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**REVIEW**

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## New and Investigational Triazole Agents for the Treatment of Invasive Fungal Infections

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### Summary

**The incidence of invasive fungal infections (IFIs) caused by both common and uncommon opportunistic fungi is increasing along with emerging fungal resistance. Since traditional agents (amphotericin B, fluconazole, itraconazole) are limited by an inadequate spectrum of activity, drug resistance or toxicity, there is a great interest in the development of new antifungal agents for treatment of IFIs in high-risk populations. In recent years a number of systemic antifungal drugs have become available and options for treatment of IFIs have expanded. A new generation of triazole agents (voriconazole, posaconazole, isavuconazole, ravuconazole and albaconazole), with a broad spectrum of activity and sufficient improvements in potency to overcome resistance have emerged and represent an alternative to conventional antifungals for the prevention and treatment of IFIs. This article focuses on the microbiology, pharmacology, clinical efficacy and safety of the new antifungal triazole generation..**

**Key words: Voriconazole, posaconazole, isavuconazole, ravuconazole, albaconazole, invasive fungal infections.**

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### INTRODUCTION

The incidence of invasive fungal infections (IFIs) has increased dramatically during the past 30 years<sup>1</sup>. The most notable explanation for this increase is a rise in the number of immunocompromised patients due to advances in transplantation, the emergence of AIDS, and a rise in the number of invasive surgical procedures<sup>2</sup>. Until few years ago the treatment options for patients with deadly fungal infections were primarily amphotericin B and the azoles, fluconazole and itraconazole. These agents are limited by an inadequate spectrum of activity, drug resistance or toxicity. Thus, new agents with improved activity and safety profiles are greatly needed. Most recently a new triazole generation has been developed to meet the increasing need for new antifungals and address the rising incidence of IFIs and the emergence of fungal resistance<sup>3,4,5,6,7,8,9</sup>.

Voriconazole and posaconazole have been licensed by the FDA while isavuconazole, ravuconazole and al-

baconazole are currently in various stages of clinical development.

This review summarizes the potential role of the new triazole generation based on data available from microbiological, pharmacological and clinical studies.

### MECHANISMS OF ACTION AND RESISTANCE

Azole antifungals belong to the group of ergosterol biosynthesis inhibitors<sup>10</sup>. Azoles diffuse passively into fungal cells where they inhibit cytochrome P450-dependent lanosterol 14a-demethylase (CYP51) present in practically all yeasts and molds. This enzyme is involved in the synthesis of ergosterol, which is a major and essential lipid constituent of the cell membrane of fungi, not present in mammalian cells. Exposure of fungi to azoles leads to accumulation of methylated sterols, depletion of ergosterol, and inhibition of cell growth<sup>11</sup>. The lack of or shortage of ergosterol will weaken the stability of the fungal cell membrane, the

transport of nutrients and the chitin synthesis. This will finally interfere with the replication of fungal cells and will enhance their susceptibility to host-defense mechanisms. The different affinity of azole compounds to the various cytochrome P450 isoenzymes has been described<sup>12</sup>.

The growing prominence of antifungal azole resistance is becoming a major problem. There are several mechanisms by which yeasts can become resistant to azole antifungals. Resistance can result from: (i) altered cellular accumulation of azole antifungal due to increased expression of efflux pumps; (ii) ergosterol biosynthesis pathway modification; (iii) increased cellular content of CYP51; (iiii) decreased affinity of CYP51 to azoles<sup>13,14,15</sup>.

### VORICONAZOLE

Voriconazole is structurally similar to fluconazole, with the major difference being the substitution of a fluoropyrimidine group in place of a triazole moiety<sup>16</sup>. Voriconazole was approved by FDA in May 2002 for the treatment of invasive aspergillosis and infections caused by *Scedosporium apiospermum* and *Fusarium* spp. in cases of intolerance to or refractoriness of other antifungal agents. In November 2003, a license was granted for its use in the treatment of esophageal candidiasis. In December 2004, voriconazole was approved for the treatment of disseminated candidiasis.

#### *In vitro* susceptibility testing

Compared to reference triazoles, voriconazole is several-fold more active than fluconazole and itraconazole against most fungal species studied. The minimum inhibitory concentration (MIC) breakpoints proposed by the Clinical and Laboratory Standards Institute (CLSI) for voriconazole and *Candida* spp. are as follows: susceptible, 1 µg/mL and resistant, 4 µg/mL. Voriconazole exhibits broad-spectrum activity at concentrations of 0.06 µg/mL against yeasts and 0.10 µg/mL against dermatophytes<sup>17,18</sup>. MIC<sub>90</sub> values for *Epidermophyton* spp. are 1 µg/mL<sup>19</sup>. Voriconazole is active against all *Candida* spp., including those that are inherently fluconazole-resistant, although cross-resistance has been observed<sup>10,20,21</sup>. As described by Sheehan *et al.*<sup>10</sup> for some, but not all, fluconazole-resistant strains of *C. albicans*, MICs of voriconazole are higher than those noted for fluconazole-susceptible strains. Abraham *et al.*<sup>22</sup> also found that voriconazole maintains activity against itraconazole-resistant *Aspergillus fumigatus* isolates, showing only a modest rise in the MICs. This suggests that voriconazole may have additional mechanisms of fungal killing since complete cross-resistance did not develop.

