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New pharmacological opportunities for the treatment of invasive mould diseases

Marie-Pierre Ledoux[1], Elise Toussaint[1], Julie Denis[2] and Raoul Herbrecht[1]*

[1]*Department of Oncology and Haematology, Hôpital de Hautepierre and Université de Strasbourg, Strasbourg, France;* [2]*Laboratoire de Parasitologie et de Mycologie Médicale, Hôpitaux Universitaires de Strasbourg, Strasbourg, France*

*Corresponding author. Department of Oncology and Haematology, Hôpital de Hautepierre, 1 av Molière, 67100 Strasbourg, France. Tel: +33-88-11-6788; E-mail: herbrecht@chru-strasbourg-strasbourg.fr

Recently, several randomized studies have been published that will shape treatment decisions in the prevention and management of invasive mould infections. Liposomal amphotericin B is an option for empirical or targeted treatment of invasive aspergillosis or mucormycosis, but for prophylaxis therapy, the triazole class now predominates. The triazole voriconazole is currently regarded as a drug of choice for the treatment of proven or probable invasive aspergillosis, and has shown significantly higher response rates than amphotericin B deoxycholate in this setting, with fewer severe drug-related adverse events. Isavuconazole, the newest triazole agent, offers the advantages of once-daily dosing, a wider spectrum of antifungal activity than voriconazole, predictable pharmacokinetics and fewer CYP enzyme-mediated drug interactions. A recent large randomized clinical trial showed mortality to be similar under isavuconazole or voriconazole in patients with invasive mould disease, with fewer drug-related adverse events in isavuconazole-treated patients. Another study has indicated that isavuconazole is also effective in mucormycosis infections but patient numbers were small and confirmation is awaited. Experimental studies combining different drug classes with antimould activity have been promising, but the clinical database is limited. A large randomized trial of combination therapy compared voriconazole plus the echinocandin anidulafungin versus voriconazole monotherapy in patients with invasive aspergillosis. Results showed the overall response rate to be similar, but combination therapy improved survival for the subpopulation of patients in whom the diagnosis was confirmed by serum and/or bronchoalveolar lavage fluid galactomannan positivity. This active field of research is likely to continue evolving rapidly in the coming years.

Introduction

The selection of an antimould agent to prevent or manage invasive infections can be complex. Many factors affect the decision, including likely fungal pathogens, the underlying disease, toxicity profile, drug interactions (e.g. with chemotherapy or immunosuppressive agents), contraindicated concomitant medication, previous infections, prior therapy, requirement for therapeutic drug monitoring and cost. Certain principles are well-established. In severely immunosuppressed patients, who are at the highest risk for invasive fungal disease, prophylaxis necessarily takes the form of a broad-spectrum agent active against yeasts and moulds, despite the risk of interference with the *Aspergillus* galactomannan detection test.[1] If a patient develops a suspected fungal infection while receiving fluconazole prophylaxis, empirical therapy with mould-active coverage should be initiated since the cause is likely to be a fluconazole-resistant *Candida* infection or an invasive mould infection. If an invasive fungal infection is suspected in a patient already receiving a mould-active prophylaxis, switching to an intravenous antimould agent in a different class is prudent.[2] In addition, given the relatively toxic nature of many antimould therapies, the agent with the most favourable safety profile should be preferred as long as efficacy can be maintained.

Within these accepted principles, however, the clinician is faced with a widening choice of drug classes and specific agents. Amphotericin B deoxycholate was historically the standard antimould agent in the management of invasive fungal infections but has high toxicity, including nephrotoxic effects and infusion-related side effects. Since the late 1990s, a number of antimould preparations have been introduced that demonstrate similar efficacy to amphotericin B but with less toxicity. As well as improved formulations of amphotericin B, these have included second-generation broad-spectrum triazoles (voriconazole, itraconazole, posaconazole, isavuconazole) and the echinocandin antifungals (caspofungin, micafungin and anidulafungin). This dramatic expansion in the antimould armamentarium is reflected in expert recommendations for antimould agents as prophylactic (Table 1), empirical (Table 2)[3–7] or targeted therapy (Tables 3 and 4).[3,4,6–8]

This is a rapidly evolving field and in the last 2 years several key randomized studies have been published that will shape future treatment decisions for invasive mould infections. These trials are

Table 1. Overview of international expert recommendations for choice of prophylaxis of invasive fungal infections including aspergillosis and empiric therapy for invasive aspergillosis

