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Micafungin in Premature and Non-premature Infants
A Systematic Review of 9 Clinical Trials

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Background: Invasive fungal infections cause excessive morbidity and mortality in premature neonates and severely ill infants.

Methods: Safety and efficacy outcomes of micafungin were compared between prematurely and non-prematurely born infants <2 years of age. Data were obtained from all completed phase I–III clinical trials with micafungin that had enrolled infants (<2 years of age) that were listed in the Astellas Clinical Study Database. Demographics, adverse events, hepatic function tests and treatment success data were extracted and validated by the Astellas biostatistical group for all micafungin-treated patients, <2 years of age, using the unique patient identifier.

Results: One-hundred and sixteen patients included in 9 clinical trials, 48% premature [birth weight (BW) <2500 g and/or gestational age <37 weeks], 52% non-premature, received ≥1 dose of micafungin. Among premature patients, 14.5% were low BW (1500–2499 g), 36.4% very low BW (1000–1499 g) and 49.1% extremely low BW (<1000 g). Ninety patients (78%) completed the studies; 13 [11% (4 premature)] died. Significantly more non-premature than premature patients discontinued treatment ($P = 0.003$). Treatment-related adverse events were recorded in 23% of patients with no difference between groups. More extremely low BW (n = 4, 15%) and very low BW (n = 8, 40%) infants experienced treatment-related adverse events than low BW (n = 0) and there was no relation to micafungin dose or duration. For a subgroup of 30 patients with invasive candidiasis, treatment success was achieved in 73% in both premature and non-premature groups. Prophylaxis was successful in 4/5 non-premature hematopoietic stem cell transplant patients.

Conclusion: Micafungin has a safe profile in premature and non-premature infants with substantial efficacy.

Key Words: pediatric, neonatal, micafungin, candidiasis, antimicrobial

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Prevalence of invasive fungal infection (IFI) has increased in very low birth weight (VLBW) preterm neonates (<1500 g), as more neonates born at the youngest gestational ages survive past the immediate postnatal period.[1,2] These neonates are not yet fully immunocompetent and often require invasive procedures, such as the use of central venous catheters and endotracheal tubes. Additionally, they are commonly exposed to broad-spectrum antibiotics, parenteral nutrition, H_2 blockers and corticosteroids. All these factors place neonates at high risk of IFI, particularly from *Candida* species. Invasive *Candida* infection (ICI) causes severe morbidity and mortality in VLBW preterm neonates in neonatal intensive care units.[3–5] In multicenter studies, ICI has an associated mortality rate of 21–32%, increasing to 40–50% in the most immature infants [ie, <28 weeks gestational age and extremely low birth weight (ELBW), ie, <1000 g].[6–9] Late neurodevelopmental impairment is common in ELBW infants who develop ICI.[4] The challenge is to establish adequate prevention and treatment strategies in such vulnerable populations.

Research has focused on identifying efficacious and well-tolerated antifungal drugs that can prevent and treat neonatal IFI. Historically, first-line options for treating neonatal IFI have been amphotericin B deoxycholate (AMB-D) and fluconazole.[10] However, nephrotoxicity limits AMB-D and uncertainties remain about its appropriate dosing and safety in premature infants.[10] An alternative AMB formulation, liposomal amphotericin B (L-AMB), is effective in VLBW infants with few reports of nephrotoxicity,[11–13] although adequate trial data do not exist. Fluconazole is only active against yeasts[14–16] and some species such as *Candida glabrata* and *Candida krusei* may be fluconazole resistant.[17,18] The echinocandins (anidulafungin, caspofungin and micafungin) are the most recently developed antifungal drug class, with broad-spectrum efficacy against *Candida* species including fluconazole-resistant strains and some activity against *Aspergillus* species. Among the echinocandins, the efficacy and safety of micafungin have been studied in clinical trials in neonates[19] along with pharmacokinetic studies.[20–22] The European Medicines Agency has licensed micafungin as the only echinocandin for neonatal use based on these data.

The inclusion of pediatric patients (<2 years of age), including full-term and premature neonates, in Phase I–III clinical trials of micafungin provided the opportunity to analyze patient-level data in this population. The aim of this study was to review the data regarding the safety and efficacy of micafungin in neonates and infants <2 years of age. We focused on the outcomes of premature compared with non-premature infants, with further stratification of premature infants based on degree of prematurity.

METHODS

Design and Data Sources

This retrospective study was conducted through database analysis of the demographic, safety and efficacy data obtained during all completed Phase I–III clinical trials in the Astellas Clinical Study Database. The trials were conducted from 1999 to 2012. Inclusion criteria were all infants <2 years of age treated with micafungin, prophylactically or for confirmed/suspected ICI or other IFI, regardless of dosages and duration of micafungin treatment.