Voriconazole and selected comparators were tested against 6970 invasive isolates of *Candida* spp. from worldwide sites<sup>23</sup>. Voriconazole was comparable in spectrum against the recently isolated *Candida* spp. to fluconazole, but it showed a spectrum of activity

greater than that of itraconazole. The MIC<sub>90</sub> values for voriconazole against all *Candida* spp. were 0.25 mg/mL<sup>23</sup>.

An international survey tested a total of 4169 clinical isolates of *Candida* spp. and *Cryptococcus neoformans* against voriconazole and 2 comparator agents. Voriconazole was very active against *Candida* spp. and *C. neoformans* with MIC<sub>90</sub> values of 1 µg/mL<sup>24</sup>. Increases in resistance among individual *Candida* spp. to voriconazole were not detected by the SENTRY Antimicrobial Surveillance Program during 2003<sup>25</sup>. Voriconazole showed excellent *in vitro* activity against *Candida* spp. and *Aspergillus* spp. with MIC<sub>90</sub> value of 1 µg/mL<sup>25</sup>. In other susceptibility studies voriconazole has exhibited pronounced activity against most *Aspergillus* spp. (MIC<sub>90</sub> 0.01 to 2 µg/mL)<sup>26,27</sup>. Furthermore, voriconazole is also effective against a variety of *Fusarium* spp, such as *Scedosporium* spp., as well as dimorphic fungi *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Coccidioides immitis*<sup>28,29,30,31</sup>. The drug is fungicidal *in vitro* for a majority of *Aspergillus* spp.<sup>32</sup>. In contrast, it appears to exhibit fungistatic activity against *Candida* spp.<sup>33</sup>. Zygomycetes are known to be resistant to voriconazole *in vitro* and *in vivo*<sup>31</sup>.

#### Pharmacokinetics

The pharmacokinetic properties of voriconazole have been defined in various studies in healthy volunteers, patients, and special populations<sup>16,34,35</sup>. Voriconazole is well absorbed, with an oral bioavailability of >95%. It takes 1 to 2 hours to reach maximum plasma concentrations (C<sub>max</sub>) after dosing. However, the bioavailability is decreased and the time to reach maximum drug concentration in plasma (t<sub>max</sub>) extends when voriconazole is administered with a high-fat meal<sup>16,36</sup>. Absorption is not diminished when voriconazole is administered with gastric acid-suppressing agents such as cimetidine, ranitidine, or omeprazole<sup>16</sup>. The pharmacokinetic properties of voriconazole are similar whether given intravenously or orally<sup>35,36,37</sup>. It is moderately protein bound (58%) and extensively distributed into tissue<sup>16</sup>. Voriconazole exhibits nonlinear pharmacokinetics, possibly due to saturable first-pass metabolism and systemic clearance. Dose-dependent accumulation and decreased systemic clearance are observed following administration of multiple doses<sup>34,35,36</sup>. Voriconazole is extensively metabolized in the liver to the N-oxide metabolite. The main hepatic cytochrome P (CYP) 450 enzyme responsible for voriconazole's metabolism is CYP2C19, although CYP2C9 and CYP3A4 are also involved. Allelic polymorphisms of CYP2C19 have been shown to be the most important determinants of voriconazole clearance, resulting in two phenotypes: poor and extensive metabolizers. Poor metabolizers also have higher plasma accumulation after multiple dosing<sup>37,38,39,40</sup>.

#### Clinical studies

Voriconazole has been assessed in patients with invasive aspergillosis, esophageal candidiasis and febrile neutropenia. To evaluate its efficacy and safety in acute invasive aspergillosis, an open, noncomparative study enrolled 141 patients, 116 of whom were considered evaluable. Voriconazole was given as primary therapy in 60 (52%). Good responses were seen in 56 (48%); 16 (14%) showed complete response and 40 (34%) partial response. A **stable** response was seen in 24 patients (21%), and 36 (31%) of the infections failed to respond to therapy<sup>41</sup>.

A subsequent large, randomized trial demonstrated a superior response rate and survival advantage for patients with invasive aspergillosis receiving voriconazole as compared with deoxycholate amphotericin B<sup>42</sup>. A total of 144 patients in the voriconazole group and 133 patients in the amphotericin B group with definite or probable aspergillosis received at least one dose of treatment. At week 12, there were successful outcomes in 53% of the patients in the voriconazole group and 32% of those in the amphotericin B group. The survival rate at 12 weeks was 71% in the voriconazole group and 58% in the amphotericin B group. This study shows the superiority of voriconazole over amphotericin B as initial therapy for invasive aspergillosis, in terms of response rate, survival rate, and safety<sup>42</sup>. Voriconazole is likely to be a better treatment choice in infections due to *Aspergillus terreus*, which is intrinsically resistant to amphotericin B<sup>43</sup>.

