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Randomized, Double-Blind Trial of Anidulafungin Versus Fluconazole for Prophylaxis of Invasive Fungal Infections in High-Risk Liver Transplant Recipients

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Invasive fungal infections (IFIs) are a common complication in liver transplant recipients. There are no previous randomized trials of an echinocandin for the prevention of IFIs in solid organ transplant recipients. In a randomized, double-blind trial conducted at University-affiliated transplant centers, 200 high-risk liver transplant recipients (100 patients per group) received either anidulafungin or fluconazole for antifungal prophylaxis. Randomization was stratified by Model for End-Stage Liver Disease score $\geq$30 and receipt of a pretransplant antifungal agent. The primary end point was IFI in a modified intent-to-treat analysis. The overall incidence of IFI was similar for the anidulafungin (5.1%) and the fluconazole groups (8.0%) (OR 0.61, 95% CI 0.19–1.94, $p = 0.40$). However, anidulafungin prophylaxis was associated with less *Aspergillus* colonization or infection (3% vs. 9%, $p = 0.08$), lower breakthrough IFIs among patients who had received pretransplant fluconazole (0% vs. 27%, $p = 0.07$), and fewer cases of antifungal resistance (no cases vs. 5 cases). Both drugs were well-tolerated. Graft rejection, fungal-free survival, and mortality were similar for both groups. Thus, anidulafungin and fluconazole have similar efficacy for antifungal prophylaxis in most liver transplant recipients. Anidulafungin may be beneficial if the patient has an increased risk for *Aspergillus* infection or received fluconazole before transplantation.

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; ICU, intensive care unit; IFI, invasive fungal infection; MELD, Model for End-Stage Liver Disease; MIC, minimum inhibitory concentration; M-ITT, modified intent-to-treat; MSG, Mycoses Study Group

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Introduction

Invasive fungal infections (IFIs) are a significant complication in organ transplant recipients. Among solid organ transplant recipients, liver transplant patients have one of the highest incidences and also the greatest mortality from fungal infection (1). Consequently, based upon existing randomized clinical trials (2,3), both the American Society of Transplantation Infectious Diseases Community of Practice and the Infectious Disease Society of America clinical practice guidelines recommend fluconazole for liver transplant recipients at high risk for IFIs (4,5). A survey of liver transplant programs in North America also found that fluconazole is the most commonly used agent for antifungal prophylaxis (6). Potential limitations of fluconazole, however, include the emergence of fluconazole-resistant non-albicans *Candida* species as pathogens, lack of activity for *Aspergillus*, and drug interactions with immunosuppressive agents leading to adverse events.

The echinocandins have activity for both *Aspergillus* and *Candida* species, including many *Candida* species resistant to fluconazole. The echinocandins also have a favorable safety profile and a low potential for drug interactions. Similar to the azoles, the echinocandins are both fungicidal and synergistic in combination with calcineurin-inhibitor agents for common fungal pathogens (7). In small uncontrolled studies, prophylaxis with caspofungin or micafungin appeared to be well-tolerated in liver transplant recipients (8–10). Anidulafungin is unique among echinocandins in that it is eliminated almost exclusively via biotransformation by nonenzymatic degradation in the blood without hepatic or renal elimination (11). Therefore, we conducted the first randomized, double-blind trial of an echinocandin for antifungal prophylaxis in solid organ transplant recipients by comparing anidulafungin with fluconazole for prevention of IFIs in high-risk liver transplant patients.

Methods

Study design

This was a randomized, double-blind trial involving liver transplant recipients at high risk for IFIs conducted between February 2010 and November 2011. The study was approved by the institutional review board at each participating site. Written informed consent was obtained from all patients or their legally authorized representatives.