Patient Population

All patients <2 years of age, regardless of gestational age, birth weight (BW) and indication, who had received at least 1 micafungin dose, were included in the analysis.

For the purpose of comparison, patients were categorized as non-premature if born at ≥37 weeks or premature if <37 weeks + 0 days gestational age and/or <2500 g at birth, including those readmitted to hospital and whose underlying condition was no longer prematurity but associated sequelae, such as bronchopulmonary dysplasia, intracranial hemorrhage or gastrointestinal disease of surgical interest.

Patients categorized as premature were further subcategorized by degree of prematurity, according to BW as infants with low birth weight (LBW): 1500−2499 g at birth; VLBW: 1000−1499 g at birth or ELBW: <1000 g at birth. Whenever BW was not available, we used an approximate correlation of gestational age with BW: LBW: 32 weeks + 0 days to 36 weeks + 6 days; VLBW: 28 weeks + 0 days to 31 weeks + 6 days or ELBW: ≤27 weeks + 6 days. For patients whose gestational age and BW were not available, an estimate of prematurity status and grading was made based on the weight and age of the patients at study baseline. Medical history notes from case report forms were reviewed to further clarify prematurity where necessary as certain conditions, such as those listed above, indicate a premature birth.

Outcomes and Statistical Analysis

Patient Demographics, Medical History and Disposition

Demographics, medical history, disposition and micafungin exposure were summarized for all patients, separately for non-premature and premature patients and for premature patients further subcategorized as LBW, VLBW or ELBW.

Safety

Safety data were recorded for all patients, separately for non-premature and premature patients and for premature patients further subcategorized as LBW, VLBW or ELBW.

Safety was assessed by identifying treatment-emergent adverse events (TEAEs), severe TEAEs, serious TEAEs, treatment-related TEAEs (TR-TEAEs) and TEAEs leading to discontinuation of study treatment. TEAEs were judged to be related, including "possibly related" or "not assessable" TEAEs or not related to study medication by the investigator. Relevant definitions for TEAEs can be found in Table 1. Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities version 12 (http://www.meddra.org/).

Hepatic function was assessed by laboratory tests for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. Serum creatinine was measured to assess renal function. The number and percent of patients who had either ALT or AST elevations >3, 5 or 10 times the upper limit of normal (ULN) value of 35 U/L and bilirubin elevations >2, 4 or 6 times ULN value of 1.0526 mg/dL (18 μmol) at least once during the treatment period were evaluated. This also applied to patients who had conjoint elevations of ALT or AST >3 times ULN and total bilirubin of either 1.5 or 2 times ULN. "Conjoint" was defined as 2 laboratory measures either from within the same sample or from 2 separate samples taken within 3 days. For patients from the Phase III randomized, active-controlled study of micafungin[19] shifts between baseline (before therapy) and during the study or at end of treatment (EOT) in ALT, AST, ALP (relevant change >3 times ULN), total bilirubin and serum creatinine (relevant change >2 times ULN) were evaluated.

Efficacy

Of the 9 trials analyzed,[19,20,23–29] 4 incorporated efficacy outcome measures (Table 2).[19,25,27,28] Of these 4, data from the 2 Phase III studies—the only double-blind studies with active comparators—are provided here. For the prophylactic study,[28] efficacy was measured as treatment success defined as the absence of a proven or probable IFI up to EOT plus a 4-week, post-treatment period. For the ICI study,[19] clinical response was defined as a complete or partial resolution of signs and symptoms, and mycologic response was defined as eradication or presumed eradication of the ICI. Treatment success rate was calculated as the ratio of the total number of treatment successes to the total number of patients and described where applicable by prematurity status.

Statistics

All eligible study data were pooled on a patient level and analyzed. Descriptive statistics for continuous variables included the number of subjects (n), mean and standard deviation. For categorical variables, percentages were calculated using the number of known values as denominator. Fisher's exact test was used to compare underlying conditions, treatment discontinuations, TEAEs, liver enzymes and bilirubin between non-premature and premature patients and also to evaluate the relationship between TEAE occurrence and micafungin dose (mg/kg) and duration (days). Wilcoxon rank sum test was used to compare mean daily micafungin dose and mean duration of micafungin treatment. Differences were considered significant if $P < 0.05$. Data analysis was generated using SAS/STAT software, Version 9.1 (2000–2004), SAS Institute Inc, Cary, NC.

RESULTS

Studies Retrieved

Nine clinical trials were identified, including 4 Phase I pharmacokinetic,[20,23,24,26] 2 Phase II noncomparative[25,27] and 3 Phase III studies[19,28,29] (Table 2).