A multicenter, randomized, double-blind, double-dummy study compared the efficacy, safety, and tolerability of voriconazole (200 mg twice daily) and fluconazole (400 mg on day 1, followed by 200 mg, once daily) in 391 immunocompromised patients for the treatment of esophageal candidiasis<sup>44</sup>. Primary efficacy analysis of 256 patients revealed success rates of 98.3% with voriconazole and 95.1% with fluconazole. The overall safety and tolerability of both antifungals were **acceptable**: voriconazole is at least as effective as fluconazole for the treatment of esophageal candidiasis<sup>44</sup>.

Another multicenter, randomized study has recently compared voriconazole therapy with a regimen of amphotericin B followed by fluconazole for the treatment of candidaemia in non-neutropenic patients<sup>45</sup>. Of 422 patients randomized, 370 were included in the modified intention-to-treat population. Voriconazole was non-inferior to amphotericin B/fluconazole in the primary efficacy analysis, with successful outcomes in 41% of patients in both treatment groups<sup>45</sup>.

The results of a randomized, international, multicenter trial that compared voriconazole with liposomal amphotericin B as empirical antifungal therapy, are controversial<sup>46</sup>. Voriconazole did not fulfill the protocol-defined criteria for noninferiority to liposomal amphotericin B with respect to overall response to empirical therapy, since the 95% CI fell just outside the margin allowed by 0.6%.

Voriconazole is often used for empirical treatment of febrile neutropenic patients although it failed to gain

approval for this indication by the FDA. The authors evaluated the efficacy, tolerability, and safety of voriconazole as salvage treatment for 273 patients refractory to other agents and as primary treatment for 28 patients with infections for which there is no approved therapy. Voriconazole was associated with satisfactory global responses in 50% of the overall cohort; specifically, in the patients whose infections have no approved antifungal therapy. The efficacy rates for voriconazole were 43.7% for aspergillosis, 57.5% for candidiasis, 38.9% for cryptococcosis, 45.5% for fusariosis, and 30% for scedosporiosis<sup>47</sup>.

### *Adverse effects and interactions*

The safety of voriconazole has been evaluated in patients and healthy volunteers in clinical trials<sup>16,46</sup>. The most commonly reported adverse events are visual disturbances, hepatic abnormalities, dermatological reactions, fever, nausea, vomiting, abdominal pain, headache and hallucinations. The events often responsible for discontinuation of therapy include visual disturbances and elevations in hepatic enzyme levels<sup>44,46</sup>. Visual disturbances generally occurred during the first week of therapy and were reversible after the patient discontinued therapy. Although the mechanism of action for the visual disturbances is unknown, the retina appears to be the site of action<sup>16,45,48</sup>. Recent observations suggest that hepatic toxicity and visual disturbance might be dose related<sup>48,49</sup>. Skin rashes are the second most common adverse effect observed with voriconazole therapy<sup>16</sup>. Most of these were mild and did not require treatment discontinuation. There have been, however, rare cases of patients developing serious cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme)<sup>50</sup>. Photosensitivity may occur, particularly in patients receiving long-term therapy<sup>51</sup>.

A wide array of potential pharmacokinetic interactions should be kept in mind during voriconazole treatment, since variations in its pharmacokinetics may be associated with decreased efficacy or with toxicity.

Voriconazole affects the metabolism of several drugs, and other drugs affect its metabolism as well<sup>35,37,38,39,40</sup>. Voriconazole has many potential interactions because of its extensive hepatic metabolism by CYP2C9, CYP2C19 and CYP3A4. It is both a substrate and an inhibitor of the CYP450 system. By inhibiting CYP2C9 and CYP2C19 voriconazole affects drugs such as warfarin, antiretroviral agents, cyclosporine and tacrolimus<sup>52,53,54,55</sup>. Voriconazole is also a substrate of CYP2C19. It is contraindicated with enzyme inducers such as carbamazepine, rifampin, and phenobarbital which can significantly decrease its concentration<sup>16</sup>. Other drug interactions relate to the potential of voriconazole to prolong the QT interval, such as with terfenadine, astemizole, cisapride, pimozide and quinidine<sup>16</sup>.

### *Dosage and administration*

A major advantage of voriconazole is that it is available in both intravenous and oral formulations. Voriconazole injection is supplied as a sterile lyophilized powder in a single-use vial containing 200 mg of active drug and 3200 mg of sulfobutyl ether - cyclodextrin sodium (SBECD) <sup>16</sup>. Therapy can be initiated with a loading dose of 6 mg/kg intravenously every 12 hours for 2 doses, followed by a maintenance dose of 4 mg/kg intravenously every 12 hours. If patients are unable to tolerate this dosage because of side effects, the dose may be decreased to 3 mg/kg intravenously every 12 hours.