Publication	Clinical setting	Agents (grading)
IDSA (2016)[3,4]	Prolonged neutropenia	Posaconazole (strong recommendation; high-quality evidence) Voriconazole (strong recommendation; moderate-quality evidence) Itraconazole (strong recommendation; moderate-quality evidence)
	Allogeneic HSCT with GVHD	Posaconazole (strong recommendation; high-quality evidence) Itraconazole (strong recommendation; high-quality evidence) Voriconazole (strong recommendation; moderate-quality evidence)
	Lung transplantation	Voriconazole (strong recommendation; moderate-quality evidence) Itraconazole (strong recommendation; moderate-quality evidence) Inhaled AmB product (strong recommendation; moderate-quality evidence)
ECIL-5 (2013)[5]	AML and MDS, induction chemotherapy	Posaconazole (A-I) Itraconazole (B-I) Aerosolized LAmB (B-I) (only if combined with oral/iv fluconazole) Voriconazole (B-II)
	Allogeneic HSCT, pre-engraftment	Voriconazole (B-I) Itraconazole (B-I) Posaconazole (B-II) Aerosolized LAmB combined with oral/iv fluconazole (B-II) if high risk for mould infection Micafungin (B-I) if low risk for mould infection
	Allogeneic HSCT, after engraftment	Posaconazole (A-I) Voriconazole (B-I) Itraconazole (B-I)
ECIL-4 (2014)[6]	Children: acute leukaemia	Itraconazole (B-I)[a] Posaconazole (B-I)[b] LAmB (B-II)
	Children: allogeneic HSCT without GVHD	Voriconazole (B-I)[a] Itraconazole (B-I)[a]
	Children: allogeneic HSCT with GVHD	Voriconazole (B-I)[a] Posaconazole (B-I)[b]
ESCMID/EFISG (2014)[7]	Haematological malignancies, (e.g. AML), with prolonged and profound neutropenia	Posaconazole (A-I) Aerosolized LAmB combined with oral/iv fluconazole (B-I)
	Patients undergoing allogeneic HSCT until neutrophil recovery	Posaconazole (B-II) Aerosolized LAmB combined with oral/iv fluconazole (B-II)
	Patients undergoing allogeneic HSCT with GVHD and/or intensified IS	Posaconazole (A-I)

IS, immunosuppression; iv, intravenous; LAmB, liposomal amphotericin B; MDS, myelodysplastic syndrome.
[a]In patients aged ≥2 years.
[b]In patients aged ≥13 years.
Only those recommendations graded A (good evidence to support a recommendation for or against use), B (moderate evidence to support a recommendation for or against use) or strong recommendation (for IDSA guidelines) are shown. For details please refer to the full recommendations. Quality of evidence grading: I, evidence from ≥1 properly randomized controlled trial; II, evidence from ≥1 well-designed clinical trial, without randomization; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees. Strength of recommendation grading: A, good evidence to support a recommendation for or against use; B, moderate evidence to support a recommendation for or against use; C, poor evidence to support a recommendation.

discussed here and their implications for selection of antimould therapy in different settings are considered.

Lipid formulations of amphotericin B

Innovative lipid formulations of amphotericin B [liposomal amphotericin B (LAmB), amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion] have lessened the toll of adverse events and nephrotoxicity associated with the conventional formulation.[9–11] Despite their higher cost, LAmB and ABLC have largely replaced amphotericin B deoxycholate, which is no longer recommended for empirical therapy (Table 2), or for targeted therapy of invasive aspergillosis (Table 3). A randomized comparative study suggested no benefit in efficacy for amphotericin B colloidal

Table 2. Overview of international expert recommendations for choice of empirical therapy for invasive aspergillosis

Publication	Clinical setting	Agents (grading)
IDSA (2016)[3,4]	Empirical therapy for IFD, prolonged neutropenia and persistent fever	Lipid-AmB (strong recommendation; high-quality evidence) Caspofungin (strong recommendation; high-quality evidence) Micafungin (strong recommendation; high-quality evidence) Voriconazole (strong recommendation; moderate quality evidence)
ECIL-4 (2014)[6]	Children: empirical therapy for IFD, prolonged neutropenia and persistent fever	Caspofungin (A-I) LAmB (A-I)
ESCMID/EFISG (2014)[7]	Empirical therapy for IFD in patients undergoing chemotherapy for cancer or HSCT	Caspofungin (A-I) LAmB (B-I) Voriconazole (B-II) Micafungin (B-II)

IFD, invasive fungal disease; LAmB, liposomal amphotericin B.
Only those recommendations graded A (good evidence to support a recommendation for or against use), B (moderate evidence to support a recommendation for or against use) or strong recommendation (for IDSA guidelines) are shown. For details please refer to the full recommendations. Quality of evidence grading: I, evidence from ≥1 properly randomized controlled trial; II, evidence from ≥1 well-designed clinical trial, without randomization; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees. Strength of recommendation grading: A, good evidence to support a recommendation for or against use; B, moderate evidence to support a recommendation for or against use; C, poor evidence to support a recommendation.

dispersion over amphotericin B deoxycholate for the treatment of invasive aspergillosis.[12] Limited evidence suggests that LAmB may be better tolerated than ABLC in terms of infusion-related reactions and nephrotoxicity,[13] and is usually preferred.

In the double-blind dose-finding AmBiLoad study, 201 immunocompromised patients with probable or proven invasive mould infection were randomized to LAmB dosages of 3 mg/kg versus 10 mg/kg for 14 days, after which all patients received 3 mg/kg.[14] The lower dose group achieved a similar response rate (i.e. complete or partial response at the end of treatment) to the high-dose group (50% versus 46%) but with lower rates of nephrotoxicity and hypokalaemia and a trend to improved mortality (Figure 1).[14] When the analysis was repeated in the subpopulation of patients with a microbiologically confirmed diagnosis, response rates were again similar between groups (Figure 1). On the basis of this trial, 3 mg/kg is now generally considered the standard dose when LAmB is used to treat aspergillosis.

