https://doi.org/10.23873/2074-0506-2020-12-2-104-111

Comparing the results of invasive candidiasis prevention with anidulafungin vs. the lipid formulation of amphotericin B in high-risk patients in the early postoperative period after liver transplantation

S.V. Zhuravel*[1], N.K. Kuznetsova[1], I.I. Utkina[1], M.S. Novruzbekov[1], P.V. Gavrilov[1], T.V. Chernenkaya[1], G.K. Ospanova[2]

[1]N.V. Sklifosovsky Research Institute for Emergency Medicine, 3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;

[2]National Scientific Medical Center, 42 Abylaykhan Ave., Nur-Sultan 020000 Kazakhstan

*Correspondence to: Sergey V. Zhuravel, Dr. Med. Sci., Head of the Scientific Department for Anesthesiology, Intensive and Critical Care, N.V. Sklifosovsky Research Institute for Emergency Medicine, e-mail: zhsergey5@gmail.com

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

Zhuravel SV, Kuznetsova NK, Utkina II, Novruzbekov MS, Gavrilov PV, Chernenkaya TV, et al. Comparing the results of invasive candidiasis prevention with anidulafungin vs. the lipid formulation of amphotericin B in high-risk patients in the early postoperative period after liver transplantation. *Transplantologiya. The Russian Journal of Transplantation.* 2020;12(2):104–111. (In Russ.). https:// doi.org/10.23873/2074-0506-2020-12-2-104-111

Introduction. *The development of invasive candidiasis leads to high mortality after liver transplantation. Choosing an effective prophylaxis is an important task.*

The study purpose *was to compare the results of invasive candidiasis prevention with anidulafungin vs. the lipid formulation of amphotericin B*

in high-risk patients in the early postoperative period after liver transplantation.

Material and methods. *The study included 80 patients with risk factors for the development of invasive mycosis who underwent liver transplantation. Patients were divided into 2 groups. In the first group (n = 40), anidulafungin was prescribed for prophylaxis; in the 2nd group (n = 40), the lipid complex of amphotericin B was used.*

Results*. The most common of Candida spp. isolated in the patients of our study, as expected, was Candida albicans accounting for 31.2%, significantly less than a half. Neither fungal infection breakthrough nor invasive mycosis development were reported in any patient. In group 2, renal replacement therapy was significantly more frequently used. In two cases, the amphotericin B lipid complex was canceled and the conversion to echinocandin was undertaken due to the occurrence of adverse events (chills and fever) associated, in our opinion, with the drug used.*

Conclusions. *1. Patients after liver transplantation with 2 or more risk factors have absolute indications to invasive mycosis prevention.*

2. Anidulafungin and the lipid formulation of amphotericin B are effective for prophylaxis and prevention of fungal infection breakthrough.

3. Anidulafungin has an advantage in safety over the lipid formulation of amphotericin B.

Keywords: prophylaxis of fungal infection, liver transplantation, anidulafungin, amphotericin B lipid complex

AKI, acute kidney injury

MELD, Model for End-stage Liver Disease

MLV, mechanical lung ventilation

PCR, polymerase chain reaction

Introduction

At present, infections are the most common complications after liver transplantation. No doubt, bacterial pathogens rank first, playing the leading role in the early postoperative period, being followed by viral and fungal microorganisms [1, 2].

Among fungal infections, Candida spp. and Aspergillus spp. are the most common pathogens and cause the most life-threatening complications with high mortality [3, 4].

The implementation of antifungal prophylaxis after liver transplantation has been shown efficient in reducing both the incidence and the mortality rate associated with invasive candidiasis in presence of one or more specific risk factors. The incidence of invasive candidiasis is approximately 5 to 7% and, given an extremely high percentage of adverse outcomes related to its development, deserves an increased attention. Invasive candidiasis most often develops within the first 3 months after liver transplantation with an up to 70% probability of progressing to a fatal outcome. According to recent literature, there has been a steady increase in the Candida spp. family resistance to fluconazole. The above agent has been known as the drug of choice for the prevention and treatment of candidiasis over the recent 15 years. Only a small number of studies have been conducted on the choice of a prophylactic agent in high-risk patients after liver transplantation [5–7].