Patients

Liver transplant patients ≥18 years of age who had one or more of the following risk factors for IFI were eligible for the study: retransplantation; transplantation for fulminant hepatic failure; receipt of corticosteroids for at least 2 weeks within 4 weeks preceding transplantation; hospitalization for at least 48 h in the intensive care unit (ICU) at the time of transplantation; colonization with *Candida* species at ≥2 sites within 4 weeks preceding transplantation; ≥15 U of intraoperative packed red blood cell transfusions and operative time >6 h; requirement of any form of renal replacement therapy at the time or within 7 days of transplantation; and reoperation involving the intraabdominal cavity. These variables as risk factors for IFIs in liver transplant recipients have been identified in multiple previous studies (2,12–18). Patients were excluded if they had known hypersensitivity to the azoles or the echinocandins; had life expectancy of <72 h; or had received systemic antifungal therapy for an IFI within 4 weeks preceding transplantation.

Blinding and study drug administration

Eligible patients were randomized 1:1 to receive either anidulafungin or fluconazole using permuted block randomization. Randomization was stratified within each center by Model for End-Stage Liver Disease (MELD) ≥30 and pretransplant receipt of an antifungal agent within 30 days prior to transplantation. Dosing with the study drug had to commence within 5 days of transplantation. Anidulafungin was administered as a 200 mg intravenous loading dose followed by 100 mg intravenous daily. There was no adjustment of the anidulafungin dosage for renal failure. Fluconazole was administered at a dosage of 400 mg intravenously daily. The fluconazole dosage was adjusted for renal failure as follows: creatinine clearance <50 mL/min and no dialysis (200 mg intravenously daily); continuous renal replacement therapy (400 mg intravenously daily); intermittent hemodialysis (400 mg intravenously after hemodialysis on dialysis days and saline infusion without fluconazole on nondialysis days). To maintain blinding, the study drug was dispensed in identical infusion bags with the same volume of fluid. Except for the site pharmacists, patients, research staff, and all members of the clinical team remained masked to drug assignment throughout the study.

The study drugs were continued for 21 days or until discharge. If a patient was discharged from the hospital before completion of 21 days of the study drug, the study drug was discontinued. In patients with ongoing need for renal replacement therapy, persistent liver allograft dysfunction, continued ICU stay, or increased immunosuppression for rejection in the previous 21 days, study drug could be continued beyond 21 days for a maximum of 42 days.

Assessments

The primary end point was the incidence of proven or probable IFIs within 90 days of transplantation. IFIs were defined by using the criteria of the European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) (19). Other assessments included fungal-free survival, fungal colonization, rejection, graft loss, and all-cause mortality. Fungal colonization was defined as previously reported in liver transplant recipients (2). Fungal isolates causing IFIs were tested for *in vitro* susceptibility to antifungal agents by a microbroth dilution assay, in accordance with Clinical Laboratory Standards Institute guidelines (20,21). Adverse events were recorded until 7 days after the last dose of study drug. Independent on-site clinical monitoring was conducted for source data verification and safety assessments. An independent data and safety monitoring committee provided study oversight.

Statistical analyses

IFIs have been documented in 36–50% of high-risk liver transplant recipients (14,22–24). Among patients receiving prophylactic fluconazole, 14–23% and an average of 18% developed IFIs (14,22,24). In a noncomparative study of prophylactic caspofungin in high-risk liver transplant recipients, 2.8% developed IFIs (8). Thus, assuming an incidence of IFI of 18% in the fluconazole group and 4% in the anidulafungin group, a sample size of 182 patients (91 patients in each group) would detect the aforementioned difference with a power of 80% and $\alpha = 0.05$. Adjusting for a 10% drop out rate, the study would require a total of 200 patients or 100 patients per study group.

Stata/IC (College Station, TX) was used for statistical analyses. Baseline characteristics and risk factors were compared using the chi-square test or rank sum test. The Mantel–Haenszel odds ratio was used to evaluate the effect of treatment on IFIs in a modified intent-to-treat (M-ITT) population (randomized patients with no baseline IFI and received >48 h of study drug). Breakthrough infections, defined as IFIs occurring during receipt of study drug, were similarly evaluated. The odds of any IFI or only breakthrough IFI in specific high-risk groups was assessed by the Mantel–Haenszel test.

A Kaplan–Meier estimate was calculated to evaluate the time to IFIs. Fungal-free survival between the two groups was compared using a log rank test. Patients who died without evidence of IFI were censured at the date of death. All remaining patients were censored at day 90 after transplant. The analysis was repeated using the stratification variables. The Kaplan–Meier estimate was also used to evaluate all-cause mortality. For this analysis, the entry point was the day of transplant, and the end point was date of death. Survivors were censored at day 90 after transplant.