For invasive mucormycosis, the pilot AMBIZYGO trial treated 40 patients with probable or proven disease with high-dose LAmB (10 mg/kg), and observed a 36% response rate at week 4, increasing to 45% at week 12.[15] Of note, there was marked renal toxicity at this dose, with a doubling in serum creatinine in 40% of patients, which led to interrupted treatment in 12% of cases. Patients with diabetes experienced the highest renal toxicity. High-dose lipid-based formulations of amphotericin B (5–10 mg/kg for LAmB) are usually considered the treatment of choice for first-line management of invasive mucormycosis (Table 4).[16]

Voriconazole: an update

Primary or second-line treatment for invasive aspergillosis with an antimould triazole significantly improves survival compared with non-azole management in patients with haematological malignancy.[17] Within the triazole class, voriconazole is currently regarded as a drug of choice for the treatment of proven or probable invasive aspergillosis, particularly cerebral aspergillosis (Table 3).[18–20] An analysis of randomized clinical trials in haematological patients found voriconazole to be superior to amphotericin B for response and for overall survival, as well as showing a higher response rate than LAmB.[21] Voriconazole is approved for first-line treatment of invasive aspergillosis, whereas posaconazole and itraconazole are licensed only for second-line treatment. Fluconazole has no activity against moulds.

The pivotal evidence in support of voriconazole was obtained from a randomized, unblinded trial published by the Global Aspergillus Study Group in 2002.[22] A population of 277 patients considered to have probable or proven invasive aspergillosis was randomized to receive intravenous voriconazole for at least 7 days, followed by oral voriconazole, or to receive intravenous amphotericin B deoxycholate. The primary endpoint of complete or partial response at week 12 was significantly higher in the voriconazole group versus amphotericin B [52.8% versus 31.6%; difference 21.2% (95% CI 10.4%–32.9%)]. The 12 week survival was higher in voriconazole-treated patients compared with amphotericin B-treated patients. There were also significantly fewer severe drug-related adverse events under voriconazole. The definitions of invasive fungal disease that applied at the time of the study,[23] however, were updated in 2008.[24] Notably, patients with host factors and nodular lung lesions surrounded by a halo sign were classified as probable invasive aspergillosis even if there was no mycological confirmation; under current guidelines these cases would be categorized as possible cases. Accordingly, a recent analysis re-categorized the original study population based on the 2008 definitions and, where available, on baseline galactomannan serum levels obtained from frozen samples.[25] In the original study analysis, 108, 169 and 102 patients were classified as definite, probable or uncertain/not invasive aspergillosis. These numbers were revised to 59, 178, 106 and 36 proven, probable, possible or uncertain/not invasive aspergillosis under the new criteria. Encouragingly, the

Table 3. Overview of international expert recommendations for choice of targeted treatment of invasive aspergillosis

Publication	Location of infection or clinical setting	Agents (grading)
IDSA (2016)[3,4]	General statement	Early initiation of antifungal therapy in patients with strongly suspected invasive pulmonary aspergillosis is warranted while a diagnostic evaluation is conducted (strong recommendation; high-quality evidence)
	Invasive pulmonary aspergillosis	Voriconazole (strong recommendation; high-quality evidence) Isavuconazole (strong recommendation; moderate-quality evidence) LAmB (strong recommendation; moderate-quality evidence)
	Invasive tracheobronchial aspergillosis	Mould-active triazole (strong recommendation; moderate-quality evidence) Intravenous LAmB (strong recommendation; moderate-quality evidence) Adjunctive inhaled AmB in lung transplant recipients (strong recommendation; moderate-quality evidence) Bronchoscopic debridement of airway lesions in selected cases (strong recommendation; low-quality evidence)
	Paranasal sinuses	Surgery and either voriconazole or LAmB (strong recommendation; moderate-quality evidence)
	CNS	Voriconazole (strong recommendation; moderate-quality evidence) LAmB are reserved for those intolerant or refractory to voriconazole (strong recommendation; moderate-quality evidence)
	Endocarditis, osteomyelitis, arthritis, skin (primary lesions following burns, trauma, etc.)	Surgery and antifungal therapy (strong recommendation; moderate-quality evidence)
ECIL-4 (2014)[6]	Children with cancer or HSCT, first-line therapy	Voriconazole (A-I)[a] LAmB (B-I) ABLC (B-II)
	Children with cancer or HSCT, second-line therapy	Voriconazole (A-I)[a] in voriconazole-naive patients Caspofungin (A-II) LAmB (B-I) ABLC (B-II)
ECIL-6 (2016/2017)[8]	Patients with haematological malignancy or HSCT: first line	Isavuconazole (A-I) Voriconazole (A-I) LAmB (B-I) ABLC (B-II)
	Patients with haematological malignancy or HSCT: second line	LAmB (B-II) ABLC (B-II) Caspofungin (B-II) Combination (various) (B-II) Posaconazole (B-II) Voriconazole (B-II) if not used in first line

ESCMID/EFISG (2014) guidelines are not yet published and are therefore not shown.
ABLC, amphotericin B lipid complex; AmB, amphotericin B; CNS, central nervous system; ECIL, European Conference on Infections in Leukemia; IDSA, Infectious Diseases Society of America; LAmB, liposomal amphotericin B.
[a]In patients aged $\geq$ 2 years.
Only those recommendations graded A (good evidence to support a recommendation for or against use) or B (moderate evidence to support a recommendation for or against use) are shown. For details, please refer to the full recommendations.
Quality of evidence grading: I, evidence from $\geq$1 properly randomized controlled trial; II, evidence from $\geq$1 well-designed clinical trial, without randomization; III, Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Strength of recommendation grading: A, good evidence to support a recommendation for or against use; B, moderate evidence to support a recommendation for or against use; C, poor evidence to support a recommendation.

