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Antibody response to HBV vaccination on dialysis does not correlate with the development of deNovo anti-HLA antibodies after renal transplantation

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ABSTRACT

Background: Response to Hepatitis B virus (HBV) vaccination can be diminished in some (50–80%) but not all dialysis patients. We hypothesized, that the response to vaccination on dialysis may correlate with the development of anti-HLA antibodies after renal transplantation and might therefore be a valuable parameter to predict alloresponses.

Methods: The response to HBV vaccination on dialysis and the development of deNovo anti-HLA antibodies post-transplant was analyzed in 188 non-immunized renal transplant recipients. The response to HBV vaccination was evaluated by measuring the anti-HBs titer at time of transplantation. Anti-HLA antibodies post-transplant were monitored by serial measurements by means of Luminex. Acute rejection episodes, graft loss and renal dysfunction were assessed within a median follow-up of 5.5 years.

Results: One hundred and forty-one patients (75%) exhibited an adequate immune response to HBV vaccination on dialysis. Vaccine responder (R) and none responder (NR) did not differ with respect to age, gender and BMI, while R spend significantly more time on dialysis before transplantation (4.58 ± 3.35 vs 3.23 ± 2.55 years, $p = 0.033$). More NR developed deNovo anti-HLA antibodies (27.7 vs 22.7%, $p = 0.554$) and donor-specific anti-HLA antibodies (23.4 vs 14.2%, $p = 0.173$) in comparison to R. Accordingly, the number of acute rejections was higher in NR as compared to R (36.1 vs 24.1%, $p = 0.130$) while graft survival was similar in both groups.

Conclusion: Contrary to our hypothesis antibody response to HBV vaccination on dialysis does not predict the development of anti-HLA antibodies post transplant.

1. Introduction

DeNovo anti-HLA antibodies emerge in 7–30% of non-immunized recipients after renal transplantation [1–6]. The development of donor-specific anti-HLA antibodies (DSA) after renal transplantation is a poor prognostic factor in that it is associated with antibody-mediated rejections (AMR) [4,7–9], chronic graft dysfunction [4] and diminished allograft survival [5,10]. Therefore, it would be helpful to identify those patients, who are at risk to develop DSA in time, to be able to anticipate the individual therapy.

Response to HBV vaccination on dialysis is impaired in 50%–80% of dialysis patients [11]. The diminished response to immunization has been attributed to prolonged time on dialysis [12], increasing age [13], male gender [14] and poor nutritional status [15]. In addition, end-stage renal disease (ESRD) is associated with lymphopenia in the B- and T-cell compartment [16], reduced antibody production and impaired T-cell-mediated immunity [17] with a lack of antigen-specific effector memory CD4 T cell production after vaccination [18].

We postulated, that differences in the serologic response to HBV vaccination on dialysis might predict the development of ant-HLA antibodies after transplantation. Therefore we monitored DSA production following transplantation by Luminex and correlated our findings to the anti-HBs titer obtained during dialysis treatment.

Abbreviations: Ab, antibody; AMR, antibody-mediated rejection; AR, acute rejection; BK, human polyoma virus 1; DSA, donor-specific HLA-antibody; ESRD, end-stage renal disease; HLA, Human Leucocyte Antigen; HBV, Hepatitis B virus; MFI, mean fluorescence intensity; MM, mismatch; nDSA, non-donor-specific HLA-antibody; NR, vaccine none responder; PTC, peritubular capillaries; R, vaccine responder; SAB, Single Antigen Bead Assay; SV40, simian vacuolating virus 40

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2. Materials and methods

2.1. Study design and patients

We conducted a retrospective cohort study in 188 non-immunized patients who received their first kidney transplantation between 2005 until 2012 at our center. The patients selected for the study had no anti-HLA antibodies before transplantation.

2.2. HLA-antibody screening

The development of deNovo antibodies against HLA-class I and II post-transplant were monitored by serial measurements by means of Luminex at least once a year. Positively screened patients were measured by Single Antigen Bead assay (LabScreen, One lambda, Canoga Park, CA, USA). The antibody specificity in relation to the donor was confirmed if MFI was higher than 1000.

2.3. HBV vaccination

The response to HBV vaccination, which was administered during dialysis treatment prior of transplantation, was evaluated by measuring the anti-HBs titer at time of transplantation. A titer > 10 IU/ml was considered to be a positive response.

2.4. Biopsies/Rejections

Allograft biopsies were taken when renal graft function was impaired. Rejection was determined according to the diagnostic criteria proposed at the 2011 Banff Conference [19].

2.5. Statistics

Statistical analyses were performed using GraphPad PRISM software (GraphPad Software, La Jolla, CA, USA). Descriptive statistics (number of cases and percentages for categorical variables, mean and standard deviation for metric variables) were used to characterize the study population. Statistical tests were used to investigate differences between the two groups: *t*-test for comparing the means in metric variables, Fisher's exact test for comparing proportions in categorical variables. Differences were considered to be significant at values $p < 0.05$. Kaplan-Meier curves were used to visualize graft survival in the different groups. The log-rank test was used to test for differences in survival time between groups.

