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REVIEW
Micafungin: A Brief Review of Pharmacology, Safety, and Antifungal Efficacy in Pediatric Patients

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Invasive fungal infections are a major cause of morbidity and mortality in children with hematological malignancies and those undergoing allogeneic hematopoietic stem-cell transplantation (HSCT). Although several new antifungal compounds recently became available, some are not yet approved for the use in the pediatric population. Among the new class of echinocandins, micafungin has been licensed in Europe and Japan for children including neonates. Because micafungin is well tolerated and exhibits few clinical relevant drug–drug interactions, the compound is of particular interest for prophylaxis and treatment of invasive mycoses in pediatric patients with cancer or following allogeneic HSCT. This review will focus on the currently available pediatric data of micafungin with emphasis on pharmacokinetics, efficacy, and safety. Pediatr Blood Cancer 2010;55:229–232.

Key words: cancer; children; echinocandin; micafungin; mycoses

The frequency of invasive fungal infections in children undergoing therapy for cancer or allogeneic hematopoietic stem-cell transplantation (HSCT) is increasing, and with up to 55%, the overall mortality rate is unacceptably high [1,2]. In this patient population, *Candida* spp. still represents the major pathogen, although a trend toward an increased rate of infections caused by *Aspergillus* is noted [1]. During the last decade, the antifungal armamentarium has significantly expanded with the introduction of a second generation of broad-spectrum triazoles and the new class of echinocandins, such as anidulafungin, caspofungin, and micafungin. However, the availability of new antifungal compounds in the pediatric population is still limited. This is due to the fact that pediatric dosages for some of these compounds are yet not defined and that they are therefore not approved for the use in children.

Whereas anidulafungin has not yet a pediatric label, caspofungin and micafungin are approved in pediatric age groups. Micafungin has been licensed for children including neonates in Japan since April 2006 and in Europe since April 2008. In Europe, the pediatric label of micafungin includes invasive candidiasis and prophylaxis against *Candida* infection in patients with anticipated prolonged and severe neutropenia (absolute neutrophil count $\leq$500/μl for at least 10 days) or in allogeneic stem-cell recipients. In Japan, the compound is also approved for the treatment of children with invasive aspergillosis. Although micafungin is not approved for children in the US at the writing of this article, the compound has been widely used in this patient group since 2006 [3]. Because micafungin, similar to other echinocandins, is well tolerated and exhibits few clinically relevant drug–drug interactions, the compound is of particular interest for the management of invasive fungal infections in pediatric patients with cancer or allogeneic HSCT. This review summarizes the available pediatric data of micafungin with emphasis on pharmacokinetics, efficacy, and safety (Table I).

MECHANISM OF ACTION AND IN VITRO ACTIVITY

In common with other echinocandins, micafungin inhibits the synthesis of 1,3-β-D-glucan, a major component of fungal cell wall, in a non-competitive, concentration-dependent manner. Micafungin has potent and fungicidal activity against a wide range of *Candida* spp. in vitro, including fluconazole-resistant *Candida* spp. and multidrug-resistant *Candida* spp. residing in biofilms [4,5]. Primary resistance is uncommon, and importantly, a recent 6-year prospective surveillance study did not reveal emerging resistance to micafungin among clinical isolates of *Candida* spp. [6]. Micafungin also has useful in vitro activity against *A. fumigatus*, *A. flavus*, *A. terreus*, and *A. niger* [7,8] with fungicidal effects at the hyphal tips, and its in vivo efficacy has been documented in a variety of clinically relevant experimental animal models of invasive *Candida* and *Aspergillus* infections [9]. Micafungin does not have clinical useful activity against *Cryptococcus* spp., the *Zygomycetes*, and non-*Aspergillus* hyalohyphomycetes [10]. In general, the combination of micafungin with fluconazole, itraconazole, or voriconazole has indifferent effects on the antifungal activity against the majority of *Candida* spp. isolates tested in vitro, but simultaneous administration of micafungin with liposomal amphotericin B in immunosuppressed mice with disseminated *C. glabrata* infection resulted in a significant improvement in antifungal activity compared with monotherapy [4,11].