Results

Patient characteristics

A total of 200 high-risk liver transplant recipients were randomized to receive either fluconazole or anidulafungin (100 patients per group). The two groups were similar in terms of demographic characteristics and risk factors for IFIs (Table 1). Approximately, 75% of the patients in each group had a MELD ≥30, while 60% in each group required renal replacement therapy. The median duration of prophylaxis was 21 days for both fluconazole (range, 5–43) and anidulafungin patients (range, 5–46). Thirty-six fluconazole patients received <21 days of study drug due to early discharge from the hospital (31 patients), early death after transplantation (1 patient), development of an IFI (2 patients) or withdrawal of study drug by the primary physician (2 patients). Similarly, 42 anidulafungin patients received <21 days of study drug due to early discharge from the hospital (37 patients), early death (2 patients), development of an IFI (2 patients) or possible adverse event related to study drug (1 patient).

Table 1: Patient characteristics of intent-to-treat population

Characteristic[1]	Fluconazole (N = 100)	Anidulafungin (N = 100)
Median age (range), years	58 (27–74)	58 (19–75)
Gender		
Male	72 (72%)	67 (67%)
Female	28 (28%)	33 (33%)
Primary liver disease[2]		
Hepatitis C virus	39 (39%)	49 (49%)
Alcoholic cirrhosis	34 (34%)	37 (37%)
Primary sclerosing cholangitis	13 (13%)	9 (9%)
Primary biliary cirrhosis	3 (3%)	1 (1%)
Nonalcoholic steatohepatitis	2 (2%)	4 (4%)
Cryptogenic cirrhosis	9 (9%)	5 (5%)
Concomitant hepatocellular carcinoma	20 (20%)	21 (21%)
Liver–kidney transplant	12 (12%)	11 (11%)
Cytomegalovirus seropositive donor/seronegative recipient	14 (14%)	12 (12%)
Baseline immunosuppressive agents		
Tacrolimus	95 (95%)	97 (97%)
Cyclosporine	5 (5%)	3 (3%)
Mycophenolate mofetil	93 (93%)	86 (86%)
Azathioprine	0 (0%)	1 (1%)
Prednisone	100 (100%)	97 (97%)
T cell depleting agent	7 (7%)	8 (8%)
Risk factors for invasive fungal infection		
MELD ≥30	73 (73%)	76 (76%)
Renal replacement therapy	64 (64%)	58 (58%)
Fulminant hepatic failure	3 (3%)	2 (2%)
Corticosteroid therapy within 4 weeks of transplantation	2 (2%)	4 (4%)
Candida colonization at ≥2 sites pretransplantation	4 (4%)	3 (3%)
Intensive care stay >48 h pretransplantation	47 (47%)	34 (34%)
Receipt of systemic antifungal agent within 30 days prior to transplantation	12 (12%)	15 (15%)
Repeat liver transplant	12 (12%)	15 (15%)
Repeat abdominal surgery during study	39 (39%)	37 (37%)
Blood loss >15 U and operative time >6 h	74 (74%)	67 (67%)
Number of patients with 1 or more risk factors[3]		
1	18 (18%)	17 (17%)
2	17 (17%)	21 (21%)
3	20 (20%)	23 (23%)
4	18 (18%)	21 (21%)
>4	27 (27%)	19 (19%)

MELD, Model for End-Stage Liver Disease.
[1]None of the differences between study groups were statistically significant ($p > 0.05$) by chi-square test or rank sum test. For renal replacement therapy, intensive care stay, and blood loss, p-values were 0.35, 0.07, and 0.14, respectively.
[2]Some patients had more than one underlying liver disease.
[3]There was no significant difference between the study groups, $p = 0.756$ by chi-square test.

