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ORIGINAL RESEARCH

Comparison of the Safety and Tolerance Profile of Micafungin with that of Other Echinocandins and Azoles in Patients with Pre-existing Child–Pugh B or C Liver Disease: A Case–Control Retrospective Study

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ABSTRACT

Introduction: To assess the association between exposure to micafungin, other echinocandins, or azoles and the development of short-term liver injury (STLI) or long-term liver injury (LTLI) in patients with Child–Pugh B or C liver disease.

Methods: Multicenter case–control study of patients with Child–Pugh B or C liver disease who received antifungals (AF) for ≥ 72 h (May 2009–May 2015) in six Spanish and Italian hospitals. All micafungin patients were randomly matched with one patient who received another echinocandin and with one patient who received azole treatment. Primary outcome was development of STLI or LTLI (development of any type of liver tumor during the follow-up period).

Results: Of 2335 patients with chronic liver disease admitted to the six centers, 20 (0.85%) were found to have Child–Pugh B or C liver disease and received micafungin for ≥ 72 h. During AF treatment, the frequency of STLI was 10% in each group. Most cases of STLI were asymptomatic, and AFs had to be switched to another class of AF in only two patients (one micafungin and one azole). No patients developed acute liver insufficiency, were admitted to the ICU, or had to undergo transplantation. Follow-up data (median of 1.3 years) were

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available for 30 patients. LTLI was observed in only one patient, who had previously received treatment with azoles.
Conclusions: Our study suggests that the administration of micafungin to patients with end-stage liver disease does not imply a higher risk of developing STLI or LTLI.

Keywords: End-stage liver disease; Liver injury; Micafungin; Safety

Key Summary Points

Patients with end-stage liver disease (ESLD) are at high risk of invasive fungal infections.

Information on the efficacy and safety of micafungin compared with other antifungals in ESLD patients is scarce.

The administration of micafungin to patients with ESLD was safe and did not imply a higher risk of developing short- or long-term liver injury.

INTRODUCTION

Patients with end-stage liver disease (ESLD) are at high risk of acquiring invasive fungal infections (IFI) because of alterations in gut microbiota, gut permeability, and immune dysfunction [1, 2]. The frequency of IFI in ESLD patients ranges from 1 to 10% [3, 4], and development of IFI has a profound effect on the outcome of ESLD [5, 6].

Echinocandins are among the better tolerated antifungals in patients with ESLD [7–14]. Nevertheless, micafungin is the only echinocandin not approved in patients with ESLD because of an EMA warning on the potential development of liver tumors, as shown in preclinical studies in rats treated with high micafungin doses for either 3 or 6 months.

In humans, data on hepatotoxicity in patients treated with micafungin are scarce [15–21] and, to our knowledge, only three studies have partially evaluated this issue among ESLD patients [12–14]. However, data on the incidence of long-term liver injury (LTLI) and the relative magnitude of this risk compared with other antifungals have not been reported.

We performed a large, multicenter, case–control study in order to define, in routine clinical practice, the association between exposure to micafungin, other echinocandins, or azoles, and the development of short-term liver injury (STLI) or LTLI in a population of patients with pre-existing Child–Pugh B or C ESLD.

MATERIALS AND METHODS

Study Design and Setting

We performed a retrospective, multicenter, case–control study in six large tertiary-care hospitals in Spain and Italy. The study cohort consisted of adult patients with chronic Child–Pugh B or C ESLD [22] who received $\geq$ 72 h of therapy with micafungin, other echinocandins ,or azoles from May 2009 to May 2015.

In order to avoid bias, cases were identified in each institution based on the diagnosis and procedure codes of the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM). Patients with a primary and secondary diagnosis of chronic liver disease (ICD-9-CM codes used for that purpose are listed within the electronic supplementary

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material) were identified. Data were cross-checked with pharmacy databases consisting of all patients who received an echinocandin or an azole during the study period. Information on etiology, severity of liver disease, and antifungal exposure were then re-checked using the clinical charts.

Inclusion Criteria

To be considered cases, patients had to meet all of the following criteria: (1) ESLD classified as Child–Pugh B or C [22] on the first day that antifungal therapy was started; (2) micafungin at 100 mg daily for at least 72 h; and (3) prior and subsequent measurement of liver function.