Patients who are able to take oral medications may be switched to oral voriconazole. Oral therapy (tablets and suspension) for patients weighing 40 kg can be initiated at 200 mg orally twice a day and increased to 300 mg orally twice a day if the response is inadequate. For patients weighing <40 kg, the dose should be halved. If a patient is intolerant to treatment, the oral dose may be decreased <sup>40</sup>. Oral doses should be taken at least 1 hour before or after meals, because food reduces the rate and extent of absorption (bioavailability reduced by 22%) <sup>16, 36</sup>.

Based on the marked interindividual variability of voriconazole levels, the achievement of therapeutic drug levels appears to be mandatory to correlate serum concentrations and treatment efficacy. Thus, voriconazole therapeutic drug monitoring improves the efficacy and safety of therapy in critically ill patients. Dose adjustments must be recommended for elderly patients and subjects with chronic hepatic impairment and renal insufficiency <sup>17</sup>. In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, (SBECD), occurs <sup>16</sup>. Oral voriconazole should be administered to these patients unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. In that case serum creatinine levels should be monitored and, if increases occur, oral voriconazole therapy must be taken into account.

## POSACONAZOLE

Posaconazole is structurally derived from itraconazole by replacement of the chlorine substituents with fluorine in the phenyl ring and hydroxylation of the triazolone side chain <sup>56</sup>. Posaconazole was approved by the FDA in September 2006 for prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients <sup>57</sup>. Subsequently, posaconazole has also been approved for treatment of oropharyngeal candidiasis as first-line therapy as well as for treatment of fusariosis, chromoblastomycosis, mycetoma and coccidiomycosis infections in adult patients with refractory disease or in those who are intolerant of certain commonly used antifungals <sup>57, 58</sup>.

### *In vitro* susceptibility testing

Posaconazole has emerged as having the broadest

spectrum of *in vitro* activity against *Candida* spp., *C. neoformans*, *Aspergillus* spp., Zygomycetes and other opportunistic and endemic fungal pathogens <sup>57,59,60,61,62,63</sup>. Posaconazole has not been assigned interpretive breakpoints by the CLSI. For purposes of comparison, Pfaller *et al.* <sup>64</sup> applied the voriconazole MIC breakpoints to posaconazole (susceptible, 1 µg/mL; resistant, 4 µg/mL). A global antifungal surveillance program examined the *in vitro* activities of posaconazole, voriconazole, and fluconazole against 3932 isolates of *Candida* spp. and 237 isolates of *C. neoformans* obtained from over 100 medical centers worldwide during 2001 and 2002. Voriconazole and posaconazole were very active against *Candida* spp. (97-98% susceptible at MICs of 1 µg/mL) and *C. neoformans* (98-100% susceptible at MICs of 1 µg/mL). *Candida albicans* (MIC<sub>90</sub>, 0.015-0.03 µg/mL) was the most susceptible species of *Candida* to both agents and *Candida glabrata* (MIC<sub>90</sub>, 1-2 µg/mL) was the least susceptible. Both posaconazole and voriconazole were more active than fluconazole against all *Candida* spp. and *C. neoformans* <sup>24</sup>.

In a recent study, posaconazole and several comparison antifungal agents were tested against 19,000 clinically important strains of yeasts and molds <sup>62</sup>. MIC<sub>90</sub> values against all yeasts and molds were 1 µg/mL. In this comparative study, posaconazole was more potent than fluconazole against all organisms tested and was frequently more potent than itraconazole, voriconazole, and amphotericin B. Among the triazoles, posaconazole was the only agent that exhibited consistent activity against the Zygomycetes. Posaconazole has also shown good activity against the vast majority of organisms that cause aspergillosis, candidiasis, cryptococcosis, chromoblastomycosis, mycetoma, and phaeohyphomycosis, confirming its potential as a useful agent for patients with serious systemic mycoses <sup>62</sup>.

