outcome and its etiologic agent.** *Rev Iberoam Micol* (2004) **21**(3):143-146.

97. Severo LC, de Mattos Oliveira F, Londero AT: **Cryptococcosis due to *Cryptococcus neoformans* var. *gattii* in Brazilian patients with AIDS. Report of three cases.** *Rev Iberoam Micol* (1999) **16**(3):152-154.

98. dos Santos IS, Severo LC, Pasqualotto AC: **Susceptibility of clinical isolates of *Cryptococcus neoformans* and *Cryptococcus gattii* to voriconazole.** *European Congress of Clinical Microbiology and Infectious Diseases, Helsinki, Finland* (2006) **16**:Abs R2163.

99. Trilles L, Fernández-Torres B, Lazéra Mdos S, Wanke B, Guarro J: ***In vitro* antifungal susceptibility of *Cryptococcus gattii*.** *J Clin Microbiol* (2004) **42**(10):4815-4817.

100. Perkins A, Gomez-Lopez A, Mellado E, Rodriguez-Tudela JL, Cuenca-Estrella M: **Rates of antifungal resistance among Spanish clinical isolates of *Cryptococcus neoformans* var. *neoformans*.** *J Antimicrob Chemother* (2005) **56**(6):1144-1147.

101. Pfaller MA, Messer SA, Boyken L, Rice C, Tendolkar S, Hollis RJ, Doern GV, Diekema DJ: **Global trends in the antifungal susceptibility of *Cryptococcus neoformans* (1990 to 2004).** *J Clin Microbiol* (2005) **43**(5):2163-2167.

102. Morera-López Y, Torres-Rodríguez JM, Jiménez-Cabello T, Baró-Tomás T: ***Cryptococcus gattii*: *In vitro* susceptibility to the new antifungal albaconazole versus fluconazole and voriconazole.** *Med Mycol* (2005) **43**(6):505-510.

103. Thompson GR 3rd, Wiederhold NP, Fothergill AW, Vallor AC, Wickes BL, Patterson TF: **Antifungal susceptibilities among different serotypes of *Cryptococcus gattii* and *Cryptococcus neoformans*.** *Antimicrob Agents Chemother* (2009) **53**(1):309-311.

104. Illnait-Zaragozi MT, Martínez GF, Curfs-Breuker I, Fernández CM, Boekhout T, Meis JF: ***In vitro* activity of the new azole isavuconazole (BAL4815) compared with six other antifungal agents against 162 *Cryptococcus neoformans* isolates from Cuba.** *Antimicrob Agents Chemother* (2008) **52**(4):1580-1582.

105. Yamazumi T, Pfaller MA, Messer SA, Houston A, Hollis RJ, Jones RN: ***In vitro* activities of ravuconazole (BMS-207147) against 541 clinical isolates of *Cryptococcus neoformans*.** *Antimicrob Agents Chemother* (2000) **44**(10):2883-2886.

106. Miller JL, Schell WA, Wills EA, Toffaletti DL, Boyce M, Benjamin DK Jr, Bartroli J, Perfect JR: ***In vitro* and *in vivo* efficacies of the new triazole albaconazole against *Cryptococcus neoformans*.** *Antimicrob Agents Chemother* (2004) **48**(2):384-387.

107. Groll AH, Walsh TJ: **Uncommon opportunistic fungi: New nosocomial threats.** *Clin Microbiol Infect* (2001) **7**(Suppl 2):8-24.

108. Husain S, Alexander BD, Munoz P, Avery RK, Houston S, Pruett T, Jacobs R, Dominguez EA, Tollemar JG, Baumgarten K, Yu CM *et al*: **Opportunistic mycelial fungal infections in organ transplant recipients: Emerging importance of non-*Aspergillus* mycelial fungi.** *Clin Infect Dis* (2003) **37**(2):221-229.

109. Walsh TJ, Groll A, Hiemenz J, Fleming R, Roilides E, Anaissie E: **Infections due to emerging and uncommon medically important fungal pathogens.** *Clin Microbiol Infect* (2004) **10** (Suppl 1):48-66.

110. Johnson EM, Szekely A, Warnock DW: ***In vitro* activity of voriconazole, itraconazole and amphotericin B against filamentous fungi.** *J Antimicrob Chemother* (1998) **42**(6):741-745.

111. Cuenca-Estrella M, Ruiz-Díez B, Martínez-Suárez JV, Monzón A, Rodríguez-Tudela JL: **Comparative *in vitro* activity of voriconazole (UK-109,496) and six other antifungal agents against clinical isolates of *Scedosporium prolificans* and *Scedosporium apiospermum*.** *J Antimicrob Chemother* (1999) **43**(1):149-151.