For each case, we selected two matched controls: one receiving another class of echinocandins (caspofungin loading dose of 70/50 mg followed by 50/35 mg once daily or anidulafungin loading dose of 200 mg then 100 mg once daily) and one receiving an azole (fluconazole 400 mg once daily or voriconazole loading dose of 6 mg/kg then 4 mg/kg twice daily). To be considered matched controls, patients had to be Child–Pugh B or C ESLD and fulfill the following conditions: (1) same sex; (2) antifungal therapy at about the same time as the case; (3) antifungal therapy with the same indication as the case (empirical or targeted treatment); and (4) survival for as long as the case after administration of antifungal drugs.

Patients who underwent liver transplantation were eligible for the study only if the graft was affected by a chronic disease (i.e., patient with recurrence of HCV cirrhosis after liver transplant). For both cases and controls, the index date was defined as the date of the first administration of the study drug.

Follow-Up and Outcomes

Outcomes were assessed during a follow-up period that began on the index date and ended on the date of death or the last clinical visit until the end of June 2016.

The *primary outcome* of the study was the incidence of short- or long-term toxicity in patients with Child–Pugh B or C ESLD. STLI was defined as an increase during antifungal treatment in transaminase levels to > 3 times the upper limit of normal for patients who started antifungal therapy with normal liver function. If patients started antifungal treatment with abnormal baseline transaminase levels (i.e., $> 50\%$ greater than the upper limit of normal), STLI was defined as a doubling of the baseline transaminase level. LTLI was defined as the development of any type of liver tumor during the follow-up period.

Secondary outcomes were cumulative incidence of patients stopping treatment owing to abnormal liver function, cumulative incidence of patients needing transplantation owing to hepatotoxicity, re-admission for any cause in the following year, and number of episodes of ascitic decompensation or gastrointestinal bleeding during the following year.

Clinical Data

Data collected included demographic data, etiology of liver disease, underlying disease, and clinical course. When available, laboratory data were collected at days -7, -3, 0, $+1$, $+3$, $+5$, $+7$, $+14$, $+28$, $+45$, $+60$, $+120$, and $+180$ and included the international normalized ratio, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, gamma glutamyl transferase, creatinine, and albumin. Detailed data were also collected on concomitant drugs, type of invasive fungal infection, and pathogens.

Ethics

The study was approved by the institutional review board of the coordinating center (Hospital General Universitario Gregorio Marañón, MICRO.HGUGM.2014-017) and was in accordance with the declaration of Helsinki. Informed consent was deemed unnecessary due to the retrospective nature of the study.

Statistical Analysis

Patients who received micafungin were compared with those who received other

echinocandins or azoles. To detect significant differences between groups, we used the Chi square test or Fisher exact test for categorical variables and a 2-tailed *t* test or Mann–Whitney test for continuous variables, when appropriate. Values are expressed as mean ± standard deviation (continuous variables) or as percentages of the group from which they were derived (categorical variable).

A multivariable logistic regression analysis was performed to assess risk factors for STLI. Variables associated with the development of STLI in the univariate analysis (P value ≤ 0.3) were selected for possible inclusion. Statistical significance was set at $P < 0.05$. The results were analyzed using SPSS, v.17.0 (SPSS, Chicago, IL, USA).

RESULTS

Between May 2009 and May 2015 (6 years), 2335 patients with a diagnosis of chronic liver disease were admitted to the six study centers (Hospital General Universitario Gregorio Marañón, 537 patients; Nuovo Santa Chiara University Hospital, 520; Santa Maria Misericordia Hospital, 450; Hospital Universitario Ramón y Cajal, 400; Hospital Puerta de Hierro, 260; and Hospital del Mar, 168). Of these, 20 patients who fulfilled the criteria of Child–Pugh B or C liver disease received micafungin for ≥ 72 h. Overall, patients receiving micafungin represented 0.85% of all those with a diagnosis of chronic liver disease.