The posaconazole MIC<sub>90</sub> for 1903 yeast isolates from France was 1 µg/mL (range, 0.015 to 8 µg/mL). Ninety percent of isolates with fluconazole MICs of 8 µg/mL (n = 509) and 90% of those with voriconazole MICs of 2 µg/mL (n = 80) were inhibited by 2 and 8 µg/mL of posaconazole, respectively. *C. neoformans* isolates were highly susceptible to posaconazole, and slightly higher posaconazole MIC<sub>50</sub> values than those of voriconazole were found <sup>63</sup>. Posaconazole has shown potent *in vitro* activity against *Aspergillus* spp. <sup>57,59,61,65</sup>. A global antimicrobial surveillance program evaluated the *in vitro* activity of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi. Overall, posaconazole was the most active compound, inhibiting 94% of isolates at a MIC of 1 µg/mL <sup>66</sup>. Diekema *et al.* <sup>61</sup> examined the *in vitro* activity of posaconazole, caspofungin, voriconazole, ravuconazole, itraconazole, and amphotericin B against 448 recent clinical mold isolates. Posaconazole, voriconazole, and caspofungin are more potent than amphotericin

B against *A. fumigatus*. All three new triazoles and caspofungin were more potent than amphotericin B against *A. terreus*<sup>61</sup>. Furthermore, posaconazole is also effective against *C. neoformans* and *Fusarium* spp.<sup>57,59,65,67</sup>. The MIC<sub>90</sub> values for posaconazole against *C. neoformans* isolates were 1 mg/mL. Posaconazole has MIC<sub>90</sub> values ranging from 0.25 to >8 mg/mL against *Fusarium* spp. The antifungal activity of posaconazole includes *Rhizopus* spp., *B. dermatitidis*, *C. immitis*, *H. capsulatum* and other dimorphic fungi<sup>57,59,65,68</sup>.

### Pharmacokinetics

Posaconazole is available only as an oral suspension. Dosing frequency and prandial state appear to be the main factors influencing its absorption<sup>69,70,71</sup>. In a randomized, open-label, crossover, single-dose study a high-fat meal increased the bioavailability of posaconazole by 40%. Subjects were given posaconazole 200 mg as suspension with a high-fat breakfast, as suspension with a non-fat breakfast, or as tablets with a high-fat breakfast after 10 hours fasting<sup>70</sup>. In the fasting and fed states, administration of an antacid did not significantly influence the bioavailability of posaconazole (+ 15% fasting, -12% fed)<sup>70</sup>. Mean area under the curve (AUC) and C<sub>max</sub> were four times greater when posaconazole was administered with a high fat meal than when it was administered after fasting<sup>70</sup>. Similarly administration of posaconazole with a nutritional supplement (Boost Plus) increased the C<sub>max</sub> and AUC values<sup>72</sup>.

In a study of healthy male volunteers administered posaconazole 800 mg/day under fasting conditions, 200 mg four times a day and 400 mg twice a day dosing was associated with increases in C<sub>max</sub> and t<sub>max</sub> compared with once-daily dosing. These data suggest that divided daily administration (every 12 or 6 hours) significantly increases posaconazole exposure under fasting conditions<sup>71</sup>. Posaconazole is extensively distributed into body tissues including, bone, central nervous system and eye tissue<sup>73,74,75,76</sup>. It is highly bound to proteins (>90%) and has a long half-life (t<sub>1/2</sub>) ranging from 25 to 31 hours in healthy subjects<sup>69</sup>; whereas t<sub>1/2</sub> is shorter (from 12 to 17 hours) in patients with IFI or a history of bone marrow transplantation<sup>77</sup>. Posaconazole is primarily metabolized in the liver, undergoing glucuronidation to inactive metabolites<sup>78</sup>. Although posaconazole is not a substrate of hepatic CYP3A4, it has been found to significantly decrease the hepatic activity of this enzyme<sup>79</sup>. Posaconazole is mainly eliminated in the feces (77%) as unchanged compound and a small amount (14%) is excreted in the urine<sup>73</sup>. Limited renal elimination allows use of posaconazole without age restrictions associated with possible renal dysfunction<sup>80</sup>.

### Clinical studies

Compared with other antifungal agents posaconazole appears efficacious in patients with invasive as-

pergilliosis who were refractory to or intolerant of conventional antifungal therapy<sup>81</sup>. Two phase III clinical studies for posaconazole indicate that the drug was at least noninferior to a standard-of-care azole antifungal agent for preventing IFIs caused by *Candida* or *Aspergillus* in highly immunosuppressed patients<sup>82,83</sup>. In the first study posaconazole was compared with fluconazole for prophylaxis against IFIs in patients with graft-versus-host disease (GVHD) receiving immunosuppressive therapy<sup>82</sup>. At the end of the study period the authors concluded that posaconazole was similar to fluconazole for prophylaxis against fungal infections among patients with GVHD<sup>82</sup>. The second trial compared posaconazole with both fluconazole and itraconazole as a prophylactic treatment of neutropenic patients after receipt of cancer chemotherapy<sup>83</sup>. The finding showed that prophylaxis with posaconazole was superior to prophylaxis with fluconazole or itraconazole in the prevention of proven or probable IFI and resulted in lower mortality from any cause and longer survival free from proven or probable IFI<sup>83</sup>.