Patient Demographics, Medical History and Disposition

From the 9 eligible studies, 116 patients <2 years of age were identified as having received at least 1 micafungin dose and were included in the pooled analysis. Of these, 60 (52%) were non-premature and 56 (48%) were premature; Table 3 shows demographics and

TABLE 1. Definitions of TEAE

Type of TEAE	Definition
TEAE	An AE that occurred during the treatment period or within 72 hours after last study medication administration
Severe TEAE	An AE that prevented the performance of daily activities
Serious TEAE	An AE that resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, required inpatient hospitalization or led to prolongation of hospitalization and other medically important events
TEAE "possibly related" to treatment	An AE that occurred with a reasonable time frame relative to drug administration, but which could also have been explained by concurrent disease or other drugs

TABLE 2. Clinical Trials Included in the Systematic Review

Study Type and Design	Key Enrollment Criteria	Micafungin Dose	Follow-Up Assessment Criteria	Micafungin Patients <2 Years of Age
Prophylaxis[23] Phase I, open-label, repeat dose, safety and pharmacokinetic study	Patients ≥4 months to ≤16 years Planned hematopoietic cell stem transplant	1.0 mg/kg for patients ≥25 kg and 1.5 mg/kg for patients <25 kg	Pharmacokinetic analysis Safety—physical examination, vital signs, 12-lead electrocardiogram, laboratory assessments, AEs	11
Treatment[24] Phase I, open-label, repeat dose, safety and pharmacokinetic study	Patients ≥4 months to <24 months Proven or probable esophageal candidiasis documented within 5 days	4.5 mg/kg	Pharmacokinetic analysis Safety—physical examination, vital signs, 12-lead electrocardiogram, laboratory assessments, AEs	9
Treatment[20] Phase I, open-label, single-dose, safety and pharmacokinetic study	Infants ≤40 weeks post-conceptional age Sepsis, pneumonia or other infections caused by *Candida* species	0.75 mg/kg, 1.5 mg/kg and 3.0 mg/kg in premature infants weighing >1 kg	Pharmacokinetic analysis Safety—physical examination, vital signs, clinical laboratory assessments, AEs	23*
Treatment[26] Phase I, open-label, repeat dose, safety and pharmacokinetic study	Patients >48 hours to <120 days of life Suspected candidemia or invasive candidiasis	10 mg/kg for patients <1 kg, 7 mg/kg for patients ≥1 kg	Pharmacokinetic analysis Safety—physical examination, vital signs, clinical laboratory assessments, AEs	13
Treatment[27] Phase II, open-label, noncomparative, efficacy and safety study	Adult and pediatric patients Confirmed diagnosis of candidemia (new or refractory)	1 or 2 mg/kg	Treatment success (defined as complete or partial response—clinical and mycologic) Safety—physical examination, clinical laboratory assessments, AEs.	17
Treatment[25] Phase II, open-label, noncomparative, efficacy and safety study	Adult and pediatric patients Proven or probable invasive aspergillosis	75 mg/d	Treatment response (defined as complete, partial, stabilization of disease or failure) Safety—physical examination, clinical laboratory assessments, AEs	5
Prophylaxis[28] Phase III, double-blind, randomized controlled, prophylactic, efficacy and safety study with fluconazole as reference therapy	Patients >6 months of age Allogeneic (any indication) or autologous (hematologic malignancy) hematopoietic stem cell trasnplant	1.0 mg/kg for patients <50 kg	Treatment success (defined as absence of proven, probable, or suspected invasive fungal infections to the end of prophylaxis plus a 4-week post-treatment period)	5
Treatment[29] Phase III study, uncontrolled, open-label	Pediatric patients Deep mycosis fungal infections caused by *Aspergillus* and *Candida* species	1.0 mg/kg starting dose (or 2.0 mg/kg or 3.0 mg/kg) dose escalation possible up to 300 mg	Pharmacokinetic analysis	3
Treatment[19] Phase III, randomized controlled, double-blind, efficacy and safety study with liposomal amphotericin B as reference therapy	Patients <16 years old Clinical signs of systemic *Candida* infection	2.0 mg/kg for patients ≤40 kg, 100 mg for patients >40 kg Dose increase up to 4.0 mg/kg or 200 mg permitted	Response rate: (defined as complete or partial clinical response and actual or presumed mycologic eradication) Safety—clinical laboratory assessments, AEs	30

*10 patients from this Phase I single-dose pharmacokinetic study were subsequently included in the Phase II, open-label, non-comparative, efficacy and safety study.[20]
ClinicalTrials.gov. NCT00606268.
†ClinicalTrials.gov. NCT00607763.

medical history. For the premature group, where gestational age was recorded (n = 25), the mean age was 26.5±2.7 weeks.