Comparison of ESLD Patients Receiving Micafungin with Those Treated with Other Echinocandins or Azoles

The demographics and baseline characteristics of the three groups (20 patients each) selected for the case–control study are summarized in Table 1. Univariate analysis revealed no significant differences between cases and controls regarding etiology of liver disease, other comorbidities, previous antibiotic therapy, and rate of cirrhosis-related complications. However, when compared with patients who received azoles, those with micafungin and other echinocandins had a higher MELD score and a higher Child–Pugh score. No differences were detected between patients who received micafungin and other echinocandins, although those with micafungin were significantly older (61.2 vs. 52.8 years, $P = 0.01$).

Comparison Between STLI and LTLI

Exposure to antifungal treatment is reported in Table 1. Antifungals were mostly administered as targeted therapy against *Candida* spp. (60%). The most frequent indications for antifungal treatment were bloodstream infections (33.3%) and urinary tract infections (10%), with no significant differences between groups. Length of therapy was significantly longer among patients receiving azoles (mean duration 19.2 days) than among those treated with micafungin (12.3 days) or other echinocandins (10.9 days). In contrast, compared to azoles, septic shock was more frequent in patients who received micafungin (35% vs. 0%, $p = 0.08$) or other echinocandins (50% vs. 0%, $p = 0.03$).

Six of 60 patients (10%) patients developed STLI: two patients with micafungin, two patients with other echinocandins, and two patients with azoles. The rate of STLI was 0.81 cases per 100 patient-days for micafungin, 0.91 cases per 100 patient-days for other echinocandins, and 0.51 cases per 100 patient-days for azoles.

The increase in serum aminotransferase was asymptomatic in all patients who experienced STLI, and antifungal discontinuation was required in only two cases: one patient who was receiving micafungin and another who was receiving azoles. Figure 1 shows how laboratory values changed over time. There were no relevant differences in liver function over time between the groups. Interestingly, in all evaluable patients, transaminase levels returned to normal after withdrawal or switching of antifungal therapy. No patients developed acute liver insufficiency requiring ICU admission or liver transplantation.

Overall, in-hospital mortality was 35% for cases treated with micafungin, 45% for other echinocandins, and 25% for azoles ($p = 0.39$).

Table 1 Clinical characteristics of the study population and exposure to antifungal treatment

Characteristics	Total $n = 60$	Micafungin $n = 20$	Other echinocandins $n = 20$	Azoles $n = 20$	p
Age (years) (mean ± SD)	58.2 ± 14.5	61.2 ± 11.2	52.8 ± 9.6	60.6 ± 20.1	0.13
Male sex	45 (75.0)	15 (75.0)	15 (75.0)	15 (75.0)	1
Race					
White	59 (98.3)	20 (100)	20 (100)	19 (95.0)	1
Non-white	1 (1.7)	0	0	1 (5.0)	
Pre-existing liver disease					
HCV-associated cirrhosis	26 (43.3)	7 (35.0)	12 (60.0)	7(35.0)	0.64
HBV-associated cirrhosis	7 (11.6)	3 (15.0)	1 (5.0)	3 (15.0)	0.11
Alcohol-associated cirrhosis	18 (30.0)	7 (35.0)	5 (25.0)	6 (30.0)	0.52
Cryptogenic cirrhosis	4 (6.6)	0	1 (5.0)	3 (15.0)	0.78
Hepatocellular carcinoma	8 (13.3)	2 (10.0)	4 (20.0)	2 (20.0)	0.15
Other causes[a]	7 (11.6)	3 (15.0)	3 (15.0)	1 (5.0)	0.56
Baseline MELD score	17.7 ± 7.3	18.6 ± 7.6	19.6 ± 5.8	14.9 ± 7.9	0.10
Baseline child–pugh class B	35 (58.3)	12 (60.0)	8 (40.0)	15 (75.0)	0.08
Baseline child–pugh class C	25 (41.6)	8 (40.0)	12 (60.0)	5 (25.0)	0.08
Baseline child–pugh score	9.1 ± 1.4	9.1 ± 1.4	9.6 ± 1.2	8.6 ± 9.1	0.07
Complications within previous year					
Episode of ascites	17 (28.3)	5 (25.0)	8 (40.0)	4 (20.0)	0.34
Episodes of gastrointestinal bleeding	5 (8.3)	1 (5.0)	2 (10.0)	2 (10.0)	0.80
Antibiotic exposure	46 (76.6)	14 (70.0)	18 (90.0)	14 (70.0)	0.22
Other comorbidities					
Heart failure	6 (10.0)	3 (15.0)	2 (10.0)	1 (5.0)	0.57
Renal chronic disease	12 (20.0)	4 (20.0)	6 (30.0)	2 (10.0)	0.28
Respiratory disease	7 (11.6)	3 (15.0)	2 (10.0)	2 (10.0)	0.85
Diabetes mellitus	16 (26.6)	8 (40.0)	6 (30.0)	2 (10.0)	0.09
Cancer	12 (20.0)	6 (30.0)	3 (15.0)	3 (15.0)	0.39
HIV infection	5 (8.3)	3 (15.0)	1 (5.0)	1 (5.0)	0.41
Reason for starting AF therapy					
Empirical therapy	24 (40.0)	10 (50.0)	9 (45.0)	5 (25.0)	0.23
Targeted therapy	36 (60.0)	10 (50.0)	11 (55.0)	15 (75.0)	

