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Original article

Randomised, multicentre trial of micafungin vs. an institutional standard regimen for salvage treatment of invasive aspergillosis

Oliver A. Cornely,[1] Lambertus Meems,[2] Raoul Herbrecht,[3] Claudio Viscoli,[4] Ronald G. M. van Amsterdam[2] and Markus Ruhnke[5]

[1]*University of Cologne, Cologne, Germany,* [2]*Astellas Pharma Global Development, Leiden, The Netherlands,* [3]*Hôpital de Hautepierre, Strasbourg, France,* [4]*University of Genova (DISSAL) and IRCCS San Martino-IST, Genova, Italy and* [5]*Charité Universitätsmedizin, Berlin, Germany*

Summary

Invasive aspergillosis remains associated with significant morbidity and mortality, necessitating new options for salvage therapy. The objective of this study was to evaluate the efficacy and safety of micafungin as salvage monotherapy in patients with invasive aspergillosis. Patients with proven or probable invasive aspergillosis, who were refractory or intolerant to previous systemic antifungal therapy, were randomised 2 : 1 to receive 300 mg day^{-1} intravenous micafungin monotherapy or an intravenous control monotherapy [lipid amphotericin B (5 mg kg^{-1} day^{-1}), voriconazole (8 mg kg^{-1} day^{-1}) or caspofungin (50 mg day^{-1})] for 3–12 weeks. Patients underwent final assessment 12 weeks after treatment start. Seventeen patients with invasive aspergillosis (proven, $n = 2$; probable, $n = 14$; not recorded, $n = 1$) participated in the study (micafungin arm, $n = 12$; control arm, $n = 5$). Three patients each in the micafungin (25.0%; 95% CI: 5.5–57.2) and control arm (60.0%; 95% CI: 14.7–94.7) had successful therapy at end of treatment as assessed by an Independent Data Review Board. Eleven patients died; six due to invasive aspergillosis. No deaths were considered related to study treatment. During this study it became increasingly common to use combination treatment for salvage therapy. Consequently, enrolment was low and the study was discontinued early. No clear trends in efficacy and safety can be concluded.

Key words: Combination therapy, invasive aspergillosis, micafungin, monotherapy, salvage.

Introduction

Invasive aspergillosis is still associated with significant morbidity and mortality rates.[1–6] Immunocompromised patients, such as those receiving cancer chemotherapy, immunosuppressive drug regimens, allogeneic haematopoietic stem cell and solid organ transplantations, and those with immunologic diseases, are particularly at risk of developing life-threatening systemic fungal infections caused by *Aspergillus* spp. As prognosis may be worse if first-line therapy fails or is not tolerated, new options for salvage therapy are warranted.

Historically, treatment of invasive aspergillosis has consisted of three general pharmacologic approaches, each with their own limitations. For decades amphotericin B deoxycholate (later followed by liposomal,

Correspondence: Prof. O. A. Cornely, Department I of Internal Medicine, Clinical Trials Centre Cologne, ZKS Köln, BMBF 01KN1106, Center for Integrated Oncology CIO Köln Bonn, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne 50924, Germany.
Tel.: +49 221 478 6494. Fax: +49 221 478 3611.
E-mail: oliver.cornely@zks-koeln.de

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colloidal dispersion and lipid complex formulations) was considered the standard treatment for invasive aspergillosis.[7] The lipid-based formulations have an improved safety profile; however, this agent remains associated with toxic effects and suboptimal response rates.[8–11]

Voriconazole was the first promising alternative to amphotericin B,[12,13] and is currently recommended as first-line therapy for invasive aspergillosis.[14] Survival rates with voriconazole (~71%) are significantly higher compared with amphotericin B deoxycholate (~58%); however, triazoles are associated with hepatotoxicity and drug–drug interactions.[13,15] The echinocandins, anidulafungin, caspofungin and micafungin, are generally well tolerated, and few significant drug interactions have been reported.[14]

For salvage therapy, recommended agents include lipid-based formulations of amphotericin B; the triazoles, posaconazole and itraconazole; and the echinocandins, caspofungin and micafungin.[7] Current guidelines recommend a change in class to amphotericin B or an echinocandin for salvage therapy.[14] However, it is also recognised that due to their distinct mechanisms of action and compatible safety profiles, combinations of agents from these different classes may be deployed.