The aim of our study was to compare the results of prophylaxis with anidulafungin and the lipid formulation of amphotericin B in high-risk patients in the early postoperative period after liver transplantation.

Material and methods

We conducted a comparative, single-centre, randomized trial on the prophylactic use of antifungal drugs in high-risk patients.

The study enrolled 80 patients. The patients were allocated into two treatment groups as follows: in the 1st group (n = 40), anidulafungin was administered for prophylaxis, and in the 2nd (n = 40), the lipid form of amphotericin *B* was used.

Inclusion criteria:

1) The patient age of 18–70 years old.
2) The presence of two or more risk factors for the development of invasive candidiasis:
   a) orthotopic liver transplantation;
   b) blood loss of more than 3500 mL;
   c) liver retransplantation;
   d) relaparotomy within 5 days after surgery;
   e) Candida spp. colonization of one or more loci (oropharynx, rectum, urine, vagina, postoperative wound) in the perioperative period;
   f) MELD score (Model for End-stage Liver Disease) over 30;
   g) use of corticosteroids after transplantation;
   h) total parenteral nutrition for more than 3 days;
   i) mechanical lung ventilation (MLV) for over 48 hours;
   j) fulminant liver failure.

Exclusion criteria:

1. Primary graft non-function.
2. Intolerance to echinocandins or to the lipid formulation of amphotericin *B.*

The treatment outcomes, complications, adverse events related to the study drugs, the clinical efficacy of prevention therapy and the development of invasive fungal infection were monitored. Microbiological monitoring was performed before surgery, after surgery, and further 2 times a week. The blood, urine, wound discharge, oropharynx and rectum content were cultured, followed by the analysis of

colony growth on selective media. In addition, diagnostic polymerase chain reaction (PCR) assays for Candida albicans, Candida glabrata, Candida parapsilosis, Candida crusei, Candida tropicalis, Candida fungi were performed using PCR kits manufactured by Vector-Best ZAO.

Statistical Analysis

Statistical data processing was performed using the Statistica 10 software package. Quantitative data are presented as medians and quartiles (25 and 75%). The Mann–Whitney test was used to compare the results in the groups. Statistical significance was set up at p value <0.05.

Results

All patients underwent orthotopic liver transplantation. The indication for surgical intervention was cirrhosis of various etiology. Meanwhile, in most patients, both in the 1st and 2nd groups, the indication for liver transplantation was liver cirrhosis in the outcome of hepatitis *C*. The median age was 54 years (37; 57) in the 1st group, and53 years (43; 57) in the 2nd group (p> 0.05, statistically insignificant) (Table 1).

Table 1. Patients profile

Parameter	Anidulafungin, n=40	Amphotericin B lipid complex, n=40
Median age	54 (37; 57)	53 (43; 57)
Gender: Male (%) Female (%)	 28 (70) 12 (30)	 22 (55) 18 (45)
Etiology of cirrhosis, abs. (%)		
Cirrhosis in the outcome of hepatitis C	13 (32.5)	15 (37.5)
Cirrhosis in the outcome of	3 (7.5)	3 (7.5)

hepatitis B		
Autoimmune cirrhosis	3 (7.5)	5 (12.5)
Primary biliary cirrhosis	1 (2.5)	3 (7.5)
Alimentary cirrhosis	2 (5)	6 (15)
Cryptogenic cirrhosis	3 (7.5)	3 (7.5)
Liver cirrhosis, hepatocellular carcinoma	5 (12.5)	3 (7.5)
Polycystic liver disease	0	1 (2.5)
Primary sclerosing cholangitis	3 (7.5)	0
Cirrhosis in the outcome of hepatitis C + B	1 (2.5)	0
Cirrhosis in the outcome of hepatitis B + delta	6 (15)	1 (2.5)

All patients had at least two risk factors for the development of invasive candidiasis in the postoperative period. Meantime, 4 (10%) and 3 (7.5%) patients in the 1st and 2nd groups, respectively, had more than four risk factors for the development of invasive candidiasis (Table 2).