PHARMACOKINETICS AND DOSE FINDING IN PEDIATRIC PATIENTS

Micafungin has poor oral bioavailability and is only available for intravenous administration. The compound is extensively (>99%) bound to plasma proteins, metabolized by the liver, and excretion

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predominantly occurs via the fecal route. The pharmacokinetics of micafungin are not altered to a clinically significant extent when the compound is co-administered with amphotericin B, cyclosporine, fluconazole, itraconazole, mycophenolate mofetil, posaconazole, prednisolone, rifampicin, sirolimus, tacrolimus, or voriconazole; nor did micafungin significantly alter the pharmacokinetics of these drugs to a significant extent (reviewed in Ref. [4]).

A multicenter, phase I, open-label, sequential dose-escalation study assessed safety, tolerability, and pharmacokinetics of micafungin given as a 1-hr infusion once daily at dosages ranging from 0.5 to 4 mg/kg to 77 children from 2 to 17 years of age with febrile neutropenia [12]. The pharmacokinetic profiles for micafungin demonstrated dose linearity; clearance, volume of distribution, and half-life remained constant and did not change with repeated administration. The overall plasma pharmacokinetic profile was similar to that observed in adults; exposure following a dose of 1 mg/kg corresponded to that following 50 mg, and that following a dose of 2 mg/kg to that of 100 mg in adult subjects. There was an inverse relation between age and clearance. For patients 2- to 8-year old, clearance was approximately 1.35 times to that of patients $\geq$9 years of age. The half-life of micafungin was between 11.6 and 17.3 hr and similar to that observed in 19 Japanese children aged 1–15 years with deep mycoses (13.1 hr) [13]. There was no evidence of dose-limiting toxicity as defined as any grade 3 or higher toxicity. Population-based pharmacokinetic modeling of the dataset of the pivotal dose finding trial confirmed the achievement of exposures similar or higher to that observed after the therapeutic standard adult dose of 100 mg once a day (QD) with the selected therapeutic pediatric dose of 2 mg/kg QD throughout the investigated age range of 2–17 years [14].

In neonates, pharmacokinetic studies covering a dose range from 0.75 to 3 mg/kg also showed linear disposition but a considerably faster clearance rate as compared to children, adolescents, and adults; micafungin was well tolerated in this population [15,16]. Similarly, further studies exploring elevated doses of micafungin in premature neonates revealed no safety concerns at dosages of up to 15 mg/kg/day [16].

TREATMENT OF CANDIDEMIA AND OTHER TYPES OF INVASIVE CANDIDA INFECTIONS

A double-blind, randomized, multinational non-inferiority trial compared micafungin with liposomal amphotericin B (L-AmB) as first-line treatment for candidemia and invasive candidiasis [17]. In the pediatric substudy, a total of 106 patients <16 years of age were enrolled (intent-to-treat population, ITT), and 98 patients were included in the modified ITT population (48 patients in the micafungin group, 50 in the L-AmB group, MITT) [18]. Micafungin was given at a daily dosage of 2 mg/kg QD, and L-AmB at a dosage of 3 mg/kg QD. Under predefined conditions, the dosages of micafungin and L-AmB could be increased to 4 mg/kg and 5 mg/kg/day, respectively. Fifty-seven patients were younger than 2 years, including 19 children who were premature at birth, and 41 children were between 2- and 16-year old. Most patients (92.9%) had candidemia. Treatment success was comparable in the two groups [72.9% in the micafungin group vs. 76.0% in the L-AmB group (ITT)], independent of the neutropenic status and age of the patient. All infective *Candida* species were associated with low rates of mycologic persistence after both micafungin and L-AmB treatment. However, consistent with the larger dataset in adult patients, micafungin was better tolerated with a lower incidence of adverse events leading to study drug discontinuation (3.8% vs. 16.7% in the L-AmB group; $P = 0.05$).

Further treatment and safety experience has been accrued by an open, non-comparative phase II study, which has been presented in abstract form (Arrieta et al., 17th European Congress of Clinical Microbiology and Infectious Diseases, 2007, München; p211; http://www.blackwellpublishing.com/eccmid17/abstract.asp?id=56047; accessed on December 21, 2009). This study included 55 pediatric patients $\leq$15 years of age with systemic candidiasis who received micafungin for a time period between 5 days and 6 weeks A total of 16 patients had received systemic antifungals for <48 hr for newly diagnosed *Candida* infection and subsequently received micafungin monotherapy, whereas 39 patients had received more than 5 days of prior antifungal therapy and were therefore switched for refractory infection either to micafungin monotherapy (n = 8) or combination therapy with other antifungal agents (n = 31). The overall treatment success was consistent across all age groups. Treatment failure was seen in six of the 16 patients (36.5%) with de novo systemic candidiasis, in one of the six patients (16.7%) with refractory infection who received micafungin as monotherapy, and in 11 of 31 patients (35.5%) with refractory candidiasis treated with combination therapy. Elevated liver enzymes and rash were the most common adverse events occurring in up to four patients (7.5%) each.