superiority of voriconazole in terms of response rates at week 12, the primary endpoint, was confirmed when current definitions were applied. Survival at week 12 was also higher under voriconazole versus amphotericin B in the newly defined subpopulation with possible, probable or proven infection (73.7% versus 59.1%, $P = 0.0028$) (Figure 2).[25] Based on these excellent results, voriconazole is now regarded worldwide as the gold standard for the treatment of invasive aspergillosis.[3,4,7,8]

Itraconazole

The licence for itraconazole differs between countries, but it is variously indicated for prophylaxis of invasive fungal infection in high-risk patients (e.g. neutropenia, haematological malignancy or HSCT), primary treatment of blastomycosis, onychomycosis, dermatomycoses, aspergillosis and histoplasmosis, and treatment of systemic aspergillosis, candidiasis or

Table 4. Overview of international expert recommendations for choice of targeted treatment of mucormycosis

Publication	Location of infection or clinical setting	Agents (grading)
ECIL-4 (2014)[6]	Children with cancer or HSCT, first-line therapy	LAmB, 5–10 mg/kg/day (B-II) ABLC, 5–7.5 mg/kg/day (B-II)
	Children with cancer or HSCT, second-line therapy	Posaconazole (B-II) Lipid-AmB + caspofungin (B-III)
ECIL-5 (2013)[8]	General statement	Management includes antifungal therapy, control of underlying conditions[a] and surgery (A-II)
	First-line therapy	LAmB, 5 mg/kg/day (B-II) ABLC (B-II)
	Second-line therapy (failure to first line)	Posaconazole (B-II) Combination Lipid-AmB + caspofungin (B-III) Combination Lipid-AmB + posaconazole (B-III)
	Second-line therapy (maintenance)	Posaconazole (B-III)

ABLC, amphotericin B lipid complex; LAmB, liposomal amphotericin B.
[a]Control of underlying condition includes control of diabetes, haematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy.
Only those recommendations graded A (good evidence to support a recommendation for or against use) or B (moderate evidence to support a recommendation for or against use) are shown. For details please refer to the full recommendations.
Quality of evidence grading: I, evidence from ≥1 properly randomized controlled trial; II, evidence from ≥1 well-designed clinical trial, without randomization; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Strength of recommendation grading: A, good evidence to support a recommendation for or against use; B, moderate evidence to support a recommendation for or against use; C, poor evidence to support a recommendation.

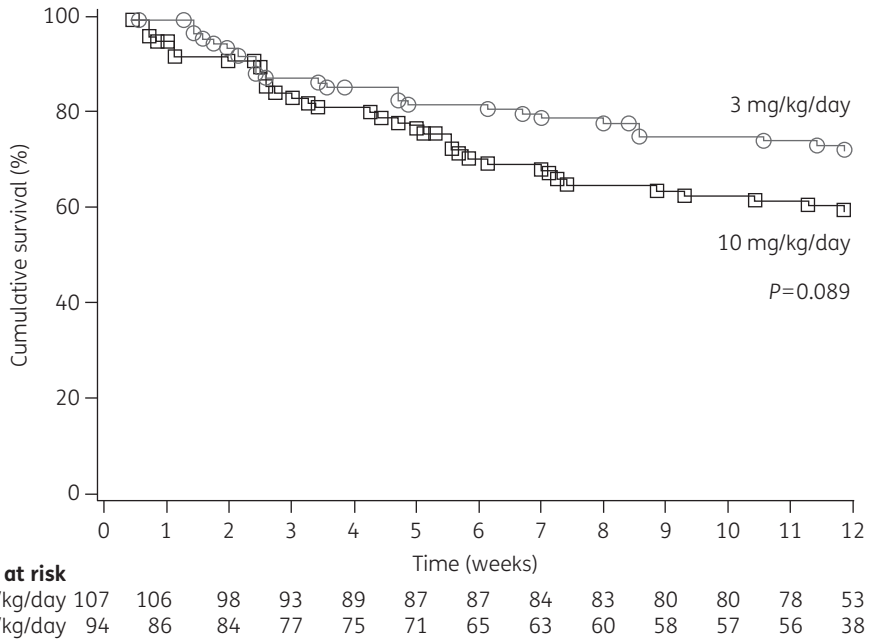

Figure 1. Kaplan–Meier estimates of survival in patients with probable or proven invasive mould infection randomized to LAmB 3 or 10 mg/kg/day for 14 days, followed by 3 mg/kg/day (AmBiLoad study). Reproduced with permission from Cornely *et al.*[14]

cryptococcosis where other antifungal drugs are inappropriate or ineffective. An intravenous formulation is available only in some countries. The major limitations for this triazole are its poor oral bioavailability, restricted access to the intravenous formulation, very limited data in invasive aspergillosis and an absence of activity against Mucorales.