Table 2. Risk factors of invasive candidiasis development

Parameter	Anidulafungin, abs. (%), n=40	Amphotericin B lipid complex, abs. (%), n=40
Liver transplantation	40 (100)	40 (100)
Total parenteral nutrition for over 3 days	40 (100)	40 (100)
Corticosteroids after transplantation	10 (25)	11 (27.5)
Candida colonization of two or more loci in the perioperative period	13 (32.5)	10 (25)
Retransplantation	1 (2.5)	0
Relaparotomy within 5 days after transplantation	3 (7.5)	6 (15%)
Blood loss more than 3500 L	2 (5)	1 (2.5%)
Cold ischemia for over 8 hours	4 (10)	3 (7.5)

MLV for over 48 hours	2 (5)	2 (5)
MELD score over 30	1 (2.5)	1 (2.5)
The number of risk factors, abs. (%)		
1	40 (100)	40 (100)
2	40 (100)	40 (100)
3	14 (35)	16 (40)
4	8 (20)	9 (22.5)
more than 4	4 (10)	3 (7.5)

In microbiological and PCR studies of biological material, fungal colonization of two or more loci was detected in 23 patients (28.7%). These patients were considered as a risk group for the development of invasive candidiasis (Table 3).

Table 3. Candida spp. colonization in the ICU patients after orthotropic liver transplantation.

Patients	Colonized, abs. (%)	Colonization of one locus, abs. (%)	Colonization of two loci, abs. (%)	Colonization of three or more loci, abs. (%)
80 (100%)	34 (42.5)	11 (13.75)	16 (20)	7 (8.7)

The microbiological cultures and PCR assays demonstrated that the most common type of Candida spp. in our study was Candida albicans followed by Candida tropicalis, Candida parapsilosis, and Candida glabrata, Candida fungi, Candida crusei. We should note that quite often in a patient, different microorganisms were isolated from different loci (Table 4).

Table 4. The treatment for Candida spp. colonization

Parameter	Anidulafungin, abs. (%), n=40	Amphotericin B lipid complex, abs. (%), n=40
Total, (n)	13 (32.5)	10 (25)
Candida albicans	7 (17.5)	5 (12.5)
Candida glabrata	2 (5)	3 (7.5)

Candida parapsilosis	3 (7.5)	3 (7.5)
Candida crusei	2 (5)	1 (2.5)
Candida tropicalis	3 (7.5)	2 (5)
Candida fungi	2 (5)	3 (7.5)

The median duration of antifungal prophylaxis was 7 (3; 5) days. In group 2, the renal replacement therapy was used significantly more often. In 2 cases, the amphotericin *B* lipid complex was cancelled due to adverse events (chills and fever) being, in our opinion, related to the drug used and the conversion to echinocandin was undertaken (Table 5).

Table 5. Outcomes and complications

Parameter	Anidulafungin, abs. (%), n=40	Amphotericin B lipid complex, abs. (%), n=40
Death within 30 days	2 (5)	3 (7.5)
Death while on the drug therapy	0	0
Renal replacement therapy	4 (10)	10 (25)*
Hyperthermia associated with the drug therapy	0	2
Drug withdrawal	0	2
Invasive candidiasis	0	0

* $p < 0.05$

Discussion

A high mortality rate associated with invasive candidiasis necessitates a due choice of adequate antifungal therapy, which is of paramount importance among patients in the early period after liver transplantation. Candida albicans is the most common microorganism, meantime, the identification of Candida non-albicans is associated with a higher mortality rate. It should be noted that various transplant centres adhere to their own prophylaxis protocols, which can vary significantly between the centres. In recent years, much attention has been paid to increasing resistance to fluconazole [5]. Candida spp. resistance to antifungal drugs is a growing problem, the overall resistance rate to

fluconazole is approximately 5% in Candida albicans. The results of various studies report an overall resistance rates to fluconazole of up to 57%, which can be explained by a high detection rate of Candida non-albicans strains and previous antifungal prophylaxis. Some investigators point to the need for such prophylaxis after liver transplantation in high-risk patients only [5].

