

Effect of Angiotensin II Receptor Type 1 Antibodies on Kidney Allograft Function

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Introduction. Non-human leukocyte antigen antibodies are an independent risk factor for acute rejection in kidney transplant recipients. Among them, angiotensin II receptor type 1 (ART1) antibodies can induce various effects, but their clinical importance in kidney transplant recipients has not been properly explained. This study aimed to evaluate the effect of ART1 antibodies on allograft function and hypertension in stable kidney transplant recipients. **Materials and Methods.** Eighty-one kidney recipients from non-human leukocyte antigen antibodies-matched donors with stable allograft function were examined for estimated glomerular filtration rate (Chronic Kidney Disease-Epidemiology Collaboration formula) and ART1 antibodies (measured using an enzyme-linked immunosorbent assay method). The result was considered positive if the anti-ART1 level was greater than 17 U/mL.

Results. The mean age of the participant was 51.1 ± 11.9 years with the mean time from transplantation was 83.5 ± 6.5 months. Fifteen recipients (18.5%) had a high ART1 antibodies level. Those with low titers of ART1 antibodies had better allograft function. The mean estimated glomerular filtration rate was 63.0 ± 13.7 mL/min in those with low ART1 antibodies and 42.3 ± 13.9 mL/min in those with high ART1 antibodies ($P < .001$). There were no significant correlation between high ART1 antibodies levels and hypertension, cause of end-stage renal disease, age, sex, transplant and dialysis duration, cytomegalovirus infection, antihypertensive medication, or immunosuppressive agents.

Conclusions. A high level of ART1 antibodies was a risk factor for allograft function; however this indicator was not correlated with hypertension in our study.

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INTRODUCTION

Angiotensin II receptor type 1 (ART1) is a transmembrane G-protein that binds to angiotensin II and is responsible for blood pressure regulation and salt and water balance. Antibodies to ART1 (ART1 antibodies) were first described in 22 pregnant woman with preeclampsia. They explained these immunoglobulin G antibodies had agonist activity after binding to receptor.¹

In 2003, Dragun and colleagues² reported these

antibodies in 9 kidney transplant recipients with acute vascular resistant rejection and resistant hypertension. Since then, several studies showed non-human leukocyte antigen (HLA) antibodies as risk factor for acute rejection and graft loss. The ART1 antibodies were introduced as important antibodies before and after transplant that can be a risk factor for graft rejection and graft loss.³ However, there are not enough data to show if they have a long-term effect on graft function.

Therefore, we conducted a study to evaluate the prevalence and effect of ART1 antibodies on our stable kidney transplant recipients.

MATERIALS AND METHOD

In this cross-sectional study, we selected 81 first kidney transplant recipients from transplant clinic with no history of clinical acute rejection and stable graft function. Kidney source was from non-HLA-matched donors with 83.5 ± 6.5 months duration of transplantation. They were 47 men and 34 women with a mean age of 51.1 ± 11.9 years.

Most the patients were on cyclosporine and mycophenolate mofetil (86.5%). Other immunosuppressive drugs were tacrolimus in 4.8%, azathioprine in 5.8%, and sirolimus in 7%. Also, 5.8% of the patients were on prednisolone-free protocol. All data were collected from patient's chart, and blood samples sent to a reference laboratory. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease-Epidemiology Collaboration formula.

We stored the blood samples in -80°C to complete samples collection. We measured ART1 antibodies in 1 session with an enzyme-linked immunosorbent assay method (Eastbiopharm Co) based on manufacturer's instructions, and the results were extracted and calibrated on a curve. A positive results was considered if ART1 antibodies level was greater than 17 U/mL. The SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, IL, USA) used to analyze data. The independent *t* test was used to compare mean values and the chi-square

test, for categorical variables. All *P* values were two tailed and values less than .05 were considered significant.

RESULTS

Among the 81 kidney transplant recipients 15 (18.5%) had high anti-ART1 levels (Table). Patients with low titers of ART1 antibodies had better allograft function in comparison to the recipients with high ART1 antibodies levels. The mean estimated glomerular filtration rate and serum creatinine level were 63.0 ± 13.7 mL/min and 1.20 ± 0.21 mg/dL in those with low ART1 antibodies and 42.3 ± 13.9 mL/min and 1.70 ± 0.43 mg/dL in those with high ART1 antibodies, respectively ($P < .001$; Table). We did not find any correlation between ART1 antibodies and hypertension, cause of end-stage renal disease, age, sex, transplant duration, dialysis duration, cytomegalovirus infection, antihypertensive medications, or immunosuppressive medications (Table).