Table 1 continued

Characteristics	Total $n = 60$	Micafungin $n = 20$	Other echinocandins $n = 20$	Azoles $n = 20$	p
Length of AF treatment (median, range)	14.1 ± 8.0	12.3 ± 6.5	10.9 ± 5.6	19.2 ± 9.1	< **0.001**
Invasive fungal infection					
Bloodstream infection	20 (33.3)	5 (50.0)	6 (54.5)	9 (60.0)	0.88
Abdominal infection	5 (8.3)	2 (20.0)	0	3 (20)	0.13
Urinary tract	6 (10.0)	2 (20.0)	2 (18.9)	2 (13.3)	0.89
Lung	2 (3.3)	0	1 (9.1)	1 (6.7)	0.64
Other[a]	3 (5.0)	1 (10.0)	2 (18.9)	0	0.24
Isolated pathogens[b]					
Candida spp.	34 (94.4)	10/10 (100)	10/11 (90.1)	14/15 (93.3)	0.49
Aspergillus spp.	2 (5.6)	0	1/11 (9.1)	1/15 (6.7)	
Septic shock	17 (28.3)	7 (35.0)	10 (50.0)	0	0.22
SOFA score (mean ± SD)	6.8 ± 3.2	6.5 ± 3.2	8.1 ± 2.8	5.8 ± 3.2	0.06
Development of short-term hepatotoxicity	6 (10.0)	2 (10.0)	2 (10.0)	2 (10.0)	1
In-hospital mortality	22 (36.6)	8 (40.0)	9 (45.0)	5 (25.0)	0.39

Bold value indicate $p < 0.05$

AD ascitic decompensation

[a] Hepatocellular carcinoma

[b] Overall, a pathogen was isolated in 36 out of 60 patients (60.0%)

No deaths were considered related to the antifungal drugs. Causes of death were mostly related to worsening of underlying disease (nine patients), invasive fungal infection (six patients).

Follow-up information was available for 30 patients until a median of 1.3 years after discharge. During the following year, no differences were observed between groups with respect to rate of re-hospitalization [50.0% (6/12) for micafungin vs. 85.7% (6/7) for other echinocandins and 81.8% (9/11) for azoles, $p = 0.23$)], number of episodes of ascitic decompensation [(16.6% (2/12) vs. 14.3% (1/7) vs. 27.3% (3/11)], gastrointestinal bleeding (0% in each group), or mortality rate [33.3% (4/12) vs. 28.7% (2/7)vs 36.3% (4/11)]. Only 1 patient in the azoles group experienced LTLI with a new diagnosis of hepatocellular carcinoma 3 years after the index date.

Risk Factors for Liver Injury

We performed a univariate analysis in order to identify potential risk factors for STLI, including the following variables: age, other underlying conditions, severity of liver disease, septic shock, baseline liver and renal function, and length of antifungal treatment. The only variables associated with STLI were presence of septic shock at the time of antifungal therapy (66.7% vs. 24.1%, $p = 0.04$) and higher MELD score (24.6 ± 8.6 vs 1.6.9 ± 6.8, $p = 0.01$) (Table 2). However, differences were not significant for any variables in the multivariate analysis.