Table 2: Incidence and types of invasive fungal infection in modified intent-to-treat population[1]

Fungal infection or pathogen	Fluconazole (N = 99)	Anidulafungin (N = 98)	p-Value[2]
Invasive fungal infection	8 (8.0%)	5 (5.1%)	0.40
Invasive candidiasis[3]	6 (6.0%)	5 (5.1%)	0.75
Candidemia	4	4	
Candida albicans	0	1	
Candida glabrata	1	2	
Candida tropicalis	1	1	
Candida krusei	1	0	
Candida dublinensis	1	0	
Intraabdominal infection, abscess, peritonitis	2[4]	1	
Candida albicans	0	1	
Candida glabrata	1	0	
Candida kefyr	1	0	
Invasive aspergillosis[3]	2 (2.0%)	0 (0.0%)	0.49
Pulmonary	2	0	
Aspergillus fumigatus	2	0	

[1]Modified intent-to-treat population excludes one fluconazole patient withdrawn on study day 1 by primary physician and two anidulafungin patients found to have invasive aspergillosis at study entry.
[2]p-Value from Cochran–Mantel–Haenszel test.
[3]Two *C. glabrata* infections, one *C. krusei* fungemia and both cases of invasive aspergillosis in the fluconazole group and one case each of *C. glabrata* and *C. albicans* fungemia in the anidulafungin group were breakthrough infections occurring during receipt of study drug. Other fungal infections occurred after the study drug administration period.
[4]One fluconazole patient had abdominal abscess with both *C. glabrata* and *C. kefyr*.

Efficacy

Two patients randomized to the anidulafungin group were subsequently found to have invasive aspergillosis at time of initiation of study drug and received <48 h of anidulafungin. Another patient randomized to fluconazole was withdrawn on study day 1 by the primary physician and received less than 24 h of fluconazole. These three patients were excluded from the M-ITT population used for efficacy analyses. As shown in Table 2, IFIs developed in 8% of fluconazole and in 5.1% of anidulafungin patients ($p = 0.40$). In the fluconazole group, there were six cases of invasive candidiasis (all caused by nonalbicans *Candida* species) and two cases of invasive aspergillosis. All the IFIs in the anidulafungin group were due to *Candida* species. No patients developed invasive aspergillosis on prophylactic anidulafungin. The median time from initiation of study drug to onset of IFI was longer in the anidulafungin group (43 days, range 7–87) compared to the fluconazole group (29 days, range 8–76), however this difference was not statistically significant ($p = 0.35$). Breakthrough IFIs on study drug occurred in two anidulafungin patients (2.0%) and in five fluconazole patients (5.0%). Among patients who had received a systemic antifungal agent prior to transplantation (fluconazole in all cases), breakthrough IFIs occurred in none of 14 anidulafungin patients but in 3 of 11

fluconazole patients (27.3%) ($p = 0.07$). There was no significant difference in breakthrough IFIs among patients not receiving a systemic antifungal agent prior to transplantation (2 in 84 anidulafungin patients or 2.4% vs. 2 in 88 fluconazole patients or 2.3%, $p = 0.96$). The breakthrough IFIs were treated with caspofungin alone (three patients), voriconazole alone (one patient), micafungin plus fluconazole (two patients) and voriconazole plus caspofungin or micafungin (one patient). None of these IFIs were fatal, and there were no adverse effects of antifungal therapy.

IFIs in all patients were diagnosed on the basis of a culture positive for a fungal pathogen and EORTC/MSG criteria. Fungal isolates (*Candida* species 8, *Aspergillus* species 1) from nine patients (fluconazole 6, anidulafungin 3) with IFIs were available for susceptibility testing. All nine isolates were sensitive to anidulafungin (minimum inhibitory concentration [MIC] $\leq 0.25\,\mu g/mL$). In contrast, five of the eight *Candida* isolates were resistant to fluconazole with MICs $\geq 16\,\mu g/mL$. Of the six fluconazole-resistant fungal isolates in study patients, five caused infection in the fluconazole group and one caused infection in the anidulafungin group. Three anidulafungin patients, who developed candidemia after completing 42 days of prophylactic anidulafungin, had *Candida* isolates still sensitive to anidulafungin.