Resistance to echinocandins is currently found in less than 2% of patients being treated for Candida spp. [9].

Prevention of the invasive candidiasis development involves a comprehensive approach, including monitoring of fungal pathogens, assessing risk factors, and administering an adequate prophylaxis or empirical therapy.

Our results have shown that anidulafungin and the amphotericin *B* lipid complex are efficient in the prevention of candidemia and invasive candidiasis in high-risk patients after liver transplantation.

Clinically significant adverse events related to the use of the amphotericin B lipid complex, which were reported in our study, are consistent with the previously available information about the drug.

The median duration of prophylactic therapy in our study was 7 days. In general, the results of the study have shown that liver recipients are at risk of Candida infection, including that of non-albicans strains. Colonization of the mucous membranes, involvement of the oropharynx, esophagus, rectum, and vagina are usually not diagnosed as invasive candidiasis, but when the pathogenic strains are isolated from these sites, an antifungal agent should be administered; all specialists in this field agree to this, and the relevant guidelines are being entered into the protocols of postoperative patient management.

According to our results, one should take into account a higher risk of acute kidney injury (AKI) when using the amphotericin B lipid

complex. The AKI development in the early postoperative period is a factor affecting the patient's length of stay in the intensive care unit, the length of hospital stay, and the entire treatment duration. Absent nephrotoxicity of anidulafungin is an undoubted advantage, especially in case of choosing a drug for high-risk patients after liver transplantation.

Currently, echinocandins are the most commonly administered antifungal agents for candidemia treatment not only in patients with transplanted organs. We should note the results of six pooled prospective studies in assessing the efficacy and safety of using anidulafungin in patients with Candida parapsilosis candidemia. The authors concluded that anidulafungin was effective for the treatment of Candida parapsilosis candidemia (the study included 70 patients with Candida parapsilosis candidemia, with only 3 cases showing resistance) [10].

Anidulafungin exhibits the least hepatotoxicity and minimal drug interactions when compared with other groups of antifungal agents. We emphasize once again that a high level of resistance to fluconazole should be considered when choosing antifungal prophylaxis/empirical therapy. Local monitoring results, reported risk factors for invasive candidiasis contribute to the development of a dynamically updated strategy for the prevention, diagnosis, and management of invasive fungal infections.

Conclusion

For the prevention of invasive mycosis, an adequate preventive antifungal therapy is of great importance in the patients in the early period after liver transplantation, especially in those with several risk factors identified in combination with the detected colonization of two or more loci with fungal microorganisms.

When choosing an antifungal agent for prophylaxis, the greater, safety of anidulafungin should be considered in comparison with the amphotericin *B* lipid complex.

Conclusions

1. Patients after liver transplantation with two or more risk factors have absolute indications to the invasive mycosis prevention.
2. Anidulafungin and the lipid formulation of amphotericin B are efficient for the prophylaxis and prevention of the fungal infection “breakthrough”.
3. Anidulafungin has an advantage in safety over the lipid formulation of amphotericin B.