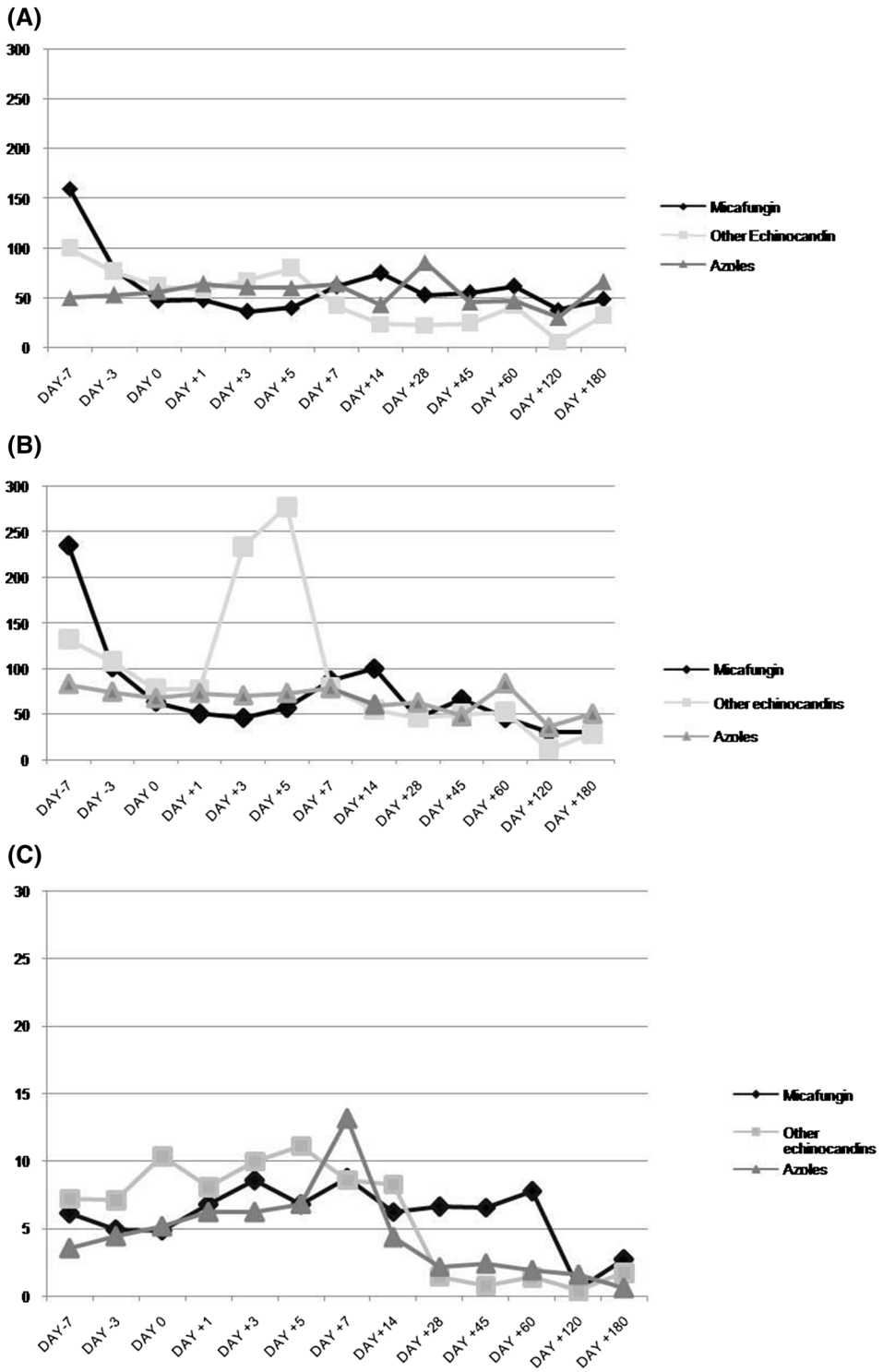

Fig. 1 Mean AST (**a**), ALT (**b**) and mean bilirubin (**c**) level according to specific study drug