The risk for IFI with anidulafungin prophylaxis compared to fluconazole prophylaxis by prespecified established risk factors for IFI is summarized in Table 3. For all subgroups, there were no significant differences in the overall risk for IFI between anidulafungin patients and fluconazole patients. However, for patients who had a MELD score $\geq$30, required renal replacement therapy, were given >15 U of packed red blood cells during transplant surgery, or had received fluconazole before transplantation, there was a lower risk for a breakthrough IFI with anidulafungin prophylaxis.

Fungal colonization

Assessment of fungal colonization was based on results of cultures of the oropharynx, respiratory secretions and urine performed as part of standard patient care. Colonization was documented in 38 of 99 fluconazole patients (38%) and in 39 of 98 anidulafungin patients (39.7%; $p = 0.93$). The incidence of *Candida* colonization was similar for the two study groups; *Candida albicans* and *Candida glabrata* were the predominant organisms associated with colonization in each group. Colonization with *Aspergillus* was more frequent in the fluconazole group (7 of 99 patients, 7%) than the anidulafungin group (3 of 98 patients, 3%; $p = 0.18$). All seven *Aspergillus* isolates associated with colonization and available for antifungal susceptibility testing were sensitive to anidulafungin (MIC $\leq 0.125\,\mu g/mL$). The overall incidence of *Aspergillus* infection or colonization was 9% (9 of 99 patients) in the fluconazole and 3% (3 of 98 patients) in the anidulafungin group ($p = 0.08$).

Safety

Primary immunosuppressive therapy included tacrolimus in 96% of all patients. Fluconazole patients compared to anidulafungin patients had significantly higher median tacrolimus levels at week 1 (5.4 vs. $4.8\,\mu g/mL$, $p = 0.036$) and at week 2 (8.2 vs. $7.1\,\mu g/mL$, $p = 0.020$) during the study. Nonetheless, there were no significant differences in renal function, neurological events or other adverse events between fluconazole and anidulafungin patients. Similarly, there were no significant differences in serum creatinine and liver function tests between the two study groups. Adverse events leading to discontinuation of the

Table 3: Odds of invasive fungal infection with anidulafungin prophylaxis compared to fluconazole prophylaxis in prespecified high-risk groups[1]

Prespecified risk group (N = number of patients)	Odds of any IFI[2] with anidulafungin compared to fluconazole in specified risk group, odds ratio [95% CI], p-value	Odds of breakthrough IFI[2] with anidulafungin compared to fluconazole in specified risk group, odds ratio [95% CI], p-value
MELD $\geq$30 (N = 146)	0.34 [0.08–1.35], 0.11	0.00 [0.00–0.70], 0.02[3]
Renal replacement therapy (N = 119)	0.45 [0.11–1.87], 0.26	0.00 [0.00–1.05], 0.056[3]
Fulminant hepatic failure (N = 5)	No IFI	No IFI
Pretransplant corticosteroids (N = 6)	No IFI	No IFI
Pretransplant *Candida* colonization (N = 7)	One IFI	No IFI
Pretransplant intensive care unit stay >48 h (N = 79)	0.67 [0.15–2.92], 0.59	0.00 [0.00–1.99], 0.14[3]
Pretransplant systemic antifungal agent (N = 25)	0.21 [0.02–2.70], 0.18	0.00 [0.00–0.87], 0.04[3]
Repeat liver transplant (N = 25)	1.66 [0.12–22.52], 0.70	1.66 [0.12–22.52], 0.70
Repeat abdominal surgery (N = 75)	0.49 [0.80–2.88], 0.42	0.00 [0.00–1.96], 0.16[3]
Blood loss > 15 U PRBC during transplant surgery (N = 142)	0.47 [0.12–1.91], 0.28	0.00 [0.00–0.85], 0.03[3]

CI, confidence interval; IFI, invasive fungal infection; MELD, Model for End-Stage Liver Disease; PRBC, packed red blood cells.
[1]Mantel–Haenszel test.
[2]Any IFI within 90 days of starting study drug or breakthrough infection while receiving study drug.
[3]Exact CI not calculated due to no breakthrough IFI in the anidulafungin group; fixed effect correction added to estimate CI.