TREATMENT OF INVASIVE ASPERGILLOSIS

A multinational, non-comparative study examined the use of micafungin in *Aspergillus* species infection in a wide variety of patient populations, either as single agent or in combination with other systemic antifungal agents [7]. A subgroup analysis, presented in abstract form, included 58 pediatric patients (age 9 ± 4.3 years, range 3 months–16 years) who received micafungin alone (n = 2) or in combination (n = 56; Flynn et al., 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2006, San Francisco, CA; M-891; http://www.aspergillus.org.uk/indexhome.htm?secure/conferences/confabstracts/inputform.php~main; accessed on December 21, 2009). The infection was refractory in 54 patients, whereas it was newly diagnosed in four patients. Micafungin was given at a dosage of 2.0 ± 1.2 mg/kg/day for a median of 67 ± 85 days (maximum 425 days). The overall response rate (complete and partial response) was 45% (26/58), and 44.4% (12/27) in children <10 years of age; nine patients (16%) had a complete response, 17 (29%) a partial response, and six (10%) stable disease. A response was seen in 41% (20/49) of patients with pulmonary aspergillosis, and in 67% (4/6) of patients with disseminated disease; of note, 54 of the 56 patients had received micafungin as part of antifungal combination treatment.

PROPHYLAXIS

A randomized, double-blind clinical trial compared micafungin and fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing autologous or allogeneic HSCT [19]. Micafungin was administered at a daily dosage of 50 mg (1 mg/kg for patients weighing <50 kg), and fluconazole at a daily dosage of 400 mg (8 mg/kg for patients weighing <50 kg). Among the 882 patients enrolled were 84 children (39 in the micafungin

TABLE I. Clinical Studies on the Use of Micafungin in Children

References	Study characteristics	Number of patients	Age (years)	Indication for micafungin
Seibel et al. [12]	Prospective, safety, pk	77	2–17	Febrile neutropenia
Heresi et al. [15]	Prospective, safety, pk	18	Premature	Various
Kawada et al. [16]	Prospective, safety, efficacy, pk	25	Premature	Prophylaxis
Smith et al. [21]	Prospective, safety, pk	12	Premature	Suspected systemic infection
Arrieta et al. [abstract]	Prospective, safety, efficacy	55	<15	Systemic canididasis
Queiroz-Telles et al. [18]	Prospective, double-blind randomized versus L-AmB	98	0–16	Candidemia/systemic candidiasis
Flynn et al. [abstract]	Prospective, open label, safety and efficacy	58	0.3–16	Proven/probable invasive aspergillosis
van Burik et al. [19]	Prospective, double-blind randomized versus fluconazole	84	<16	Prophylaxis during neutropenia (after HSCT)
Kusuki et al. [20]	Retrospective, safety and efficacy	40	1–17	Prophylaxis during neutropenia (after chemo/HSCT)

pk, pharmacokinetics; L-AmB, liposomal amphotericin B; HSCT, hematopoietic stem-cell transplantation. Arrieta et al., 17th European Congress of Clinical Microbiology and Infectious Diseases, 2007, München; p211. Flynn et al., 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2006, San Francisco, CA; M-891.

group, 45 in the fluconazole group). Success was defined as the absence of suspected, proven, or probable invasive fungal infection through the end of therapy and as the absence of proven or probable invasive fungal infections through the end of the 4-week period after treatment. The overall efficacy of micafungin was superior to that of fluconazole as antifungal prophylaxis during the neutropenic phase after HSCT [80.0% in the micafungin arm vs. 73.5% in the fluconazole arm (difference, 6.5%; $P = 0.03$)]. Efficacy in children <16 years of age, was 69.2% in the micafungin group and 53.3% in the fluconazole group (difference 15.9%). Micafungin was well tolerated with safety and tolerance being similar in both study arms.

In a retrospective analysis from Japan, 40 children between 1 and 17 years of age were analyzed who received daily micafungin (3 mg/kg) during neutropenia either due to chemotherapy or after HSCT [20]. Treatment success defined as the absence of possible, probable, and proven invasive fungal infection, was seen in 93.9% of the 131 patient cycles after chemotherapy and in 80% of the 15 patients after HSCT. No adverse events were observed that could be related to micafungin prophylaxis.