Posaconazole

Posaconazole has a broad spectrum of activity including *Aspergillus* and most Mucorales. In the absence of data relating to first-line therapy of invasive mould diseases, and as per its licence, posaconazole is mostly used for oral maintenance and second-

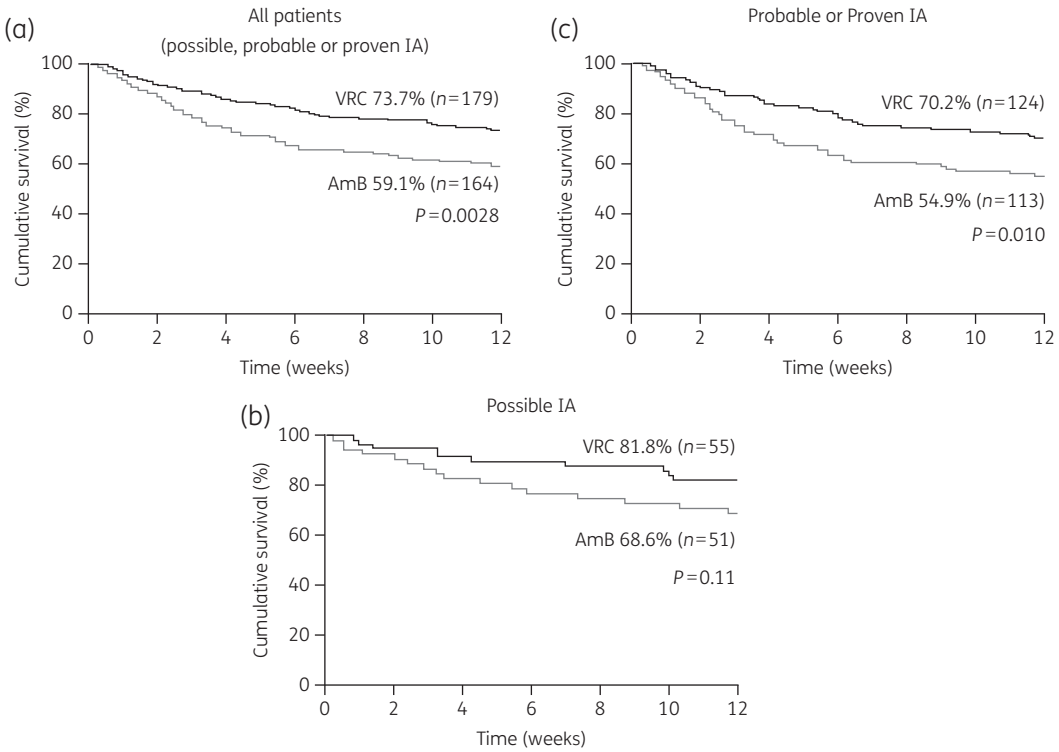

Figure 2. Kaplan–Meier estimates of survival to week 12 in (a) all patients with possible, probable or proven IA (b) possible IA (c) probable or proven IA, randomized to VRC (intravenous for ≥7 days, then orally administered) or intravenous AmB, based on application of EORTC/MSG 2008 definitions for invasive fungal disease[18] to original study data.[22,25] VRC, voriconazole; AmB, amphotericin B; IA, invasive aspergillosis. Reproduced with permission from Herbrecht *et al*.[25]

line therapy in both aspergillosis and mucormycosis.[3,4,26] A study comparing intravenous posaconazole versus voriconazole for primary therapy of invasive aspergillosis is ongoing and is expected to be completed in 2018.[27] In addition, a major role for posaconazole in the prevention of aspergillosis has been clearly established for allogeneic stem cell transplant recipients with acute graft-versus-host disease (GVHD), and for patients with acute myeloid leukaemia or myelodysplastic syndrome undergoing intensive chemotherapy (Table 1).[28,29]

Posaconazole oral solution, the first available formulation of this triazole, is limited by inconsistent oral absorption. The recent introduction of both a solid tablet and an intravenous formulation now enables appropriate serum levels to be reached in most cases, advances that have expanded the use of this agent for targeted therapy of invasive fungal diseases.

Isavuconazole

Introduction of the triazole class of drugs represented a major evolution in antimould management, but each agent has disadvantages. Voriconazole has considerably improved the efficacy of treatment for invasive aspergillosis and other mould infections but has also shown some limitations. The most critical of these are a lack of activity against Mucorales, non-linear pharmacokinetics and adverse events such as transient visual disorders, skin disorders (the most severe of which is phototoxicity, potentially resulting in squamous cell carcinoma during prolonged use) and hepatotoxicity, which may preclude its use in patients with pre-existing liver impairment. Posaconazole and itraconazole are largely restricted to prophylaxis or second-line therapy since robust clinical data are lacking for their application in first-line directed treatment. Itraconazole, in addition, has variable absorption and a narrower antifungal spectrum of activity than other triazoles. Novel triazole therapies have therefore been investigated.

The newest triazole agent, isavuconazole, is administered as a prodrug as either an oral or intravenous formulation, and has a long half-life that permits once-daily dosing, after an initial six loading doses are given over a 2 day period.[30] It is water soluble, so the intravenous formulation does not include cyclodextrin, a nephrotoxic compound, which is included in the intravenous formulations of voriconazole, itraconazole and posaconazole to enhance solubility. Compared with voriconazole, isavuconazole also has the advantages of a wider spectrum of antifungal activity, including activity against most Mucorales, predictable and linear pharmacokinetics that are likely to obviate the need for therapeutic drug monitoring, and fewer CYP enzyme-mediated drug interactions.[31] Very recently, two trials have been reported that provided the basis for isavuconazole's licence to treat invasive aspergillosis, and to treat invasive mucormycosis (in Europe, the latter indication is for cases where amphotericin B is inappropriate).[32,33]

The first study, SECURE, was a randomized, double-blind study in 527 patients, which compared isavuconazole with voriconazole for the primary treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi.[32] The presence of