DISCUSSION

In our study, 18.5% of our transplant recipients had high levels of ART1 antibodies. The serum levels of ART1 antibodies were an independent risk factor for allograft function. Recipients with high levels of ART1 antibodies had significantly lower estimated glomerular filtration rate. We could not find a significant difference in hypertension levels of those with high versus low ART1 antibodies levels. Our results were compatible with a recently published meta-analysis by Zhang and colleagues.⁴

Characteristics of Kidney Transplant Recipients by Angiotensin II Receptor Type 1 (ART1) Antibody Status*

Characteristic	ART1 Antibodies		P
	< 17 U/mL	> 17 U/mL	
Number of participants	66	15	...
Sex			
Male	38	9	
Female	28	6	> .99
Diabetes mellitus	12	2	.72
Hypertension	45	9	.56
ACEI or ARB use	9	3	.69
Serum creatinine, mg/dL	1.20 ± 0.21	1.73 ± 0.43	.001
GFR, mL/min	63.0 ± 13.7	42.3 ± 13.8	.001
Transplant duration, mo	83.4 ± 6.6	84.2 ± 6.1	.67
Dialysis duration, mo	16.9 ± 25.2	13 ± 9.6	.31
Angiotensin II receptor type 1	3.8 ± 2.2	4.47 ± 2.7	.32

*Values are mean \pm standard deviation or frequencies. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and GFR, glomerular filtration rate.

They showed a significant relationship between ART1 antibodies and graft failure (relative risk, 3.02; 95% confidence interval, 1.77 to 4.26) in 1771 kidney transplant recipients. There were also an increased risk of acute rejection (relative risk, 1.66; 95% confidence interval, 1.23 to 2.09).

The ART1 antibodies can be detected in serum before transplantation. Giral and colleagues³ showed patients with pretransplant ART1 antibodies had a 2.6-fold higher risk of graft failure and a 1.9-fold higher risk of experiencing an acute rejection episode within the first 4 months of transplantation. Of the antibody-mediation rejections, 71.4% were associated with ART1 antibodies. They concluded that pretransplant ART1 antibodies were independent risk factor of long-term graft loss and higher risk of acute rejection episodes. The importance of ART1 antibodies is that they can induce antibody-mediated rejection when donor specific anti-HLA antibodies are undetectable. In a study of 72 patients with antibody-mediated rejection, 12 recipients had no donor specific anti-HLA antibodies.⁵ Angiotensin II receptor type 1 are distributed in many cell types including vascular endothelial cells and smooth muscle cells. Activation of ATR1 by agonistic activity of ART1 antibodies can trigger transcription factor expression in endothelial and vascular smooth muscle cells. These result in secretion of proinflammatory messengers. After transplantation, they activate ART1s located on endothelial cells of donor and induce vascular rejection. Based on this theory it is understandable why the prominent pathologic feature in kidney biopsies of patients with acute rejection are glomerulitis and capillaritis. Philogene and coworkers⁶ showed the main pathological features in ART1 antibody-positive recipients. They found out high glomerulitis and peritubular capillaritis scores, which independently correlated with increased ART1 antibodies concentration in the absence of donor specific anti-HLA antibodies. They could not find a correlation of ART1 antibodies to cell-mediated rejection and inflammation.

In our study, however we could not measure donor specific anti-HLA antibodies level, we found a significant correlation of kidney function with ART1 antibodies. Hypertension, diabetes mellitus, age, transplantation and dialysis duration, sex, and angiotensin receptor level were not related to ART1 antibodies in our study. Further studies

with a larger sample size can be more informative. We also suggest a pre- and post-transplant ART1 antibodies level with serial biopsy samples to evaluate pathologic differences in these two groups of recipients.

CONCLUSIONS

Monitoring of ART1 antibodies can predict allograft outcome. In future, more studies to confirm the associations of the pathological findings, donor specific anti-HLA antibodies level to ART1 antibodies should be designed. Evaluation of the therapeutic effect of angiotensin receptor blockers on the rate of antibody-mediated rejection and graft loss ART1 antibodies recipients could be valuable.

CONFLICT OF INTEREST

None declared.

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