Table 2 Univariate models predicting short-term liver toxicity

Characteristics	No liver injury $n = 54$	Hepatotoxicity $n = 6$	p
Age (years) (mean ± SD)	57.8 ± 14.8	61.5 ± 13.1	0.56
Male sex	42 (77.8)	3 (50.0)	0.15
Severity of liver disease			
Child B	32 (37.0)	3 (50)	0.68
Child C	22 (40.7)	3 (50)	0.68
Baseline child–pugh score	9.0 ± 1.4	10.0 ± 1.5	0.12
Baseline MELD score	16.9 ± 6.9	24.9 ± 8.5	**0.001**
Reason for starting AF therapy			
Empirical therapy	20 (37.0)	4 (66.7)	0.20
Targeted therapy	34 (63.0)	2 (33.3)	
Septic shock	13 (24.1)	4 (66.7)	**0.04**
Length of AF treatment	14.5 ± 8.2	10.5 ± 5.2	0.24
Micafungin treatment	18 (33.3)	2 (33.3)	1

Significant p values shown in bold
SD standard deviation, *ICU* intensive care unit, *AF* antifungal

Table 3 Incidence of STLI according to baseline MELD score

Meld score	Micafungin $n = 20$	Other echinocandins $n = 20$	Azoles $n = 20$
< 10	0/1 (0)	0/0	0/4
10–20	1/10 (10.0)	1/10 (10.0)	0/13
> 20	1/9 (11.1)	1/10 (10.0)	2/3 (66.7)

Given that only one patient had LTLI, univariate analysis was not performed to identify risk factors for long-term liver complications.

The incidence of STLI according to the baseline MELD score is reported in Table 3. When the baseline MELD score was > 20, the incidence of STLI was significantly higher in patients with azoles (2/3, 66.6%) than in those treated with micafungin (1/9, 11.1%) or other ecchinocandins (1/10; 10%). The median time between the index date and the development of STLI was 7 days (range 3–14 days).

DISCUSSION

To our knowledge, the present study is the first to show that, compared with other echinocandins or azoles, exposure to micafungin in patients with ESLD does not increase the risk of STLI or LTLI.

The incidence of IFI among patients with advanced liver disease has been reported to be as high as 10% [23, 24], with a mortality rate up to 98% [2, 5, 25–27]. In addition, liver disease has been found to be an independent risk factor for mortality [25], possibly because of abnormalities of the immune system [6, 28–30]. This risk is proportional to the level of hepatic impairment [5, 31].

The choice of antifungals in patients with ESLD is limited by a number of factors, including medical comorbidities, drug–drug

interactions, and antifungal resistance [32], although the main factor limiting treatment is the hepatotoxicity of antifungal drugs [33]. Liposomal amphotericin B and azoles are both associated with a significant risk of hepatotoxicity (27%) [21, 33–35]. Moreover, liposomal amphotericin B has been associated with an increasing risk of nephrotoxicity and infusion-related reactions [36], whereas azoles have a limited spectrum of antifungal activity and can cause severe drug–drug interactions [37]. Thus, the use of alternative antifungal drugs for the treatment of IFIs in patients with pre-existing liver disease is of particular clinical relevance.

Echinocandins have an excellent safety profile and are promising agents for the treatment of IFI in patients with ESLD. Both anidulafungin and caspofungin have been studied for this indication, although information is mainly from patients with Child–Pugh A or B liver disease, while experience in Child–Pugh C disease is very limited [7–11].

Micafungin has a broad in vitro spectrum, potent in vivo activity, a favorable safety profile, and excellent bioavailability, and is indicated for the treatment of invasive candidiasis [38, 39], esophageal candidiasis [40], and antifungal prophylaxis in patients with hematological disease [41].

Micafungin is generally safe in patients who do not have chronic liver disease, with no evidence of a greater risk of STLI than other antifungal drugs [38–41]. A systematic review and meta-analysis [21] showed that abnormal liver function test results during treatment with micafungin were observed in 3% of the patients, with only 2.7% discontinuing treatment for hepatotoxicity. In a more recent study, no increased risk of short-term liver injury was observed in comparison to other antifungals (fluconazole, caspofungin, voriconazole and amphotericin B) in a cohort of pediatric and adult patients without chronic renal and liver conditions who received micafungin [15].