Of the 56 premature patients, 55 were further categorized by degree of prematurity as LBW (n = 8), VLBW (n = 20) or ELBW (n = 27). BW was recorded for 12 patients and BW was extrapolated from recorded gestational age for 13 patients. An estimate of prematurity status and grading was made based on the weight and age of the patients at study baseline for 30 patients. It was not possible to subcategorize 1 patient from the available data. Table 4 summarizes patient demographics and medical history.

Ninety (78%) patients completed the studies, 13 (11%) died, 6 (5%) were lost to follow up, 4 (3%) did not complete studies for

non-specified reasons and data were missing for 3 patients. Twenty-four (21%) patients discontinued treatment, with significantly more non-premature than premature infants discontinuing (32% vs. 9%, respectively; *P* = 0.003).

Of the 13 patients who died, 9 were non-premature. Death was deemed unrelated to micafungin in the majority of cases. Death in 2 non-premature patients was considered a result of lack of efficacy. The first patient suffered from *Aspergillus* endocarditis and received combination therapy with L-AMB, micafungin and flucytosine for 134 days. The second patient died after 8 days' L-AMB and micafungin treatment for *Candida* peritonitis and sepsis because of *Candida albicans*.

For the 55 patients categorized by degree of prematurity, 45 (82%) completed the study: 5 (63%) LBW, 16 (80%) VLBW and 24 (89%) ELBW. Two patients in both the LBW and VLBW groups were lost to follow up and 1 was lost in the ELBW group. Mortality was low with 4 deaths: 1 LBW patient, 2 VLBW and 1 ELBW. One LBW (13%), 2 (10%) VLBW and 2 (7%) ELBW patients discontinued treatment. Tables 3 and 4 show the mean daily dose and duration of micafungin for premature and non-premature patients.

Safety

TEAEs occurred in 105 (91%) patients. There was no significant difference in the incidence of severe, serious or TR-TEAEs between non-premature and premature infants (Fig. 1). Incidence of overall TEAEs was similar across patients categorized by degree of prematurity. Although more ELBW and VLBW infants seemed to experience severe or serious TEAEs and TR-TEAEs than LBW infants, differences were not statistically significant (Fig. 2). No relationship was apparent between the occurrence of TEAEs, severe TEAEs, serious TEAEs and TR-TEAEs with micafungin dose or treatment duration in non-premature and premature groups or for premature patients categorized by degree of prematurity.

Figure 3 shows the most common TEAEs occurring in 10% or more of non-premature or premature patients. Eleven TEAEs led to 9 (8%) patients discontinuing treatment: 2 (4%) premature and 7 (12%)

TABLE 3. Demographics and Medical History for All Patients and by Prematurity Status

	Total (N = 116)	Non-premature (N = 60)	Premature (N = 56)	P Value
Female, n (%)	50 (43)	25 (42)	25 (45)	Not tested
Weight at time of enrollment, kg				
Mean ± standard deviation	4.6 ± 3.77	7.53 ± 3.04	1.47 ± 0.72	Not tested
Allogeneic HSCT, n (%)	15 (13)	15 (25)	0	Not tested
Autologous HSCT, n (%)	3 (3)	3 (5)	0	Not tested
None	98 (85)	42 (70)	56 (100)	Not tested
Neutropenic* at baseline, n (%)	4 (3)	4 (7)	0	Not tested
Not neutropenic at baseline, n (%)	110 (95)	56 (93)	54 (96)	Not tested
Not assessed, n (%)	2 (2)	0	2 (4)	Not tested
History of congenital heart disease, n (%)	43 (38)	17 (29)	26 (47)	0.05
Congenital heart disease status unknown†, n	2	1	1	
History of gastrointestinal disease, n (%)	29 (25)	11 (19)	18 (32)	0.13
Gastrointestinal disease status unknown†, n	1	1	0	
Catheter in place at baseline, n (%)	49 (82)	27 (90)	22 (73)	Not tested
Catheter removed and replaced during therapy	28 (57)	16 (59)	12 (55)	
Catheter removed and not replaced during therapy	9 (18)	5 (19)	4 (18)	
Catheter not removed	12 (24.5)	6 (22.2)	6 (27)	
No catheter in place at baseline, n (%)	11 (18)	3 (10)	8 (27)	
Catheter status unknown†, n	56	30	26	
Micafungin dose, mg/kg				
Mean ± standard deviation	2.80 ± 2.33	2.19 ± 1.34	3.44 ± 2.94	0.04
Micafungin treatment duration, days				
Mean ± standard deviation	17.2 ± 18.65	22.1 ± 22.7	11.8 ± 10.9	<0.001

*Absolute neutrophil count <500 cells/μL.
†Patients not included in the calculations as baseline status of parameter was not recorded.

