Human Immunology 77 (2016) 115–120

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Early post-transplant neopterin associated with one year survival and bacteremia in liver transplant recipients

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ARTICLE INFO

Article history:
Received 6 August 2015
Revised 10 November 2015
Accepted 10 November 2015
Available online 12 November 2015

Keywords:
Liver
Transplantation
Neopterin
Outcome

ABSTRACT

Bacterial infections are the most common complications, and the major cause of mortality after liver transplantation (Tx). Neopterin, a marker of immune activation, is produced in monocyte/macrophages in response to inflammation. The aim of our study was to investigate whether early post-operation serum levels of neopterin were associated with post-transplant bacteremia and mortality in liver transplant recipients. We studied 162 of 262 liver Tx patients between January 2008 and February 2011 of whom pre- and early post-Tx sera samples were available.

Pre- and early post-operative risk factors of infection and mortality were evaluated in 45 bacteremic patients and 117 non-bacteremic patients. During one-year follow-up, 28 of 262 patients died because of graft failure, septicemia and other diseases.

Post-Tx serum neopterin on day 10 ($p < 0.001$) were significantly higher in bacteriemic patients than in patients without bacteremia. Logistic regression analyses showed that day 10 post-Tx neopterin serum level $\geqslant$40 nmol/l has a predictive value (OR = 6.86: $p < 0.001$) for bacteremia and mortality (OR = 3.47: $p = 0.021$).

Our results suggest that early post-Tx neopterin serum levels are very sensitive predictive markers of one-year post-Tx bacteremia and mortality in liver Tx recipients.

1. Introduction

The success of liver transplantation (Tx) can be limited by infectious complications [1]. The most frequent infection after solid organ Tx is bacterial infection which is more frequent in organ Tx involving the abdominal cavity, such as liver or pancreas transplantation [1,2]. Bacterial infections are not only one of the most common complications, but also the major cause mortality after liver Tx [3,4]. There are some known risks factors related to organ and operation including ischaemia–reperfusion injury, amount of intra-operative blood transfusion, level and type of immunosuppression, rejection, prolonged ICU stay with dialysis or ventilation, type of biliary drainage, repeat operations, re-transplantation, antibiotics, antiviral regimen, and environment (malnutrition). Donor risk factors include infection, prolonged ICU stay, quality of the donor liver and viral status. For the recipient the most important are high MELD score and association of APACHE-score,

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; AUC, area under curve; BMI, body mass index; CMV, cytomegalovirus; CVD, cardiovascular diseases; CsA, cyclosporine A; ELISA, enzyme linked immunosorbent assay; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCs, healthy controls; HCV, hepatitis C virus; ICU, intensive care unit; IFN, Interferon; INR, International Normalized Ratio; Tx, transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; ROC, Receiver Operating Characteristic; RPM, round per minute; SPSS, Statistical Package for the Social Sciences; Tac, tacrolimus.

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http://dx.doi.org/10.1016/j.humimm.2015.11.003
0198-8859/

malnutrition, renal failure, acute liver failure, presence of infection or colonzation and immune status for viruses like CMV [5–8]. Associations of pre- and early post-Tx neopterin with outcome in liver Tx has not been studied vastly [2].

Monocyte/macrophages produce neopterin in response to activated T-cells [9]. This is probably the origin of markedly elevated blood and urine neopterin in patients with viral infection, malignant disorders, graft versus host disease and gluten enteropathy [9]. Neopterin is produced from guanosine triphosphate by activated human monocytes, monocyte-derived dendritic cells and macrophages [10]. Release and production of neopterin is stimulated mainly by IFN-γ released by activated Th1-lymphocytes during the cellular immune response [10]. The association between neopterin and mortality in renal Tx recipients, patients with cardiovascular disease, malignancies and patients admitted to ICU because of sepsis and multiorgan dysfunction were already studied by others [10–13]. The aim of the present study was to assess and determine the association of pre- and early post-Tx neopterin with mortality and bacterial infection -especially bacteremia- in liver Tx recipients.