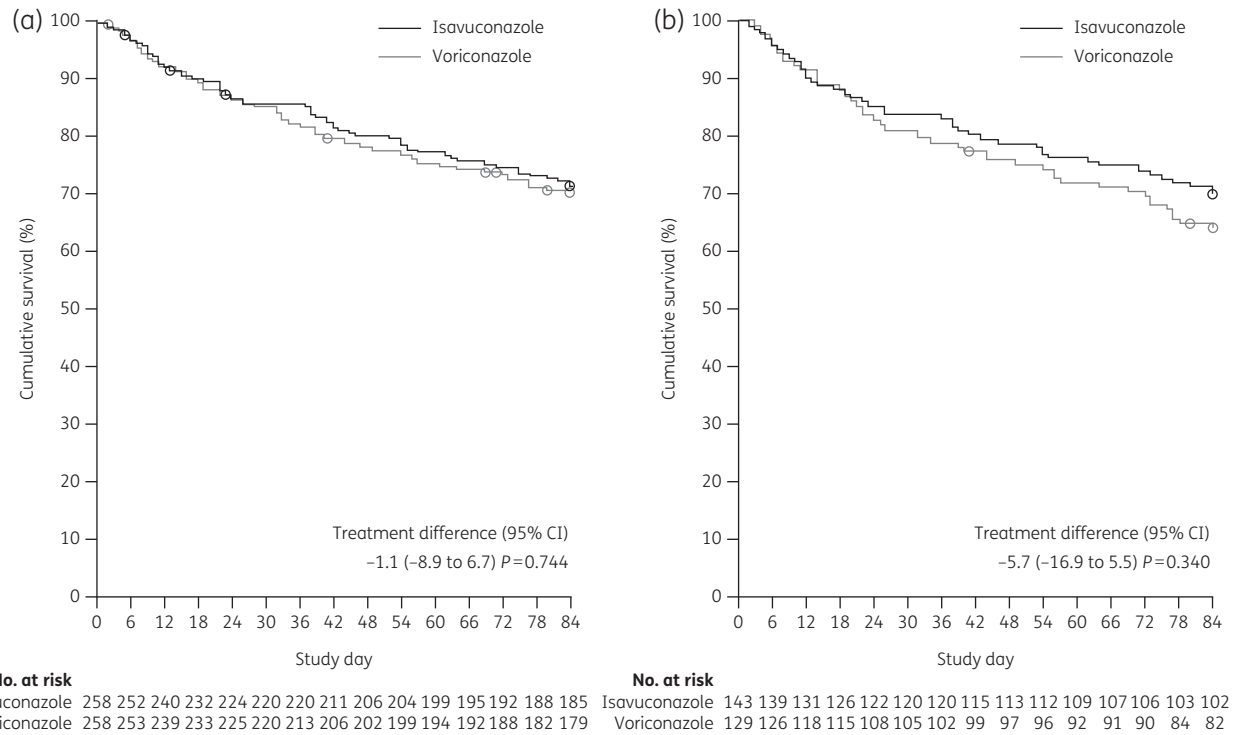

Figure 3. Survival in patients with suspected invasive mould disease randomized to isavuconazole or voriconazole, from first dose to week 12 for (a) the intent-to-treat population and (b) intent-to-treat patients with probable or proven invasive mould disease (SECURE study). Data were censored at last known survival status, indicated by circles. Reproduced with permission from Maertens *et al.*[32]

possible, probable or proven infection was based on current European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria.[24] The primary endpoint, all-cause mortality by week 6, met the criteria for non-inferiority for isavuconazole versus voriconazole [18.6% versus 20.2%, adjusted treatment difference −1.0 (95% CI −7.8% to 5.7%)] (Figure 3). All-cause mortality was also similar when the analysis was repeated at week 12, and in the subpopulations of patients with probable or proven invasive fungal disease ($n = 272$) or mycologically confirmed invasive aspergillosis ($n = 231$). Of note, drug-related adverse events were less frequent under isavuconazole (42% of patients versus 60% with voriconazole, $P < 0.001$), with lower rates of drug-related hepatobiliary disorders, laboratory investigations, eye disorders and psychiatric disorders. Fewer isavuconazole-treated patients discontinued therapy due to adverse events (14% versus 23%).[31]

The second recent study, VITAL, was a single-arm trial performed at 34 centres in patients with kidney impairment and either invasive aspergillosis or rare invasive fungal disease.[33] In a prespecified subpopulation, 37 patients with probable or proven invasive mucormycosis, as confirmed according to EORTC/MSG criteria,[24] were treated with isavuconazole until resolution of the fungal disease, failure or a minimum of 180 days. Twenty-one patients received isavuconazole as primary treatment, 11 for refractory disease and 5 after intolerance to other antifungal therapies. By week 6, 11% of patients showed a partial response, 43% had stable invasive fungal disease, 3% showed progression and 35% had died (information was missing in the remaining 8% of patients). The worldwide FungiScope Registry of rare invasive fungal diseases[34] was used to identify 33 matched controls treated first-line with amphotericin B deoxycholate or as a lipid formulation. These controls were compared with the 21 patients in the VITAL study who received isavuconazole as first-line treatment. Rates of surgical intervention, and the proportion of patients with haematological malignancies, were similar in the two groups. Immunosuppressant therapy, GVHD and disseminated disease were more frequent in the isavuconazole cohort, factors that would tend to predispose patients to poor outcomes. Nevertheless, all-cause mortality rates at weeks 6 and 12 were similar in the isavuconazole and amphotericin B-treated patients.[34] Isavuconazole was continued for a median of 102 days compared with only 18 days for amphotericin B (followed by switch to posaconazole in several cases), consistent with the favourable tolerability profile for isavuconazole in the SECURE study.[32] Given the rarity of invasive mucormycosis, comparisons of different therapies may need to rely on matched control data of this type since randomized trials are impractical. Analysis of another prespecified subpopulation from the VITAL study, patients with proven infection with *Cryptococcus* spp. ($n = 9$) or dimorphic fungi (*Paracoccidioides* spp. 10, *Coccidioides* spp. 9, *Histoplasma* spp. 7 and *Blastomyces* spp. 3) who were intolerant or refractory to other antifungal agents ($n = 38$), has shown isavuconazole to have clinical activity against these rare endemic fungi, and to be well tolerated.[35] At the end of treatment, 24 of 38 patients (63%) showed a successful response.