TABLE 4. Demographics and Medical History for Premature Patients Categorized by Degree of Prematurity

	LBW (N = 8)	VLBW (N = 20)	ELBW (N = 27)
Female, n (%)	2 (25)	9 (45)	13 (48)
Gestational age, weeks			
Mean ± standard deviation	34.0*	27.7 ± 3.56†	25.7 ± 1.46‡
Median (range)	34 (34–34)	27 (24–34)	25 (24–28)
Weight at time of enrollment, kg			
Mean ± standard deviation	1.95 ± 0.23	1.64 ± 0.42	1.11 ± 0.73
Catheter in place at baseline, n (%)	6 (86)	7 (50)	9 (100)
Catheter removed and replaced during therapy	4 (67)	4 (57)	4 (44)
Catheter removed and not replaced during therapy	0	1 (14)	3 (33)
Catheter not removed	2 (33)	2 (29)	2 (22)
No catheter in place at baseline, n (%)	1 (14)	7 (50)	0
Catheter status unknown§, n	1	6	18
Micafungin dose, mg/kg			
Mean ± standard deviation	1.81 ± 0.32	2.53 ± 1.46	4.56 ± 3.72
Micafungin treatment duration, days			
Mean ± standard deviation	10.8 ± 5.06	16.7 ± 13.39	8.5 ± 9.05

One patient was not included because it was not possible to subcategorize this patient from the available data.
*Data available for 1 patient.
†Data available for 6 patients.
‡Data available for 18 patients.
§Patients not included in the calculation as baseline status of parameter was not recorded.

non-premature patients ($P = 0.17$). TEAEs leading to discontinuation in non-premature infants were increased liver enzymes (n = 3), cardiac failure (n = 2), decreased oxygen saturation, neutropenia, intracranial hemorrhage and hypotension (all n = 1). Cardio-respiratory arrest led to treatment discontinuation in an LBW patient and an abnormal liver test led to treatment discontinuation in an ELBW patient.

Regarding liver function, there were more non-premature infants with elevated ALT or AST levels than premature infants. In contrast, the incidence of bilirubin levels above ULN during the study was higher in premature patients than non-premature patients. Conjoint elevations of ALT or AST and bilirubin were similar between groups (Table 5).

For the majority of the 30 neonates from the ICI study,[19] whose ALT, AST, ALP, bilirubin and creatinine levels were calculated before, during and at EOT, there were no elevations in these parameters at any time. There was a lack of consistency in the shift patterns of these clinical laboratory evaluations in patients who did experience elevated levels. Although a few patients had elevated ALT, AST, ALP and bilirubin levels during therapy, or at EOT, from normal baseline levels, others had elevated levels at baseline which then either normalized or remained elevated during therapy or at EOT (Table 6). Serum creatinine elevations were not observed at any time.

Efficacy

The ICI study[19] included 30 patients <2 years of age who had received at least 1 micafungin dose. Of these, 15 were premature. None had undergone hematopoietic stem cell transplantation (HSCT) or were neutropenic. *C. albicans*, *Candida parapsilosis* and *Candida tropicalis* were the most common pathogens in both groups, accounting for 43% (n = 13), 20% (n = 6), and 17% (n = 5) of *Candida* species, respectively, whereas, *C. krusei*, *Candida guilliermondii*, *Candida utilis* and *Candida lipolytica* accounted for single cases. The most common infection site was the blood in 93% (n = 28) of patients. Mean micafungin daily dose and treatment duration were similar between non-premature and premature patients (Table 7). Overall, treatment success was achieved in 73% of both non-premature and premature patients. The majority of patients had a complete clinical response and complete mycologic eradication (Table 7). For the 3 patients in whom ICI recurred, the species was *C. albicans*.

Five non-premature patients <2 years of age from the prophylaxis study[28] were included in this analysis (mean weight: 11.28 ± 3.17 kg). All 5 had undergone allogeneic HSCT, none

FIGURE 1. TEAEs for patients by prematurity status. Statistical comparison of non-premature versus premature groups was by Fisher's exact test.
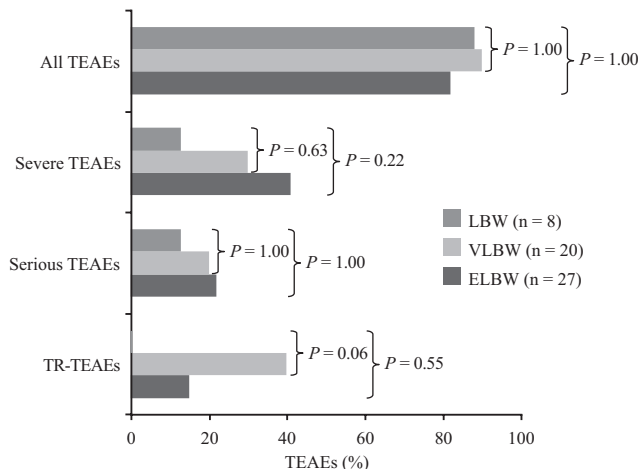