3. Results

3.1. Baseline characteristics of study population

In total, 188 patients undergoing renal transplantation were included. Two distinct populations were identified according to the response to HBV vaccination on dialysis: 141/188 (75%) patients exhibited an adequate immune response (R), while 47/188 (25%) did not respond (NR) to HBV vaccination. No significant differences were noted in recipient and donor age or gender, number of deceased donors, HLA mismatches, cold ischemia time or immunosuppressive regiments between the groups. However, within the NR group more recipients received a combined kidney transplantation. (Table 1).

Table 1
Baseline characteristics of study population according to the response (R) or non-response (NR) to HBV vaccination on dialysis.

	Responder n = 141	Non Responder n = 47	P-value
Recipient			
Sex, female (%)	52 (36.9%)	13 (27.7%)	0.291[a]
Age (years)	49.37 ± 13.40	49.98 ± 13.86	0.467[b]
BMI (kg/m^2)	25.08 ± 3.94	25.08 ± 4.35	0.764[b]
Time on dialysis (years)	4.58 ± 3.35	3.23 ± 2.55	0.033[b]
Type of Tx			0.048[a]
Kidney (n)	126 (89.4%)	36 (76.6%)	
Kidney plus other (n)	15 (10.6%)	11 (23.4%)	
Immunologic characteristics			
Mismatch (n)	3 ± 1.7	3.4 ± 1.6	0.076[b]
Donor			
Sex, female (%)	72 (51.1%)	26 (55.3%)	0.504[a]
Age (years)	49.38 ± 13.40	49.98 ± 13.87	0.917[b]
Deceased donor (%)	104 (73.7%)	37 (78.8%)	0.564[a]
Cold ischemia time (hours)	10 ± 7.3	8.5 ± 6	0.222[b]
Immunosuppression			
Induction therapy	109 (77.3%)	30 (63.8%)	0.084[a]
Tac/MPA/Steroids	49 (34.8%)	24 (51.1%)	0.058[a]
CsA/MPA/Steroids	68 (48.2%)	18 (38.3%)	0.310[a]
Others	24 (17%)	5 (10.6%)	0.357[a]

[a] Chi-quadrat test.
[b] *t*-Test.

3.2. Factors influencing response to vaccination

Vaccine responder and none responder did not differ with respect to age (49.37 ± 13.40 vs 49.98 ± 13.86 years, p = 0.467), gender (female 36.9% vs 27.7%, p = 0.291) and BMI (25.08 ± 3.94 vs 25.08 ± 4.35 kg/m^{2,} p = 0.764). In contrast to previously published data time on dialysis was significantly longer in R versus NR patients (4.58 ± 3.35 vs 3.23 ± 2.55 years, p = 0.033). No association of response to vaccination with clinical and immunological could be shown in an analysis using a Cox proportional hazards model and verified by a multivariate model by a stepwise variable selection procedure (data not shown). Furthermore, R and NR did not differ in HLA allele frequencies especially of DRB1*01 (16.3 vs 23.4%, p = 0.271), DRB1*03 (21.3 vs 25.5%, p = 0.415), DRB1*04 (24.8 vs 27.7%, p = 0.559), DRB1*08 (3.5 vs 4.3%, p = 0.677), DRB1*10 (2.1 vs 4.3%, p = 0.596) and DQB1*05 (29.8 vs 38.3%, p = 0.211).

3.3. Rejection

One hundred and five patients (55.85%) underwent at least one biopsy during the follow-up period. Acute rejection developed in 51 patients (27.2%): 50 (26.5%) patients had T-cell-mediated rejection including those with borderline changes and only 1 (0.5%) had an antibody-mediated rejection. The number of acute rejections was higher in NR as compared to R (36.1 vs 24.1%, p = 0.130), but the difference was not statistically significant.

3.4. Renal function and graft survival

Kidney-allograft dysfunction, determined by a 20% increase in serum creatinine levels in yearly intervals, did not differ between the 2 groups during the first, second or third year (data not shown). In accordance 5-year graft survival was identical between R and NR (93.6%).

3.5. DeNovo anti-HLA antibodies

Forty-five (23.9%) of 188 patients developed deNovo anti-HLA antibodies. Contrary to our hypothesis, vaccine responder developed fewer deNovo anti-HLA antibodies (22.7 vs 27.7%, p = 0.554) and less deNovo donor-specific anti-HLA antibodies (14.2 vs 23.4%, p = 0.173) in comparison to vaccine none responder. However, the difference was not statistically significant. To exclude a difference in immunosuppressive regiments as a cause for the development of anti-HLA antibodies recipients of combined transplants were excluded from the analysis. However, the rate of deNovo anti-HLA antibodies (23.0 vs 27.7%,