Overall, the extended-spectrum triazole isavuconazole appears as efficacious as voriconazole for first-line treatment of aspergillosis, with efficacy against mucormycosis and a favourable profile regarding safety, tolerability and ease of administration. Currently, therapeutic drug monitoring for isavuconazole does not appear generally relevant, although data are still relatively sparse and it may be useful in certain circumstances.[36] With further clinical experience, isavuconazole has the potential to become the drug of choice for first-line treatment of invasive mould disease. More data are required regarding treatment of patients with prior mould-active triazole prophylaxis, and in non-aspergillosis infections, as well as for specific sites such as cerebral infections. Evidence from the SECURE and VITAL studies, however, has triggered changes to recent guidelines from IDSA,[3,4] the European Fungal Infection Study Group (EFISG) of ESCMID[7] and the European Conference on Infections in Leukemia (ECIL)[8] (Table 3).

Echinocandins and other antifungal agents

Echinocandins include caspofungin, micafungin and anidulafungin. Their major clinical role in *Candida* spp. infection is well recognized. The *in vitro* spectrum of echinocandins also includes moulds such as *Aspergillus* and certain other hyaline and black moulds, but few clinical data are available in relation to these infections. No randomized comparative trial is available for first-line therapy of invasive aspergillosis with echinocandin therapy. Two non-comparative trials have been conducted by the EORTC group, which failed to show adequate efficacy for standard dose caspofungin as primary therapy for invasive aspergillosis in patients with a haematological malignancy or in allogeneic stem cell transplant recipients.[37,38] A salvage therapy study has shown clinical activity for caspofungin in patients with invasive aspergillosis who had failed to respond to itraconazole or amphotericin B therapy.[39] Caspofungin is approved in the USA and Europe in this setting.

Among other systemic antifungal agents, flucytosine has no role in the treatment of aspergillosis or mucormycosis. Terbinafine plays a major role in the treatment of skin and nail infections but has no clear role in the treatment of invasive mould infections despite a few case reports suggesting it could be combined with an azole for severe *Fusarium* spp. or *Scedosporium* spp. infections.[40–44]

Combination therapy

The expanding choice of antimould agents and the continuing high morbidity and mortality even under new regimens has prompted interest in co-administration of two or even three antifungals, in particularly difficult-to-treat cases unresponsive to monotherapy, or in patients with advanced disease or those who are severely immunocompromised. The potential advantages of combination therapy are an increased rate and extent of fungicidal activity due to a broader antimycotic spectrum, a decreased risk for resistance or fungal tolerance, and reduced toxicity by lowering exposure to individual drugs.[45] Possible disadvantages are a risk for antagonism, greater toxicity depending on the exposure and safety profile of each drug, risk for more drug–drug interactions and higher drug costs. Experimental evidence has been promising for various drug combinations[46–50] but conducting clinical trials of combination antifungal therapy for opportunistic fungal infections, often as salvage therapy, is difficult. Published studies of combination therapy for invasive mould infections are either poorly designed or underpowered,[51] and generally retrospective in nature[52–55] or observational studies involving mixed indications, pathogens and drug combinations.[56,57] The most frequent combinations attempted are a mould-active triazole drug or a formulation of amphotericin B with an echinocandin. For mucormycosis, it is rational to include a lipid-based formulation of amphotericin B.[58] Overall, however, the selection of agents and dosing levels are generally unsupported by robust data, and the optimal timing and sequencing for combination regimens are largely unexamined.[59]