References

1. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). *Clin Infect Dis.* 2010;50(8):1101–1111. PMID: 20218876 https://doi.org/10.1086/651262

2. Liu X, Ling Z, Li L, Ruan B. Invasive fungal infections in liver transplantation. *Int J Infect Dis.* 2011;15(5):e298–e304 PMID: 21345708 https://doi.org/10.1016/j.ijid.2011.01.005

3. Yang CH, He XS, Chen J, Ouyang B, Zhu XF, Chen MY, et al. Fungal infection in patients after liver transplantation in years 2003 to 2012. *Ann Transplant.* 2012;17(4):59–63. PMID: 23274325 https://doi.org/10.12659/aot.883695

4. Eschenauer GA, Kwak EJ, Humar A, Potoski BA, Clarke LG, Shields RK, et al. Targeted versus universal antifungal prophylaxis

among liver transplant recipients. *Am J Transplant.* 2015;15(1):180–189. PMID: 25359455 https://doi.org/10.1111/ajt.12993

5. Bassetti M, Peghin M, Carnelutti A, Righi E, Merelli M, Ansaldi F, et al. Invasive candida infections in liver transplant recipients: clinical features and risk factors for mortality. *Transplant Direct.* 2017;3(5):e156. PMID: 28573191 https://doi.org/10.1097/TXD.0000000000000673

6. Zhuravel SV, Chernenkaya TV, Bazhenov AI, Ospanova GK. Treatment of fungal complications in patients after liver transplantation. Discussion of clinical cases. *Transplantologiya. The Russian Journal of Transplantation.* 2015;(3):57–64. (In Russ.).

7. Khubutiya MSh, Zhuravel SV, Chernenkaya TV, Ospanova GK, Bazhenov AI, Kuznetsova NK, et al. Prevention of fungal infection in the early period after liver transplantation. *Transplantologiya. The Russian Journal of Transplantation.* 2016;(2):29–34. (In Russ.).

8. Klimko NN, Rubinchik VE, Sobol MM, Larionova VB, Tyrenko VV, Talipova LI, et al. Multicenter observational study of anidulafungin using – ERA (ERAXIS IN RUSSIA). Problems in medical mycology. 2018;20(3):21–26. (In Russ.).

9. Kullberg BJ, Vasquez J, Mootsikapun P, Nucci M, Paiva JA, Garbino J, et al. Efficacy of anidulafungin in 539 patients with invasive candidiasis: a patient-level pooled analysis of six clinical trials. *J Antimicrob Chemother.* 2017;72(8):2368–2377. PMID: 28459966 https://doi.org/10.1093/jac/dkx116

10. Kontoyiannis DP, Bassetti M, Nucci M, Capparella MR, Yan JL, Aram J, et al. Anidulafungin for the treatment of candidaemia caused by Candida parapsilosis: Analysis of pooled data from six prospective clinical stu-dies. *Mycoses.* 2017;60(10):663–667. PMID: 28597967 https://doi.org/10.1111/myc.12641

Information about authors

Sergey V. Zhuravel, Dr. Med. Sci., Head of the Scientific Department for Anesthesiology, Intensive and Critical Care, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-9992-9260;

Natalya K. Kuznetsova, Cand. Med. Sci., Leading Research Associate of the Scientific Department for Anesthesiology, Intensive and Critical Care, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-2824-1020;

Irina I. Utkina, Cand. Med. Sci., Senior Research Associate of the Scientific Department for Anesthesiology, Intensive and Critical Care, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-5685-4916;

Murad S. Novruzbekov, Dr. Med. Sci., Head of the Scientific Department for Liver Transplantation, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-6362-7914;

Pavel V. Gavrilov, Junior Research Associate of the Scientific Department for Anesthesiology, Intensive and Critical Care, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0001-9640-201X;

Tatyana V. Chernenkaya, Cand. Med. Sci., Head of the Research Laboratory for Clinical Microbiology, N.V.Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-6167-7117;

Gulbanu K. Ospanova, Cand. Med. Sci., Senior Resident, Anesthesiologist-Intensivist of the Anesthesiology, Critical and Intensive Care Department, National Scientific Medical Center, https://orcid.org/0000-0001-9673-0320

Received: March 24, 2020
Accepted for publication: March 27, 2020