Table 4: Incidence of rejection, liver graft loss and death in the intent-to-treat population

Outcome	Fluconazole (N = 100)	Anidulafungin (N = 100)	p-Value
Rejection	4 (4%)	6 (6%)	0.52
Liver graft loss	14 (14%)	13 (13%)	0.86
Death			
Within 90 days of transplantation	12 (12%)	12 (12%)	1.00
During study drug administration period	3 (3%)	4 (4%)	0.72
Causes of death			
Hepatic artery thrombosis/infarcts	4	3	
Bacterial sepsis	2	2	
Liver graft failure	1	1	
Recurrent hepatitis C	1	0	
Graft-versus-host disease	1	0	
Cardiac events	2	1	
Multi-organ failure	0	2	
Pneumonia	0	1	
Pulmonary embolism	0	1	
Intracranial hemorrhage	0	1	
Bowel infarct	1	0	

study drug occurred in 1 (1%) of 98 patients in the anidulafungin group (prolonged QT interval) and in none of the 99 fluconazole patients ($p = 0.99$).

Other outcomes and mortality

The incidence of rejection within 90 days of transplantation was similar in the fluconazole and anidulafungin groups (4% vs. 6%, $p = 0.51$). Kaplan–Meier estimates of fungal-free survival showed no significant difference between the anidulafungin group (94.5%; 95% CI, 87.4–97.7) and the fluconazole group (91.3%; 95% CI, 83.3–95.5, $p = 0.93$). The overall mortality rate at 90 days after transplantation was 12% in each study group. Causes of death in the study groups are shown in Table 4. There were no deaths due to an IFI.

Discussion

IFIs occur in 36–50% of high-risk liver transplant recipients without any effective antifungal prophylaxis (14,22–24). In the only previous randomized, double-blind trial of antifungal prophylaxis in liver transplant patients almost two decades ago, fluconazole compared to placebo significantly reduced IFIs (2). Since this pivotal study, there have been very few additional definitive clinical trials of antifungal prophylaxis in liver transplant patients or other types of solid organ transplant recipients. Similarly, despite the favorable profile of the echinocandins for antifungal prophylaxis, there have been no previous randomized, double-blind, controlled studies of an echinocandin for prevention of IFIs in organ transplant recipients or other types of complex surgical patients.

In randomized trials involving oncology patients receiving either a stem cell transplant or chemotherapy, both micafungin and caspofungin were as effective as fluconazole or itraconazole for antifungal prophylaxis (25–27). We also found that the overall incidence of IFIs in high-risk liver transplant recipients was similar for patients receiving a prophylactic echinocandin (anidulafungin) or fluconazole. The incidence of IFIs in our patients receiving prophylactic anidulafungin (5%) was similar to the incidence reported in previous small, noncontrolled studies of echinocandin prophylaxis in high-risk liver transplant recipients and close to the 4% incidence used to calculate our study's sample size (8–10). However, despite the inclusion of many extremely ill patients (MELD $\geq$ 30 in 75% of the patients) with well-established risk factors for IFI in our study, the incidence of IFI in patients receiving prophylactic fluconazole was 8% and lower than the expected incidence of 18%, which was based on existing data from studies done more than a decade ago (14,22–24). Indeed, despite the increasing acuity and sickness of patients currently undergoing liver transplantation, both patient and graft survival have improved due to advances in immunosuppression, patient management, and surgical experience (28). These factors may have contributed to the lower than expected incidence of IFI in the fluconazole patients. It is also possible that current risk factors for IFI in liver transplant recipients may differ from those risk factors previously identified in earlier studies. In two recent multivariate analyses of risk factors in the MELD era of liver transplantation, a MELD score $\geq$30 was found to be the most influential factor for IFI (17,18). The incidence of probable or proven IFI in these two studies were 28% and 24%, respectively.

Based on the incidence of IFI in our study (5.1% with anidulafungin, 8% with fluconazole) involving very sick liver transplant patients with established risk factors for IFI, an extremely large sample size ($\sim$1125 patients per study group or 2250 total patients) would be needed to demonstrate a statistically significant difference in the incidence of IFI (29). As such, it is unlikely that such a large randomized, double-blind trial comparing an echinocandin with fluconazole for antifungal prophylaxis would be feasible.