Based on the results of two randomized controlled clinical studies conducted in HIV-infected patients<sup>84,85</sup>, posaconazole was also approved for the treatment of oropharyngeal candidiasis as first-line therapy in adult patients with refractory disease or in those who are intolerant of certain commonly used antifungal agents<sup>58</sup>. Clinical evidence suggests that posaconazole is efficacious against infections caused by filamentous fungi of the Zygomycetes class and of *Fusarium* spp., that are often unresponsive to other azole antifungal agents<sup>86,87,88,89</sup>.

### Adverse events and interactions

In early clinical trials in neutropenic patients and patients with fungal infections, the most adverse events were similar to those seen in the comparator or placebo arms<sup>69,90</sup>. The most common of these are nausea, vomiting, headache, abdominal pain and diarrhea. Elevated liver enzymes may be observed.

Posaconazole inhibits CYP3A4 and, thus, has the potential for significant pharmacokinetic interactions with drugs metabolized by this isoform<sup>79</sup>. Administration of posaconazole with other substrates and/or inducers of this enzyme system requires caution<sup>79</sup>. Drug-drug interactions with posaconazole can be expected, leading to a contraindication for coadministration of posaconazole with some other drugs. Coadministration of posaconazole and rifamycins could result in a loss in therapeutic efficacy of posaconazole due to reduced systemic posaconazole exposure due to induced metabolism. Two pharmacokinetic studies in healthy subjects found that posaconazole increases cyclosporin and tacrolimus concentrations<sup>91</sup>.

### Dosage and administration

For prophylaxis of IFI, the recommended dosage of oral suspension is 200 mg three times/day until the

resolution of neutropenia or immunosuppression. For the treatment of fungal infections the recommended dosage is 800 mg daily given in two or four divided doses<sup>57</sup>. A loading dose of 100 mg twice/day on the first day, followed by 100 mg daily for 13 days is recommended for the treatment of oropharyngeal candidiasis<sup>56-59</sup>. Each dose of posaconazole should be given with a full meal or liquid nutritional supplement to enhance absorption. If a patient cannot tolerate feedings, alternative antifungals should be considered<sup>57</sup>.

### ISAVUCONAZOLE

BAL-8557 (isavuconazonium) is the water-soluble pro-drug of BAL-4815 (isavuconazole). After oral or i.v. administration, BAL-8557 is rapidly cleaved into isavuconazole, in a reaction catalyzed by plasma esterases<sup>94</sup>. Isavuconazole (BAL4815) is a promising novel broad-spectrum triazole in late-stage clinical development that has proven active *in vitro* against *Aspergillus* and *Candida* species.

An *in vitro* investigation evaluated the antifungal activities of isavuconazole, voriconazole, and fluconazole against 1007 isolates of *Zygomycete*, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species<sup>31</sup>. Isavuconazole and voriconazole had a MIC<sub>50</sub> and MIC<sub>90</sub>, respectively, of 1 and 1 µg/mL and 0.5 and 1 µg/mL against *Aspergillus* spp., and of 0.015 and 0.03 µg/mL and 0.25 and 0.125 µg/mL against *Candida* spp. (including fluconazole-resistant strains)<sup>31</sup>.

Isavuconazole was compared with six other antifungal agents against 162 *C. neoformans* isolates from Cuba<sup>92</sup>. Isavuconazole and posaconazole seem to be potentially active drugs for treating cryptococcal infections with MIC<sub>90</sub> values of 0.016 µg/mL.<sup>92</sup>

Seifert *et al.*<sup>93</sup> compared the *in vitro* activities of isavuconazole and five other antifungal agents against 296 *Candida* isolates that were recovered consecutively from blood cultures. For isavuconazole, MIC<sub>50</sub>/MIC<sub>90</sub> ranged from 0.002/0.004 µg/mL for *C. albicans* to 0.25/0.5 µg/mL for *C. glabrata*. Isavuconazole was more potent than fluconazole against all organisms tested and often more potent than itraconazole, voriconazole, amphotericin B, and flucytosine, confirming its potential as a useful agent for patients with serious systemic *Candida* infections<sup>93</sup>.

The first pharmacokinetic data of isavuconazole in humans were obtained in a single-ascending-dose study after intravenous and oral administrations of its water soluble pro-drug (BAL-8577) in healthy subjects<sup>94</sup>. In this study C<sub>max</sub> values of isavuconazole were observed 1.5-3 h after oral drug intake or at the end of the 1 h intravenous infusion. Isavuconazole was characterized by a large volume of distribution (155-292 and 304-494 L after oral and intravenous administration, respectively) and a long elimination half-life (56-77 after oral administration and 76-104 h after intravenous administration)<sup>94</sup>. The plasma clearance was low (1.9-

2.8 and 2.8-5.0 L/h after oral and intravenous administration, respectively)<sup>94</sup>.