FIGURE 2. TEAEs for premature patients categorized by degree of prematurity. Statistical comparison against LBW group as the comparator was by Fisher's exact test.
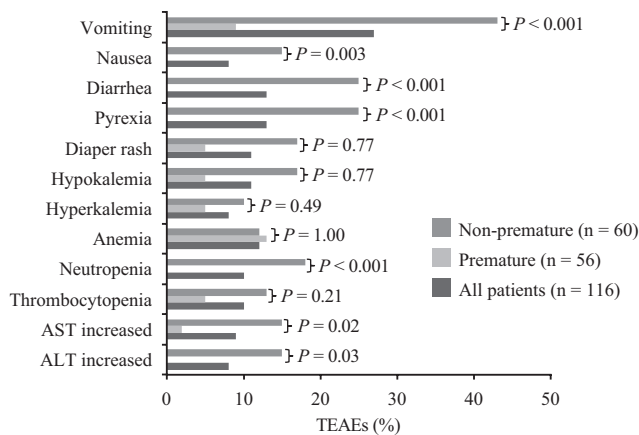

FIGURE 3. Incidence of TEAEs (>10% in either group) for all patients and for patients by prematurity status. Statistical comparison of non-premature versus premature groups was by Fisher's exact test.

had neutropenia and catheter status was unknown. Mean daily micafungin dose was 0.99 ± 0.02 mg/kg and treatment duration was 33.6 ± 10.9 days. Micafungin prophylaxis was successful in 4 patients after allogeneic HSCT and was not evaluable in 1.

DISCUSSION

This is the first study to date to comprehensively review prospectively collected data from randomized controlled trials on the safety and efficacy of an echinocandin, that is, micafungin, in infants <2 years of age, and compare non-premature and premature patients and those with various grades of prematurity. Our analysis found no unexpected safety concerns with micafungin in either premature or non-premature infants, even with the use of high daily doses and long treatment courses. Our results confirm findings that AEs because of micafungin in this population tend to be mild and seldom lead to treatment discontinuation.[30,31]

This safety analysis in premature neonates and infants <2 years of age supports and expands results found in a review of 6 clinical
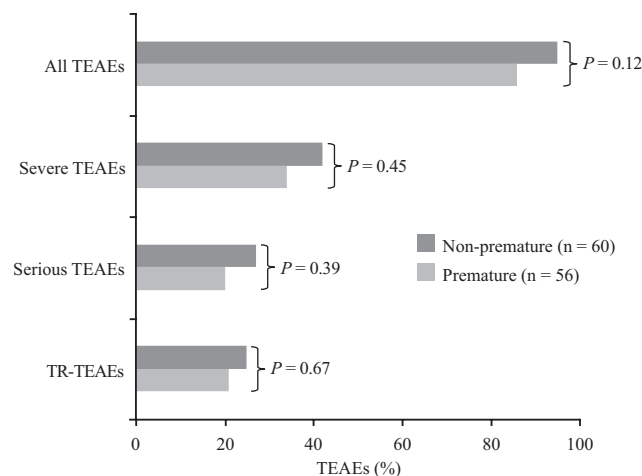
TABLE 5. Incidence of Clinically Significant Elevations in Liver Function Test at Least Once During Therapy for All Patients and for Patients by Prematurity Status

Liver Function Test	Total (N = 116)	Non-premature (N = 60)	Premature (N = 56)	P value
AST/ALT >3 × ULN, n/N (%)*	19/96 (20)	14/49 (29)	5/47 (11)	0.04
AST/ALT >5 × ULN, n/N (%)*	11/106 (10)	8/56 (14)	3/50 (6)	0.21
AST/ALT >10 × ULN, n/N (%)*	2/108 (2)	2/58 (3)	0/50	0.50
Bilirubin >2 × ULN, n/N (%)*	11/77 (14)	5/54 (9)	6/23 (26)	0.08
Bilirubin >4 × ULN, n/N (%)*	14/96 (15)	4/55 (7)	10/41 (24)	0.04
Bilirubin >6 × ULN, n/N (%)*	6/101 (6)	3/57 (5)	3/44 (7)	1.00
AST/ALT >3 × ULN and bilirubin >1.5 × ULN, n/N (%)*	10/105 (10)	5/57 (9)	5/48 (10)	1.00
AST/ALT >3 × ULN and bilirubin >2 × ULN, n/N (%)*	7/106 (7)	3/57 (5)	4/49 (8)	0.70

*Patients who did not have evaluable data were excluded (ie, not in the denominator). Statistical comparison of non-premature versus premature groups was by Fisher's exact test.