Micafungin is an echinocandin which has broad-spectrum activity, including fungicidal activity against *Candida* spp. and fungistatic activity against *Aspergillus* spp.[16] The aim of the current study was to evaluate the efficacy and safety of micafungin as salvage monotherapy in patients with proven or probable invasive aspergillosis who were refractory or intolerant to previous systemic antifungal therapy. The efficacy and safety of micafungin monotherapy, as compared with standard monotherapy, were also examined. The study was initiated in June 2006; however, after more than 2 years it was discontinued prematurely, having screened 301 patients, due to slow enrolment in association with a change in preference from monotherapy to combination therapy for salvage of invasive aspergillosis.

Patients and methods

This was a Phase II, multicentre, prospective, controlled, open-label, randomised and parallel arm clinical study (NCT00376337), conducted between 30 June 2006 and 7 September 2008. Patients were randomised 2 : 1 to receive either 300 mg once-daily (QD) intravenous micafungin monotherapy or an alternative intravenous control salvage monotherapy [amphotericin B liposomal (5 mg kg^{-1} QD), colloidal dispersion (5 mg kg^{-1} QD) or lipid complex (5 mg kg^{-1} QD); voriconazole (6 mg kg^{-1} twice daily loading dose followed by 4 mg kg^{-1} twice daily); or caspofungin (70 mg loading dose followed by 50 mg QD)] for a period of 3–12 weeks. Patients underwent their final assessment 12 weeks after the start of treatment.

Patients aged ≥18 years old were eligible for inclusion if they had proven invasive aspergillosis (probable in cases of pulmonary infection), an allogeneic or autologous haematopoietic stem cell transplant, acute leukaemia or myelodysplastic syndrome, and were refractory to a systemic antifungal agent used as first-line therapy, or intolerant to at least one dose of a systemic antifungal agent used as first-line therapy. Refractory patients were defined as those who had received at least seven consecutive days of systemic antifungal therapy prior to the start of the study and who had progression of infection (i.e. rapid worsening of clinical conditions and evidence either of new lesions or dissemination of disease with the occurrence of cerebral, cutaneous or hepatosplenic abscesses) or failure to improve [i.e. persistence of fever and lack of significant reduction (≥50%) of the number or size of known lesions]. Evidence of intolerability included doubling of serum creatinine levels within 48 h, serum creatinine ≥2.0 mg dl^{-1}, persistence of severe visual disturbance, acute hepatotoxicity or other significant drug-related toxicity which precluded continuation of treatment, e.g. allergic reaction or severe infusion reaction.

The primary efficacy endpoint was the overall treatment success at end of treatment (EOT), defined as complete or partial clinical response, i.e. resolution of all (complete), or major improvement or resolution (partial) of clinical signs and symptoms (e.g. respiratory and neurological) attributable to invasive aspergillosis, and at least a 90% (complete) or at least 50% (partial) improvement in radiological signs compared to baseline. The secondary endpoint was the overall treatment success at 12 weeks after the start of treatment.

Statistical analyses

The original study protocol had *a priori* defined extensive analysis of study data based on a projected enrolment of 135 patients (micafungin arm: $n = 90$ vs. control arm: $n = 45$), including analysis of primary and secondary outcomes. However, as a consequence of the premature discontinuation of the study and the resulting low number of patients randomised, only descriptive statistical analysis and calculation of 95% confidence intervals were performed for efficacy

endpoints based on the full analysis set (FAS; defined as all randomised patients who received at least one dose of study medication). Statistical comparisons between treatment arms were not conducted. Safety data including incidence of adverse events (AEs), serious AEs and deaths were described, but not further analysed.

Independent Data Review Board assessments

An Independent Data Review Board (IDRB) of clinical experts assessed the clinical data for all patients enrolled and included in the FAS. The IDRB assessed the fungal infection status at baseline, clinical signs and symptoms, radiological findings, clinical and mycological responses and overall success at 12 weeks after the start of treatment and at EOT, as well as the relationship of mortality to fungal infection and underlying disease. A radiologist was consulted for interpretation of the radiological results. The IDRB was treatment-blinded, i.e. enabled to see neither details regarding the systemic antifungal agents administered nor any other information that could have revealed the actual treatment used as study medication.