Evidence of hepatic toxicity in patients with chronic liver disease receiving micafungin is very limited but also generally reassuring [12–14]. Nevertheless, the relative magnitude of short-term liver risk compared to other antifungals in the ESLD population is less clear. Our data show that micafungin, in comparison to other echinocandins or azole therapy, did not incur a higher risk of hepatotoxicity in patients with ESLD. Indeed, the groups had similar rates of STLI and a comparable change in transaminase level during therapy. More specifically, the transaminase level remained stable or decreased during micafungin therapy, and discontinuation of micafungin due to its hepatic adverse effects was required in only one patient. Moreover, in our study, in comparison to fluconazole, micafungin and the other echinocandins were more commonly prescribed among patients with higher MELD score, which is by itself a risk factor for STLI.

As for LTLI, we found no major safety concerns relating the development of hepatic tumors during a follow-up period of more than 1 year. Preclinical data from animal studies reported the development of foci of altered hepatocytes and hepatocellular tumors in rats treated with high doses of micafungin for prolonged periods. Interestingly, although similar studies have never been performed for anidulafungin [42] or caspofungin [43], comparable results were also observed in long-term studies performed in animals receiving voriconazole [44] or fluconazole [45]. In the present study, we observed only one patient previously treated with azoles experiencing a new diagnosis of hepatocarcinoma during the follow-up period. We did not find evidence of liver tumors in any of the ESLD patients treated with micafungin, thus pointing to potential differences in tumor development between humans and rats. Our findings are consistent with the results from a pooled safety analysis including 3028 patients treated with micafungin [20] and support the absence of post-marketing reports of hepatic adenoma or carcinoma related to micafungin, despite more than 1,000,000 patients worldwide having received the drug.

There are several potential limitations of our study. First, its retrospective design and the relatively small number of patients included are the major weakness. However, patients were identified after checking more than 2000 patients in six large Spanish and Italian hospitals. Second, channeling bias is also likely since providers who are aware of the EMA warning

would be expected to avoid prescription of micafungin in patients with a higher risk of developing STLI or LTLI. Third, although we used a predefined definition for hepatic injury, a direct relationship between hepatotoxicity and antifungals exposure could be difficult to evaluate, especially in high-risk groups of patients in which other variables (comorbidities, global degree of immunosuppression, other hepatotoxic drugs, toxins, etc.) may have played a role leading to over- or underreporting toxicity in our analysis. Fourth, although $\sim$ 70% of patients received antibiotics within the previous 1 year, we did not have data available regarding which antibiotics and how long they were administered. Such aspects may have also been confounders for liver events. Lastly, we did not count recurrent episodes of antifungal administration in this analysis, and the risk for STLI and LTLI could be different than that for the first episode.

Strengths of our study include its multicentric design and its optimal follow-up. To our knowledge, this study is the first in-depth report on short- and long-term safety of micafungin in patients with ESLD and its comparison with other echinocandins and azoles.

CONCLUSIONS

In conclusion, according to our study hypothesis, the administration of micafungin to patients with pre-existing Child–Pugh B or C ESLD was safe and, in routine clinical practice, did not imply a higher risk of developing short- or long-term liver injury.

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Disclosures. Matteo Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Menarini, MSD, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRx and Vifor. Patricia Munoz is a consultant and/or speaker for Astellas, Gilead, Merck, Novartis and Pfizer and T2 Biosystems. Matteo Bassetti and Antonio Vena now belong to "Department of Health Sciences, Infectious Disease Clinic, University of Genoa and Hospital Policlinico San Martino-IRCCS, Genoa, Italy". Emilio Bouza, Francesco Menichetti, Maria Merelli, Santiago Grau, Jesús Fortun, María Isabel Sánchez, José María Aguado, Paloma Merino and Francisco Bonache have nothing to declare.

Compliance with Ethical Guidelines. The study was approved by the institutional review board of the coordinating center (Hospital General Universitario Gregorio Maranon MICRO.HGUGM.2014-017) and was in

accordance with the declaration of Helsinki. Informed consent was deemed unnecessary due to the retrospective nature of the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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