2. Patients and methods

2.1. Patients

2.1.1. Demographic and characteristic data

The retrospective study was conducted in accordance with local ethical guidelines and all individuals gave informed consent for analysis of their plasma samples. Between January 2008 and February 2011, 262 patients underwent liver Tx at the university hospital Heidelberg, Germany. Three groups of patients were considered: patients with bacteriemia, patients with localized bacterial infection and patients without bacterial infection. The following parameters were studied in 162 cirrhotic patients (aged 51.7 ± 10.9 years, 39 female, 3 living donors) whose pre- and early post-Tx sera were available. Surgical methods of liver transplantation were piggyback in 156, bypass in 1 and split liver in 6 patients. All patients had end to end ductal anastomosis. Forty-six patients had reduced nutritional status, 17 patients diabetes, and 51 patients renal insufficiency and/or hepatorenal syndrome. HCC was diagnosed in 46 patients. There was no known active infection in donors at the time of procurement. Five patients received grafts from marginal donors and all these patients were in the survivor and non-bacteriemic groups. Peri-operative parameters including MELD score, neopterin, bilirubin, International Normalized Ratio (INR), albumin, CMV, HBV and HCV seropositivity, recipient age and gender, transplantation number, donor age and gender, intra-operative packed cells, fresh frozen plasma, thrombocyte and total blood products infusion and blood loss were analyzed. Thirty-six HCs (16 females, age: mean ± SD 39.6 ± 10.0 years) served as controls to establish references for the studied parameters such as neopterin. Controls were free of infectious and other inflammatory illnesses. Body mass index (BMI) was available in 154 patients (25.6 ± 4.6). Thirty-five patients had cardiovascular diseases (CVD). Postoperative factors including immunosuppressive drugs, ICU and hospital stay after operation, serum levels of alanine transaminase, aspartate transaminase, total bilirubin, INR, and neopterin on day 1, 3, 5 and 10 post-Tx were evaluated. Immunosuppressive drugs included prednisolon (P) in 160, CsA in 93, Tac (T) in 64, and MMF in 49 patients. Post-Tx antiinfection prophylaxis included 3 days cefuroxime and metronidazole, 3 months cotrimoxazole, 10 days itraconazole, voriconazole or caspofungin. For recipients of CMV-positive donors, oral prophylaxis with valganciclovir was performed for a period of 3 months.

We examined the association between 1-year post-Tx bacterial infection, bacteremia and mortality with the mentioned parameters. Patients were considered bacteriemic when similar bacteria were grown in at least 2 of 3 culture media. Samples for blood culture were collected as patients were admitted to hospital.

2.2. Serum separation

Serum was collected after the blood clotting process. Serum separator tubes were centrifuged at 4000 RPM for 15 min at 4 °C. The serum was snap frozen and stored at −20 °C until testing. All serum samples were thawed only once before test.

2.3. Determination of serum neopterin

Serum neopterin was measured with the Neopterin ELISA kit (Brahms, Berlin, Germany). Based on control measurements in our HCs, >15 nmol/L neopterin was considered abnormally high. The protocols provided by the assay manufacturers were strictly followed. To exclude accumulation of neopterin because of renal function impairment in some patients during the early post-Tx period, neopterin/creatinine ratios from the respective serum creatinine of every sample were calculated.

2.4. Statistical analyses

Categorical and continuous variables were analyzed using Chi-square, Fisher exact and Mann–Whitney-*U* tests. Continuous variables were modeled stratified by a median. The most sensitive cut-off values were calculated by ROC curve analysis. Uni- and multivariable logistic regression analyses were applied and identified the greatest predictive values of risk factors for bacteremia and mortality. All statistical analyses were performed with the SPSS 18.0. After Bonferroni correction, p values <0.05 were defined as statistically significant.

3. Results

3.1. Demographic analysis

There were 65 patients without bacterial infection, 52 patients with localized infection such as urinary tract infection, pneumonia, central catheter and other infection without positive peripheral blood culture and 45 (28%) patients with bacteremia as defined by the first postoperative positive peripheral blood cultures (mean ± SD; 69 ± 63 days, range 12–300 days) (Table 1). Demographic and characteristic data of patients with localized bacterial infection and patients without bacterial infection were not significantly different and we put all in one group as non-bacteriemic patients (data not shown). Bacteremic patients had similar BMI ($p = 0.56$) and slightly higher reduced nutritional status (18/45 vs 28/117: $p = 0.042$) than non-bacteremic patients. BMI was similar in survivors and non-survivors ($p = 0.58$) and nutritional status was significantly reduced in non-surviving patients (16/28 vs 30/134: $p < 0.001$). MELD score ($p = 0.57$), serum levels of pre-Tx neopterin ($p = 0.98$) was not significantly different in patients with and without CVD. Seven of non-surviving and 39 of surviving ($p = 0.66$), 11 of bacteriemic and 35 of non-bacteriemic patients ($p = 0.49$) had HCC. Renal insuffiency and/or hepatorenal syndrome was more frequent in bacteriemic than non- bacteriemic ($p = 0.007$) and in non-surviving than in surviving patients ($p < 0.001$). Four patients in the bacteriemic and 13 patients in the non-bacteriemic group had diabetes ($p = 0.68$). All 17 diabetic patients were in the survivor group. In the non-bacteriemic group 1, 4 and 5 patients received everolimus, basiliximab, and belatacept, respectively. Only one patient in the bacteriemic group was treated with belatacept ($p = 0.69$). Seventy-one of the non-