Results

In total, 301 patients were prescreened at 64 sites in 12 countries; however, only 17 (5.6%) were enrolled to this study as the majority of patients screened received combination therapy rather than monotherapy. Patients were enrolled from nine out of the 64 participating sites in eight countries (Fig. 1).

Twelve patients were randomised to the micafungin treatment arm and five patients were randomised to the control arm (Fig. 2). Of these, seven patients completed study treatment and four patients completed the study.

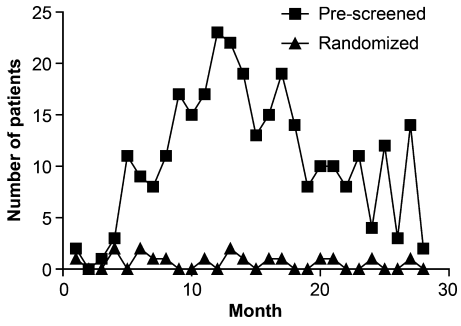

Figure 1 Number of prescreened and randomised patients by month from June 2006 to September 2008.

Patient characteristics

The majority of patients were male (n = 11; 64.7%) and Caucasian (n = 15; 88.2%). Mean patient age was 53.6 years (range 25–76 years), mean body weight was 68.5 kg (range 45–85 kg) and mean height was 173.3 cm (range 157–191 cm). Nine patients had neutropenia and five patients had received an allogeneic stem cell transplant. Primary underlying diseases were acute lymphocytic leukaemia (n = 1; 5.9%), acute myelogenous leukaemia (n = 12; 70.6%), myelodysplastic syndrome (n = 1; 5.9%) and other (n = 3; 17.6%). The status of underlying diseases at the start of the study was: active (n = 9; 52.9%), remission (n = 3; 17.6%) and relapse (n = 5; 29.4%). The therapies given for primary underlying diseases were haematopoietic stem cell transplant (n = 5; 29.4%, all in the micafungin arm), prolonged corticosteroid therapy (n = 3; 17.6%, all in the micafungin arm) and chemotherapy (n = 9; 52.9%, six in the micafungin arm).

Invasive aspergillosis status

Invasive fungal infection was proven in two patients, probable in 14 patients and not recorded in one patient. The lung was the main site of infection in all patients. Invasive aspergillosis was most frequently diagnosed using computed tomography (n = 15; 88.2%). In addition, 12 out of 16 patients (75.0%) who underwent galactomannan testing had a positive result. One patient, who did not receive a computed tomography scan, was diagnosed with probable invasive aspergillosis based on X-ray evidence of a new infiltrate, a positive galactomannan test result and symptoms of lower respiratory tract infection (including cough).

The following organisms were identified in the micafungin/control arms (n/n): *Aspergillus fumigatus* (n/n = 1/1); *Aspergillus flavus* (n/n = 1/0); unidentified *Aspergillus* spp. (n/n = 9/4); other mould, not otherwise specified (n/n = 1/0). Of the 13 patients with an unidentified *Aspergillus* spp. infection, 10 (n/n = 6/4) had a positive galactomannan antigen test result.

First-line and study treatments for invasive aspergillosis

All patients had received treatment with a systemic antifungal medication prior to the first dose of study medication. Six patients had received antifungal

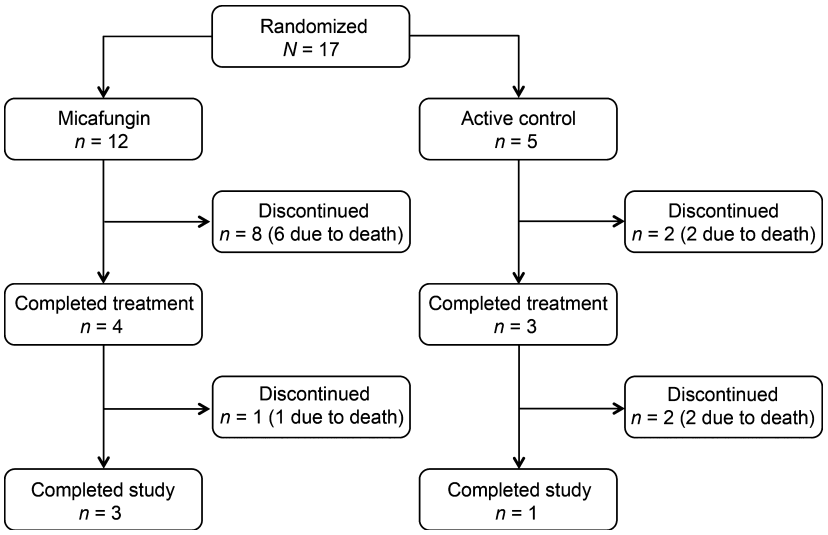

Figure 2 Disposition of patients.