Anidulafungin is active against *Aspergillus* as well as several fluconazole-resistant *Candida* species. The incidence of *Aspergillus* infection or colonization was lower in our patients receiving anidulafungin (3% vs. 9%, $p = 0.08$). In addition, more *Candida* species causing invasive candidiasis in our study were resistant to fluconazole (five isolates) than to anidulafungin (none of the isolates). There was a higher incidence of breakthrough IFIs among fluconazole patients (27%) compared to anidulafungin patients (no patients; $p = 0.07$) who had received fluconazole before transplantation. These data suggest that anidulafungin may be more beneficial for antifungal prophylaxis in patients at higher risk for *Aspergillus* infection or who were treated with fluconazole before transplantation.

The protocol for this study allowed continuation of study drug for a maximum of 42 days. During administration of study drug, there were significantly fewer breakthrough IFI on prophylactic anidulafungin among patients with a MELD ≥ 30 ($p = 0.02$), requiring renal replacement therapy ($p = 0.06$), receiving more than 15 U of packed red blood cells during transplant surgery ($p = 0.03$), or treated with fluconazole before transplantation ($p = 0.04$; Table 3). However, three anidulafungin patients developed candidemia caused by *Candida* organisms still sensitive to anidulafungin after completing 42 days of anidulafungin prophylaxis. Thus, in clinical practice, prophylaxis with anidulafungin or another effective antifungal agent will likely need to be continued for a longer period if the patient still has persistent risk factors for IFIs.

Adverse events were similar with anidulafungin and fluconazole. Both drugs were generally well-tolerated. Fluconazole in liver transplant recipients increases serum cyclosporine levels (2) and was associated with higher serum tacrolimus levels in this study. However, there was no increase in tacrolimus nephrotoxicity or neurotoxicity with fluconazole. Neither fluconazole nor anidulafungin had any apparent hepatotoxicity.

A recent meta-analysis found that antifungal prophylaxis in liver transplant recipients does not affect overall mortality despite a significant reduction of IFI as well as mortality attributable to fungal infection (3). Since IFI frequently occur in critically ill liver transplant recipients with underlying host factors (graft dysfunction, surgical complications, multiorgan failure) that also greatly influence survival, this finding is not surprising. In our study, the overall mortality rate at 90 days after transplantation was low (12% in each study group), and there were no deaths due to IFI. Frequent protocol-driven diagnostic studies in patients with suspected fungal infection and subsequent initiation of early appropriate antifungal therapy in patients with documented IFI may have contributed to the absence of fungal-related mortality.

The decision to use antifungal prophylaxis needs to consider the possible emergence of resistant organisms and cost (30). An increase in *Candida krusei* and *Candida glabrata* infections has been associated with the use of prophylactic fluconazole in some studies (31,32). There has also been an increasing number of reports of echinocandin-resistant *Candida* infections (33). Consequently, antifungal prophylaxis in transplant recipients is frequently targeted to high-risk patients with established risk factors for IFI (6). Similarly, the significantly higher cost of an echinocandin, which must be given intravenously, needs to be balanced against the lower cost of fluconazole, which has the convenience of both oral and intravenous administration. A prophylactic strategy currently recommended for stem cell transplant recipients, in which fluconazole is given for initial prophylaxis and an echinocandin or mold-active azole is reserved for patients at risk for *Aspergillus* infections or fluconazole-resistant *Candida* infections, may also be the most cost-effective approach for liver transplant recipients (34).

In conclusion, for most liver transplant recipients at high risk for IFIs, anidulafungin and fluconazole have similar efficacy for antifungal prophylaxis. Both anidulafungin and fluconazole are well-tolerated in liver transplant recipients. Prophylaxis with anidulafungin may be beneficial in patients who are at high risk for invasive *Aspergillus* or have received fluconazole prior to transplantation.

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Authors' Contributors

DJW and NS contributed to the study design, analyzed the data, and wrote the first draft of the manuscript. All authors contributed to recruitment of patients, assisted in study procedures and data collection, provided comments on the manuscript, and approved the final version of the manuscript.

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Disclosure

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