SAFETY AND TOLERANCE

In the double-blind randomized trial comparing micafungin to L-AmB in children with invasive candidiasis, the most common treatment-related adverse events in the micafungin group were infusion-related reactions (13.5%), hypokalemia (5.8%), and fever (3.8%) [18]. The incidence of treatment-related serious adverse events was slightly lower children treated with micafungin [3.8% (two patients) vs. 9.3% (five patients) in the L-AmB group], leading to treatment-discontinuation in one patient of the micafungin group and in three patients of the L-AmB group. One of the patients receiving micafungin experienced a slight increase of the serum creatinine value (0.64 mg/dl at baseline to 0.83 mg/dl at day 3), which led to discontinuation of treatment, and for the other patient, renal failure was a worsening of a baseline condition. In the L-AmB group, there was one patient each with liver damage, bilirubinemia, or worsening of candidemia, and these three patients discontinued treatment; one patient had cholestatic jaundice, another renal dysfunction.

The results of a pooled analysis of data from all pediatric clinical trials conducted by the manufacturer of micafungin (296 patients) were presented in abstract form and overall attest to the excellent safety and tolerance of micafungin (Arrieta et al., 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2007, Chicago, IL; M-1162; http://www.aspergillus.org.uk/indexhome.htm?secure/conferences/confabstracts/inputform.php~main; accessed on December 21, 2009). The most frequent adverse events irrespective of causality included vomiting (31.8%), pyrexia (22.3%), diarrhea (21.6%), nausea (21.3%), and hypokalemia (20.9%); the most common adverse events which were at least possibly related to micafungin were hypokalemia (3.0%), increased alanine aminotransferase (ALT, 3.0%), increased aspartate aminotransferase (ASP), abnormal liver function tests, hyperbilirubinemia, increased alkaline phosphatase, and hypertension (2.0% frequency each). Although approximately one-quarter of patients with normal ALT and AST at baseline had levels higher the upper limit of normal (ULN) at end of treatment (EOT), only about 10% of patients developed levels of ALT and AST $\geq 2.5 \times$ ULN at EOT. Similarly, about 5% of children treated with micafungin and normal creatinine levels at baseline had an increase above the ULN at EOT, but only about 1% had an increase to $\geq 2.5 \times$ ULN. Treatment discontinuations due to adverse events at least possibly related to micafungin therapy occurred in 7 out of the 296 patients (2.4%): neutropenia, increased liver enzymes, and rash (three patients with underlying leukemia), jaw and joint pain, hyperbilirubinemia, increased creatinine (three patients after HSCT), and increased creatinine in a premature patient.

CONCLUSION

Micafungin is the first echinocandin, which has been approved for the use in children of all age groups, including preterm and term neonates. Its favorable safety profile and documented efficacy in various types of infection make it an attractive first-line agent for prophylaxis and treatment of *Candida* infection. Available only as

intravenous formulation, the current dose recommendation is 1 mg/kg/day for prophylaxis and 2 mg/kg/day for treatment of *Candida* infection in children weighing up to 40 kg, and 50 mg/day and 100 mg/day, respectively, for patients with a body weight >40 kg. The ultimate dose for preterm and term neonates, however, remains to be defined. Whereas very young children with invasive *Candida* infection were successfully treated with micafungin at a dosage of 2 mg/kg/day [18], population pharmacokinetic studies suggest a higher dose in small children to ensure adequate drug exposure [14]. Since micafungin exerts a different mode of action compared to other antifungal compounds, there is, at least theoretically, a rationale of antifungal combination therapy with micafungin. However, due to the limited data available in children, no definitive recommendations can be made for micafungin-based combination therapy at this time.

The European Medicines Agency (EMEA) has included a warning in the label that the decision to use micafungin should take into account a potential risk for the development of liver tumors. Preclinical data from rats treated with micafungin for either 3 or 6 months (a period of time equivalent to 12.5% or 25% of the total life span of the rat, respectively) revealed the development of foci of altered hepatocytes (FAH) and hepatocellular tumors [22], the mechanism of which is likely not genotoxic. Although the relevance to patients is uncertain, careful monitoring of liver function, early discontinuation in the presence of significant and persistent elevation of ALT/AST values, and careful risk/benefit assessment in patients with liver diseases or concomitant hepatotoxic/genotoxic therapies is advised [22].

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