prophylaxis with either fluconazole (n = 2; 11.8%), itraconazole (n = 2: 11.8%) or amphotericin B (n = 2; 11.8%). Drugs administered as first-line therapies were voriconazole (n = 11; 64.7%) and amphotericin B formulations (n = 6; 35.3%). Fifteen patients (88.2%) were considered refractory to first-line therapy (nine for progression of infection and six for failure to improve) and two (11.8%) were intolerant to first-line therapy. Twelve patients (70.6%) were randomised to receive salvage therapy with micafungin and five patients (29.4%) were randomised to the control arm. Salvage therapies administered in the control arm were caspofungin (n = 4) and voriconazole (n = 1). No patients received amphotericin B salvage monotherapy.

The median study treatment duration was 10 days (range 4–34 days) in the micafungin treatment arm and 18 days (range 10–64 days) for the control arm. Reasons for discontinuation of treatment in the micafungin arm included: completed therapy (n = 2; Days 24 and 26), lack of efficacy (n = 4; Days 8, 10, 10, and 34), AEs (n = 2; Days 4 and 25) and other (n = 4; Days 5, 7, 8, and 29). In the control arm, reasons for treatment discontinuation included completed therapy (n = 2; Days 34 and 64), AEs (n = 1; Day 11) and other (n = 2; Days 10 and 18). Study duration varied between 5 and 119 days after randomisation.

Efficacy

Three patients in the micafungin treatment arm (25.0%; 95% CI: 5.5–57.2) and three patients in the control arm (60.0%; 95% CI: 14.7–94.7) had successful therapy at EOT (Table 1). Six patients in the micafungin treatment arm (50.0%; 95% CI: 21.1–78.9) and one patient in the control arm (20.0%; 95% CI: 0.5–71.6) had successful therapy at 12 weeks after the start of treatment (Table 1).

Safety

Eleven patients died during the study: five during treatment [three in the micafungin arm (25.0%) and two in the control arm (40.0%)] and six in the post-treatment period [four in the micafungin arm (33.3%) and two in the control arm (40.0%)] (Fig. 2). Six patients' deaths were considered to be attributable to invasive aspergillosis by the IDRB [four in the micafungin arm (33.3%) and two in the control arm

Table 1 Overall treatment success at the end of treatment and at 12 weeks after the start of treatment.

	Micafungin (n = 12)	Control (n = 5)
Primary endpoint		
FAS at EOT		
Successful therapy, n (%)	3 (25.0)	3 (60.0)
95% CI	5.5–57.2	14.7–94.7
Secondary endpoint		
FAS at 12 weeks after the start of treatment		
Successful therapy, n (%)	6 (50.0)	1 (20.0)
95% CI	21.1–78.9	0.5–71.6
Not recorded, n (%)	6 (50.0)	4 (80.0)

FAS, full analysis set; CI, confidence interval; EOT, end of treatment.

Table 2 Overall treatment emergent adverse events.

	Micafungin (n = 12)		Control (n = 5)		Total (N = 17)	
Total effects	Patients n (%)	Events n	Patients n (%)	Events n	Patients n (%)	Events n
AE	10 (83.3)	36	5 (100.0)	29	15 (88.2)	65
SAE	5 (41.7)	7	4 (80.0)	8	9 (52.9)	15
Causally related AE	3 (25.0)	4	1 (20.0)	1	4 (23.5)	5
Causally related SAE	0	0	1 (20.0)	1	1 (5.9)	1

Causally related: defined as probable, possible or missing relationship with study drug as assessed by investigator.

AE, adverse event; SAE, serious adverse event.

(40.0%)]. Infections, and events within the system organ classes 'respiratory', 'blood', and 'general disorders' were the causes of death. No deaths were considered related to study treatments.