112. Meletiadis J, Meis JF, Mouton JW, Rodriquez-Tudela JL, Donnelly JP, Verweij PE: ***In vitro* activities of new and conventional antifungal agents against clinical *Scedosporium* isolates.** *Antimicrob Agents Chemother* (2002) **46**(1):62-68.

113. Gilgado F, Serena C, Cano J, Gené J, Guarro J: **Antifungal susceptibilities of the species of the *Pseudallescheria boydii* complex.** *Antimicrob Agents Chemother* (2006) **50**(12):4211-4213.

114. Capilla J, Yustes C, Mayayo E, Fernández B, Ortoneda M, Pastor FJ, Guarro J: **Efficacy of albaconazole (UR-9825) in treatment of disseminated *Scedosporium prolificans* infection in rabbits.** *Antimicrob Agents Chemother* (2003) **47**(6):1948-1951.

115. Bartlett MS, Queener SF, Shaw MM, Richardson JD, Smith JW: ***Pneumocystis carinii* is resistant to imidazole antifungal agents.** *Antimicrob Agents Chemother* (1994) **38**(8):1859-1861.

116. Utili R, Durante-Mangoni E, Basilico C, Mattei A, Ragone E, Grossi P: **Efficacy of caspofungin addition to trimethoprim-sulfamethoxazole treatment for severe pneumocystis pneumonia in solid organ transplant recipients.** *Transplantation* (2007) **84**(6):685-688.

117. Hof H, Schnülle P: ***Pneumocystis jiroveci* pneumonia in a patient with Wegener's granulomatosis treated efficiently with caspofungin.** *Mycoses* (2008) **51**(Suppl 1):65-67.

118. Powles MA, Liberator P, Anderson J, Karkhanis Y, Dropinski JF, Bouffard FA, Balkovec JM, Fujioka H, Aikawa M, McFadden D, Schmatz D: **Efficacy of MK-991 (L-743,872), a semisynthetic pneumocandin, in murine models of *Pneumocystis carinii*.** *Antimicrob Agents Chemother* (1998) **42**(8):1985-1989.

119. Morales IJ, Vohra PK, Puri V, Kottom TJ, Limper AH, Thomas CF Jr: **Characterization of a lanosterol 14 α-demethylase from *Pneumocystis carinii*.** *Am J Respir Cell Mol Biol* (2003) **29**(2): 232-238.

120. Wheat LJ, Connolly P, Smedema M, Durkin M, Brizendine E, Mann P, Patel R, McNicholas PM, Goldman M: **Activity of newer triazoles against *Histoplasma capsulatum* from patients with AIDS who failed fluconazole.** *J Antimicrob Chemother* (2006) **57**(6): 1235-1239.

121. Clemons KV, Martinez M, Calderon L, Stevens DA: **Efficacy of ravuconazole in treatment of systemic murine histoplasmosis.** *Antimicrob Agents Chemother* (2002) **46**(3):922-924.

122. Thompson GR 3rd, Wiederhold NP, Sutton DA, Fothergill A, Patterson TF: ***In vitro* activity of isavuconazole against *Trichosporon*, *Rhodotorula*, *Geotrichum*, *Saccharomyces* and *Pichia* species.** *J Antimicrob Chemother* (2009) **64**(1):79-83.

123. Ghannoum MA, Isham N: **Antifungal activity of BAL4815, a novel azole, against dermatophytes.** *Trends in Medical Mycology, Berlin, Germany* (2005) **2**:Abs P009.

124. Nweze EI, Curfs-Breuker I, Janssen BGJ, De Hoog GS, Meis JF: ***In vitro* activity of posaconazole with seven antifungal agents against 80 clinical and 15 environmental isolates of *Exophiala dermatidis*.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2006) **46**:Abs M-1588.

125. Serena C, Ortoneda M, Capilla J, Pastor FJ, Sutton DA, Rinaldi MG, Guarro J: ***In vitro* activities of new antifungal agents against *Chaetomium* spp. and inoculums standardization.** *Antimicrob Agents Chemother* (2003) **47**(10):3161-3164.

126. Muñoz C, Giusiano AJ, Quindos G, Rojas G, Sosa F, Eraso MA: **Triazolic antifungal activity against *Malassezia* strains.** *Trends in Medical Mycology*, *Torino, Italy* (2007) **3**:Abs P-043.

127. Welshenbaugh AR, Angulo D, Ghannoum M: **Time kill activity of albaconazole against agents of onychomycosis and tinea capitis.** *Interscience Conference on Antimicrobial Agents and Chemotherapy* (2007) **47**:Abs M-1814.