The effect of loading doses of isavuconazole was investigated in a multiple-dose pharmacokinetic study in 24 healthy male subjects<sup>95</sup>. Loading doses of BAL8557 were equivalent to 100 mg (followed by once-daily maintenance doses of 50 mg) or 200 mg (followed by once-daily maintenance doses of 100 mg) of BAL4815. After both routes of administration, C<sub>max</sub> and AUC of BAL4815 increased proportionally to the administered dose. AUC values reflected a four- to five-fold accumulation of active drug in plasma during once-daily dosing, which is in line with the long elimination half-life of BAL4815 determined after the last administration (mean, 84.5 to 117 h). All adverse events reported were mild or moderate<sup>95</sup>.

Positive phase II results for isavuconazole in the treatment of esophageal candidiasis revealed both clinical efficacy and a safety profile comparable to standard therapy but with a potentially more flexible dosing schedule<sup>96</sup>. A pivotal phase III program including trials in invasive *Aspergillus* and *Candida* infections is ongoing.

### RAVUCONAZOLE

Ravuconazole (formerly BMS-207147 and ER-30346) is an investigational triazole agent structurally related to fluconazole and voriconazole. It is highly active *in vitro* against major pathogenic fungi such as *Candida* spp., *C. neoformans*, *A. fumigatus* and dermatophytes<sup>97,98,99</sup>. The *in vitro* activity of ravuconazole has been documented in several multicenter studies in a large number of clinical isolates of *Candida* spp. worldwide<sup>23,100</sup>.

The *in vitro* activities of ravuconazole and voriconazole were compared with those of amphotericin B, flucytosine, itraconazole, and fluconazole against 6970 isolates of *Candida* spp. obtained from over 200 medical centers worldwide. Both ravuconazole and voriconazole were very active against all *Candida* spp. (MIC<sub>90</sub> 0.25 µg/mL)<sup>23</sup>. Cuenca-Estrella *et al.*<sup>100</sup> investigated the *in vitro* activities of ravuconazole and four other antifungal agents against 1796 clinical yeast isolates, including fluconazole-susceptible and -resistant strains. Ravuconazole was active against the majority of fluconazole-resistant isolates; but for 102 of 562 (18%) resistant isolates, mainly *Candida tropicalis*, *C. glabrata*, and *C. neoformans*, ravuconazole MICs were 1 µg/mL. A SENTRY Antimicrobial Surveillance Program that compared *in vitro* activity of ravuconazole and currently marketed antifungal agents against 1548 clinical strains of yeast and filamentous fungi, confirmed the enhanced potency of ravuconazole against *Candida* spp., including fluconazole-resistant isolates<sup>25</sup>. MIC<sub>90</sub> values for the most prevalent *Candida* spp. were: *C. albicans* 0.008 µg/mL; *Candida parapsilosis* 0.12 µg/mL; *C. glabrata* 1 µg/mL; *Candida tropicalis* 0.12 µg/mL; and *Candida krusei*

0.5 µg/mL<sup>25</sup>.

In a study of 239 clinical isolates of *Aspergillus* spp. ravuconazole inhibited 92% of the isolates at a MIC of 1 µg/mL<sup>66</sup>. Yamazumi *et al.*<sup>98</sup> tested the *in vitro* activities of ravuconazole against 541 clinical isolates of *C. neoformans* and found that MIC<sub>90</sub> was 0.25 µg/mL.

Pfaller *et al.*<sup>67</sup> demonstrated the excellent activity of ravuconazole against 1811 clinical isolates of *C. neoformans* (99% of isolates susceptible at MIC of 1 µg/mL). Against the Zygomycetes, ravuconazole and itraconazole were the most active azoles, with modal MICs of 0.5–2 µg/mL<sup>101</sup>.

Cuenca-Estrella *et al.*<sup>102</sup> analyzed the *in vitro* activities of ravuconazole against 575 clinical strains of *Aspergillus* spp. and 348 nondermatophyte non-*Aspergillus* spp. Ravuconazole was active against *Aspergillus* spp., other hyaline filamentous fungi, black molds, and some *Mucorales*. Species such as *Scedosporium prolificans*, *Fusarium* spp., and *Scopulariopsis* spp. were resistant to ravuconazole<sup>102</sup>.

Ravuconazole is currently in clinical development and is available in oral and intravenous formulations. In a multiple ascending oral dose study, ravuconazole showed good oral bioavailability and a half-life of 5–7 days<sup>103</sup>. A long elimination half-life (76–202 h) and high protein binding (98%) were demonstrated in another phase II trial<sup>104</sup>.

Linear plasma pharmacokinetics were observed in healthy male subjects after intravenous administration of a water-soluble pro-drug of ravuconazole (BMS-379224)<sup>105</sup>. No toxicity was described<sup>105</sup>.

In an ascending oral dose study, single doses of ravuconazole (from 50 to 800 mg once daily) provided plasma levels above MIC of *Aspergillus* and *Candida* species after 7 days of dosing in healthy subjects<sup>106</sup>.