Fifteen patients (88.2%) experienced AEs in this study (Table 2). AEs reported by two or more patients per treatment arm were leucocytosis, neutropenia, melaena, nausea, chest pain and sepsis. Three patients in the micafungin arm experienced AEs of nausea (n = 1; 8.3%), vomiting (n = 1; 8.3%), diarrhoea (n = 1; 8.3%) and hyperbilirubinaemia (n = 1; 8.3%), which were considered related to micafungin treatment. One patient (20.0%) in the control arm experienced a serious AE of cholestasis, which was considered related to caspofungin treatment.

Discussion

This study was conducted to evaluate the efficacy and safety of micafungin as salvage monotherapy in patients with proven or probable invasive aspergillosis who were refractory or intolerant to previous systemic antifungal therapy. At the time of the study, preferences for salvage treatment of invasive aspergillosis evolved to largely preclude the use of monotherapy. Over time, this evolution increasingly conflicted with the study design, which required monotherapy at baseline. This led to low enrolment (N = 17, where N = 120 was originally intended) in 28 months and the study was discontinued prematurely.

Seventeen patients were randomised to receive either micafungin monotherapy or monotherapy with a control, i.e. caspofungin or voriconazole. Of the 17 patients, 15 received a diagnosis of invasive aspergillosis using computed tomography imaging and 10 had a positive galactomannan antigen test result. Salvage therapy in three out of the 12 patients in the micafungin treatment arm and three out of the five patients in the control arm was rated as successful at EOT by the IDRB. Eleven patients died during the study, which was not unexpected, given the high number of active and relapsed malignancies in this patient population. In addition, the majority of patients were neutropenic and five had received an allogeneic stem cell transplant, which are known predictors of mortality in invasive aspergillosis.[17] Infections, respiratory, blood and general disorders were identified as the causes of death. No new safety issues were identified in invasive aspergillosis patients who were administered micafungin. Due to the small, heterogeneous patient population and imbalance in patient numbers between treatment arms, no clear trends in efficacy could be concluded.

Treatment of invasive aspergillosis was traditionally initiated as monotherapy. However, although therapeutic responses in invasive aspergillosis have generally improved with newer treatments, outcomes remain disappointing, particularly in high-risk patients such as those patients undergoing allogeneic haematopoietic stem cell transplant.[13,18,19] In order to improve therapeutic outcomes, researchers have explored a number of different combinations of antifungal agents.[20] Regimens which partner lipid-based amphotericin B formulations or a triazole with an echinocandin are particularly attractive due to their distinct mechanisms of action and complementary safety profiles.

In a recent subgroup analysis of patients enrolled in the Prospective Antifungal Therapy Alliance registry, approximately 29% of patients with invasive aspergillosis received combination therapy as initial treatment.[21] The most commonly administered combination was voriconazole plus an echinocandin; however, 56 unique combinations of two or more antifungal agents were recorded in this cohort of patients during the 12-week follow-up period. Similar findings have also been reported by the Transplant Associated Infection Surveillance Network.[22]

Despite the growing employment of combination therapy, there have been few prospective studies conducted to examine its utility and evidence supporting its use in clinical practice is often conflicted.[23] For example, in an early retrospective cohort study, Kontoyiannis *et al.* [20] found that combination liposomal amphotericin B plus caspofungin may be useful as preemptive therapy for invasive aspergillosis and may have limited benefit as salvage therapy. Moreover, a subsequent randomised, prospective, pilot trial also found that combination therapy with these agents yielded significantly more favourable responses than

monotherapy with liposomal amphotericin B.[24] By contrast, two retrospective cohort studies demonstrated that combination therapy with lipid-based amphotericin B plus an echinocandin offers no therapeutic advantage in salvage therapy compared with monotherapy using either posaconazole[25] or an echinocandin alone.[26] Studies of other combinations, such as voriconazole plus caspofungin, yielded similarly inconclusive results.[27–29]

Notwithstanding the lack of prospective clinical trial evidence, current clinical guidelines developed by the Infectious Diseases Society of America recognise that 'in the context of salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used'.[7] Appropriate salvage therapy for invasive aspergillosis remains a major clinical challenge. Clearly, the potential for combination therapy in these patient populations merits further prospective, randomised clinical studies to compare newer treatment strategies and different combinations of agents.

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