The only large-scale randomized trial to assess combination therapy for invasive mould disease was a recent double-blind, placebo-controlled study of voriconazole plus the echinocandin anidulafungin, by Marr and colleagues.[60] Anidulafungin is licensed only for the treatment of invasive candidiasis, but *in vitro* and *in vivo* evidence has suggested the combination of voriconazole and anidulafungin may be effective in triazole-susceptible *Aspergillus* infections, with lesser impact in triazole-resistant isolates.[48,49] However, experimental evidence has not shown that addition of anidulafungin to voriconazole improves outcomes in a rat model in advanced invasive pulmonary aspergillosis,[61] and most clinical data relate to its use in managing *Candida* infections.[62] However, it has shown efficacy as antifungal prophylaxis after liver transplantation.[63] The study randomized 454 patients with possible, probable or proven invasive aspergillosis, all of whom had a haematological malignancy or had undergone HSCT, to receive a 4 week course of voriconazole plus anidulafungin, or voriconazole plus placebo.[60] After 2 weeks, investigators could switch patients to monotherapy, and after 4 weeks, all patients received voriconazole maintenance therapy. In the subpopulation of 277 patients with probable or proven invasive aspergillosis, all-cause survival at week 12 was 29.3% with the addition of anidulafungin to voriconazole versus 39.4% for voriconazole alone ($P = 0.077$). Figure 4 illustrates Kaplan–Meier estimates of cumulative survival for the two treatment groups ($P = 0.086$).[60] Survival rates overall were worse than anticipated, reducing the study's power to detect a significant between-group difference. However, when mortality was assessed *post hoc* in the cohort of patients in whom the diagnosis of invasive aspergillosis was confirmed both radiographically and by maximum galactomannan positivity ($n = 218$), the difference became significant (15.7% versus 27.3%, $P = 0.037$). The response rate (complete or partial response at week 6), however, was low in both groups [voriconazole monotherapy 43.0%, voriconazole plus anidulafungin 32.6%; treatment difference −10.4% (95% CI −21.6% to 1.2%)], although in 40% of cases the reason for patients being classified as non-responders was because they were non-evaluable.[60]

A small pilot study undertaken in 30 patients with haematological malignancies and probable or proven invasive aspergillosis randomized participants to caspofungin with standard dose LAmB (3 mg/kg) or high-dose LAmB (10 mg/kg) monotherapy.[64] The results showed high-dose LAmB and caspofungin to be a promising combination, achieving a significantly higher rate of partial or complete response (67% versus 27%, $P = 0.028$), excellent survival (100% versus 80%) and a lower frequency of nephrotoxicity (7% versus 23%).

Although data do not yet exist to support widespread use of combination therapy to treat invasive mould disease, combined

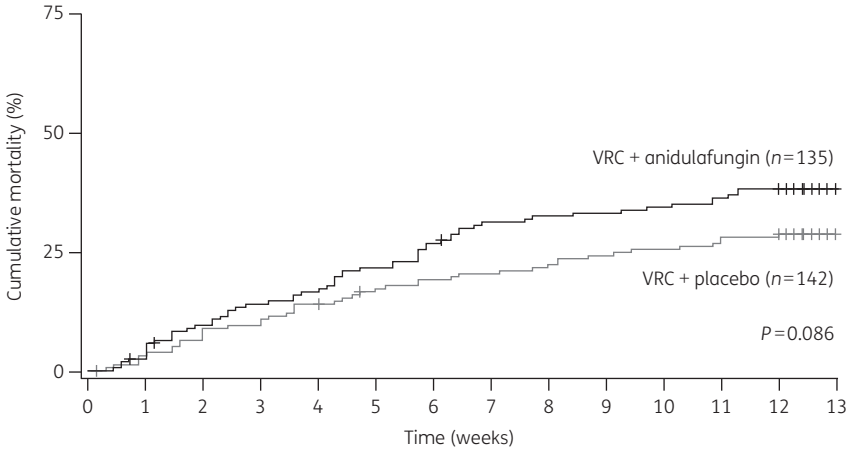

Figure 4. All-cause mortality at 6 weeks in patients with probable or proven invasive aspergillosis randomized to VRC and anidulafungin, or to VRC monotherapy, for 4 weeks, followed by VRC maintenance therapy. VRC, voriconazole. Reproduced with permission from Marr *et al*.[60]

treatment with voriconazole and anidulafungin—or with other combination regimens yet to be evaluated—may be beneficial in certain populations. Further studies are awaited.

Pharmacological therapy: looking ahead

Invasive mould infections continue to incur high morbidity and mortality, but recent trials have helped clarify the suitability of certain agents in specific contexts. Their findings have prompted revisions to expert guidelines for the prophylaxis and management of invasive mould infections. For prophylactic therapy, the recommendations now almost exclusively advise use of a mould-active triazole agent, with the strength of evidence for particular drugs varying by indication. Amphotericin B deoxycholate has been entirely replaced by lipid-based formulations, predominantly LAmB, which is a recommended option for empirical treatment. In most cases, the strength of evidence for lipid formulation of amphotericin B use as first-line directed therapy is less than for voriconazole or other triazoles.

Despite the growing array of antimould therapies available, important challenges remain, including variable drug bioavailability for some agents, drug-related toxicity, drug–drug interactions and the emergence of antifungal resistance. One promising direction for existing drugs is the development of new formulations, such as tablet forms of posaconazole.[65,66] There is a growing base of evidence to support therapeutic drug monitoring for voriconazole to achieve target plasma concentrations,[67] and wider application of concentration-controlled monitoring may help to deliver more consistent exposure and improve outcomes. Cost inevitably plays a role in treatment decisions, with drug purchasing representing the major cost of fungal infection treatment.[68] The patent for voriconazole ends in 2016 in many markets, and may trigger a shift in prescribing. Comparative trials of different agents—and combination regimens—are urgently needed, including studies in other clinical situations such as solid organ transplantation, COPD and steroid-treated patients in the intensive care unit. Future studies could also usefully examine the optimal duration of directed antifungal therapy according to the severity and duration of the underlying immune deficiency. Lastly, adoption of quantitative galactomannan screening to help monitor the response to therapy and guide decision-making about treatment discontinuation merits further investigation. This active field of research is likely to continue evolving rapidly in the coming years.

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