In another phase II trial, three regimens of ravuconazole (400 mg as a single dose, 50 mg once daily for 5 days, and 200 mg once daily for 5 days) were used to determine the efficacy of the drug in the treatment of oropharyngeal candidiasis in HIV infected subjects<sup>104</sup>. The most effective regimen was 200 mg once daily for 5 days with 85% of the subjects cured or improved<sup>104</sup>.

Ravuconazole shows promise for the treatment of oropharyngeal<sup>104</sup> and esophageal candidiasis<sup>107</sup> in immunocompromised patients and toenail onychomycosis in immunocompetent patients<sup>108</sup>.

## ALBACONAZOLE

Albaconazole (ALBA, UR-9825) is a new, broad-spectrum triazole antifungal agent presently under clinical investigation. It has shown potent activity against a broad range of organisms, including pathogens resistant to other antifungals (such as fluconazole or itraconazole)<sup>30,109</sup>. Capilla *et al.*<sup>30</sup> reported that the albaconazole MICs for the majority of filamentous fungi (*Aspergillus* spp, *Paecilomyces* spp. *Scytalid-*

*ium* spp.) ranged between 0.06 and 0.2 µg/mL.

Ramos *et al.*<sup>109</sup> evaluated the *in vitro* activity of albaconazole and compared it with that of fluconazole and itraconazole against 283 clinical isolates of *Candida* spp. Albaconazole was more potent against *Candida* spp. than both fluconazole and itraconazole, even against some *C. albicans* and *C. krusei* isolates with decreased susceptibility to fluconazole (MIC 16 µg/mL)<sup>109</sup>.

The activity of albaconazole was examined *in vitro* against a series of *C. neoformans* isolates for which the fluconazole MICs were as high as 64 µg/mL<sup>110</sup>. Albaconazole was active against all isolates<sup>110</sup>. Albaconazole showed an *in vitro* profile similar to those of the different antifungals tested (MIC 0.06 µg/mL for all the strains) against 70 strains of *Malassezia* spp.<sup>111</sup>. Ortoneda *et al.*<sup>112</sup> confirmed the generalized resistance of *Fusarium* spp. (MIC<sub>90</sub> 16–32 µg/mL) against albaconazole. However, an additive effect was observed for most of the *Fusarium* spp. tested when albaconazole was combined with amphotericin B<sup>112</sup>.

Albaconazole is undergoing Phase II clinical trials<sup>5</sup>.<sup>113</sup> Albaconazole has been shown to be rapidly absorbed in humans. C<sub>max</sub> values were reached in 2–4 h, and the drug was widely distributed through body fluids<sup>114</sup>.

A clinical multicenter study compared the efficacy and tolerability between five single oral doses of albaconazole and fluconazole 150 mg single dose in vulvovaginal candidiasis<sup>115</sup>. A single dose of albaconazole 40 mg seems to be more efficacious than fluconazole at 150 mg<sup>115</sup>.

## CONCLUSIONS

The new triazoles show excellent activity *in vitro* and *in vivo* against clinically important fungal organisms and are likely to be as effective as amphotericin B for the treatment of most IFIs in patients with a compromised immune system.

Voriconazole and posaconazole have a very broad spectrum of antifungal activity that includes *Candida* spp., filamentous fungi and the dimorphic endemic mycoses. Voriconazole is indicated for the treatment of invasive aspergillosis and serious infections caused by *S. apiospermum* and *Fusarium* spp. that are refractory to other antifungal agents. Voriconazole is available in both intravenous and oral formulations, facilitating the transition from parenteral to oral therapy. This is convenient for patients and helps contain costs. Drug-drug interactions and side effects, including hepatotoxicity, skin rashes, photosensitivity, visual disturbances and hallucination must be taken seriously into account by clinicians.

Posaconazole is the first member of the triazoles to have comparable *in vitro* activity to amphotericin B against the Zygomycetes. Posaconazole plays a significant role for the prophylaxis of IFIs in severely immunocompromised patients. Currently available only

as an oral suspension, posaconazole requires administration with food or as a nutritional supplement to assure adequate bioavailability.

Finally, the role of other antifungal triazoles (isavuconazole, ravuconazole and albaconazole) that are currently under development will be clarified in upcoming years. Isavuconazole's extended antifungal spectrum covers most yeasts and molds including fluconazole resistant *Candida* strains, *Aspergillus* and Zygomycetes. BAL-8557, a water-soluble pro-drug of isavuconazole, can be given by injection or orally. Ravuconazole shows promise for the treatment of systemic fungal infections such as candidiasis, aspergillosis and cryptococcal meningitis. In addition, it is also active against most species of the Zygomycetes class. Although isavuconazole and ravuconazole offer extended half-lives compared with other members of the triazole class, it is not clear that they carry other distinguishing characteristics. Albaconazole is also active against fluconazole-resistant *Candida* spp., *C. neoformans*, filamentous fungi and other life-threatening molds including amphotericin B-resistant strains but is not active against *Fusarium* spp.

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