TABLE 6. Shifts in Liver Enzymes, Bilirubin and Creatinine From Baseline That Occurred During Therapy or at End of Treatment in the 30 Neonate Patients From the Phase III Randomized, Active-Controlled Study of Micafungin[19]

	Number of patients		
	Normal at baseline → Elevated during therapy or at EOT	Elevated at baseline → Normalized during therapy or at EOT	Elevated at baseline → Elevated during therapy or at EOT
ALT	2	3	0
AST	2	4	0
ALP	3	2	5
Bilirubin	5	3	2
Creatinine	0	0	0

trials of micafungin in pediatric patients aged ≤16 years.[32] Together, the 2 analyses show that micafungin is well-tolerated by children of all ages, including premature neonates. In our analysis, the incidence of severe, serious or TR-TEAEs was similar in premature and non-premature infants. Although there appeared to be more severe, serious and TR-TEAEs in ELBW and VLBW infants than in those with LBW, an analysis of these TEAEs showed that there was no relationship with micafungin dose or treatment duration. This is consistent with studies in other patient groups, including older children, where no trends were observed between AEs and micafungin dose or treatment duration.[32–34]

AMB-D, a mainstay of IFI therapy, has a poor safety profile mainly associated with nephrotoxicity, hypokalemia and infusion-related local reactions.[35] AMB-D is generally better tolerated by neonates than adults;[36] however, severe nephrotoxicity has been reported in VLBW infants.[37] L-AMB was developed as a safer alternative to AMB-D, but a high incidence (16.7%) of AEs leading to treatment discontinuation has been reported in pediatric patients treated for ICI with L-AMB.[19] In contrast to L-AMB, the incidence of AEs leading to treatment discontinuation with micafungin in this study was lower (3.8%)[19] and similar to the current analysis (3.4%). These results are consistent with the pooled risk of treatment discontinuation of >10% for AMB preparations and 2.5−3.8% for fluconazole, caspofungin and micafungin reported by Wang et al,[38] and confirm that micafungin is a well-tolerated alternative to AMB preparations in pediatric populations.

In the pooled analysis of micafungin-treated pediatric patients,[32] nearly one-half had elevated baseline AST or ALT levels and one-third had elevated baseline bilirubin. The proportions of patients with elevated liver enzymes or bilirubin during treatment were far less, at 7.7% for AST, 11.7% for ALT and 4.9% for bilirubin. It is likely that in our analysis the incidence of elevated AST/ALT and bilirubin levels included patients who had raised levels at baseline or even during treatment as a result of their underlying condition, rather than being

associated with drug treatment. Shifts in AST and ALT levels were examined in the current analysis at baseline and during treatment in the 30 patients <2 years of age treated with micafungin for invasive candidiasis;[19] this showed a number of patients with high AST, ALT or bilirubin levels at baseline who normalized their values during therapy.

Neonate deaths that occurred in the studies analyzed were deemed by the participating investigator to be unrelated to micafungin in the majority of cases, although 2 deaths were attributed to a lack of efficacy. In our opinion, 1 patient, who was treated with L-AMB and micafungin for *Candida* peritonitis and sepsis because of *C. albicans*, did die because of failure of the combination therapy, as this *Candida* species is often susceptible to echinocandins and L-AMB. The other patient's death was, in our opinion, not related to micafungin; this patient suffered from *Aspergillus* endocarditis and was on combination therapy with L-AMB, micafungin and flucytosine. As echinocandins may not be fungicidal for *Aspergillus*, especially in a patient with cardiac vegetations who is on combination therapy, we consider this death cannot be attributed to micafungin failure.

Micafungin pharmacokinetics demonstrate a shorter half-life and faster clearance relative to younger age in children[39] and lower weight in neonates,[20] indicating pediatric dosing should perhaps be modified based on age or weight. The pharmacokinetics of elevated micafungin doses have been examined in a small number of young infants.[22,26] These data have prompted proposals to use high (up to 10 mg/kg) micafungin doses to treat ICI in neonates in case of potential central nervous system infection.[40–42] Clinical trial data demonstrate a micafungin dose of 2 mg/kg effectively treats pediatric patients with ICI with success rates similar to L-AMB.[19] Treatment outcomes in pediatric ICI have been reported to be similar for the different antifungal classes (67% efficacy rate for triazoles, 73% for polyenes, 73% for echinocandins).[43] The 73% success rate observed with micafungin in current analysis of neonates from the ICI study[19]

TABLE 7. Demographics, Medical History, and Treatment Success of Patients <2 Years Old From the Phase III Randomized, Active-Controlled Study in Invasive Candidiasis Infection[19]

	Total (N = 30)	Non-premature (N = 15)	Premature (N = 15)
Female, n (%)	10 (33)	4 (27)	6 (40)
Weight at time of enrollment, kg			
Mean ± standard deviation	4.16±3.33	6.56±3.21	1.76±0.53
Catheter in place at baseline, n (%)	23 (77)	13 (87)	10 (67)
Catheter removed and replaced during therapy	14 (61)	9 (69)	5 (50)
Catheter removed and not replaced during therapy	5 (22)	3 (23)	2 (20)
Catheter not removed	4 (17)	1 (8)	3 (30)
No catheter in place at baseline, n (%)	7 (23)	2 (13)	5 (33)
Micafungin dose, mg/kg			
Mean ± standard deviation	2.40±0.68	2.52±0.77	2.27±0.57
Median (range)	2.00 (1.90–4.25)	2.08 (1.97–4.25)	2.00 (1.90–3.59)
Treatment duration, days			
Mean ± standard deviation	17.5±8.34	19.3±9.80	15.7±6.40
Median (range)	15 (5–42)	17 (5–42)	14 (5–35)
Clinical response, n (%)			
Complete response	21 (70)	10 (67)	11 (73)
Partial response	2 (7)	2 (13)	0
Progression of fungal infection*	3 (10)	1 (7)	2 (13)
No evaluation	4 (13)	2 (13)	2 (13)
Mycologic response, n (%)			
Eradication	21 (70)	10 (67)	11 (73)
Presumed eradication†	2 (7)	2 (13)	0
Recurrence of fungal infection*	3 (10)	1 (7)	2 (13)
No evaluation	4 (13)	2 (13)	2 (13)

*Progression of fungal infection was also recorded as a clinical outcome and recurrence of fungal infection as a mycologic outcome.
†Eradication was presumed when a patient had a complete clinical response that was not confirmed by a culture/biopsy as this was contraindicated.

is similar to these results. Micafungin has also been shown to be efficacious against *Candida* in VLBW premature infants in a separate study.[44] Concerns regarding the efficacy of echinochandins, including micafungin, against *C. parapsilosis,* the most common non-*C. albicans* fungal pathogen in neonates,[43,45–48] have been raised because of higher *in vitro* minimum inhibitory concentrations. However, in clinical trials, the high treatment success rates of micafungin against this strain are similar to *C. albicans* and *C. glabrata.*[27,49]

In addition to treating diagnosed infections, micafungin might also be seen as an attractive alternative to fluconazole as antifungal prophylaxis as it is active against *Candida* including fluconazole-resistant *Candida* species such as *C. glabrata* and *C. krusei* and against *Aspergillus* species. In the single study of micafungin versus fluconazole as antifungal prophylaxis in adult and pediatric HSCT patients, micafungin was superior to fluconazole (*P* = 0.03) during the neutropenic phase after transplantation.[28] Among 5 patients <2 years of age evaluated in this current analysis, 4 had no breakthrough IFI during neutropenia and the fifth was lost to follow up. Results of this prophylaxis efficacy analysis are limited by the small number of patients <2 years of age included (n = 5).

Our study has some limitations. As the data analyzed came from the Astellas Clinical Study Database, this study is not a systematic review of all micafungin studies in infants <2 years of age but rather a review of data obtained during the drug's clinical development. The retrospective design of the study may also be considered a limitation. However, the strength of the data analyzed here derives from the prospective and interventional design of the 9 Phase I–III clinical trials, and from the inclusion in the analysis of the largest number of patients <2 years of age who were prospectively treated with a single antifungal (n = 116). An additional strength of this systematic analysis is the subcategorization of premature patients and comparison of micafungin efficacy and safety in patients with different degrees of prematurity. Neither this analysis, nor the 9 studies from which the data were derived, were designed to test for significant differences between subgroups. The statistical

comparisons our study provides confirm the hypothesis of no difference in the safety profile of micafungin in premature infants versus those born at full term, to a greater extent than can be ascertained by reviewing descriptive statistics of the individual studies alone. Caveats including lack of statistical powering and multiplicity of testing should be considered when interpreting, in particular, the significant differences between subgroups with regards to TEAEs.

In conclusion, in the 9 multicenter trials analyzed, micafungin was well-tolerated in premature and non-premature neonates <2 years of age and few TR-TEAEs leading to treatment discontinuation were reported.

These data suggest that micafungin can be a valuable and well-tolerated, first-line option for the treatment of ICI in premature and non-premature infants <2 years of age.

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