Effects of Rituximab on Atherosclerotic Biomarkers in Kidney Transplant Recipients

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ABSTRACT

Introduction. Cardiovascular disease is the leading cause of mortality in kidney transplant recipients. Rituximab is widely used in kidney transplantation for a variety of situations, and rituximab may inhibit some cytokines and antibodies that may play an active role in the atherosclerotic process. The aim of the study was to evaluate the efficacy of rituximab on atherosclerosis biomarkers in kidney transplant recipients.

Methods. All patients, 18 years of age and older, who underwent kidney transplantation and received at least 1 dose of 375 mg/m^2 rituximab were considered for participation in this study. The primary study endpoint was the development of cardiovascular diseases after rituximab therapy. The secondary endpoint was the onset of cytomegalovirus (CMV) disease or biopsy-confirmed BK virus nephropathy. In addition, comparison of atherosclerosis biomarkers was performed between study and control groups.

Results. There were no cardiovascular events observed during follow up. Only 8 patients in the study group suffered from CMV disease during follow up. Serum interleukin 10 levels were significantly higher in the rituximab group compared with the control group, although anti–oxidized low-density lipoprotein levels were lower in the rituximab group compared with the control group, though this did not achieve statistical significance.

Discussion. Rituximab treatment may increase the risk of CMV reactivation and decrease lymphocyte counts and interleukin 10 levels; however, significant decreases in all atherosclerotic-related biomarkers have not been shown in our study.

CARDIOVASCULAR disease is the leading cause of mortality in kidney transplant recipients [1]. Cardiovascular complications, such as endothelial dysfunction, vascular calcification, atherosclerosis, valvular disease, and left ventricular hypertrophy are the most commonly encountered clinical challenges [2]. Conventional risk factors for cardiovascular diseases such as hypertension, dyslipidemia, smoking, and low physical activity, as well as nontraditional risk factors, such as immunosuppressive drugs, anemia, inflammation, and proteinuria, contribute to cardiovascular risk in kidney transplant recipients, and inflammation plays a central role in this pathologic process [1,2].

Rituximab is a chimeric human and mouse monoclonal antibody that reacts with the CD20 antigen present on pre-B and mature B lymphocytes [3]. Rituximab is widely used in kidney transplantation for a variety of situations, such as pretransplant desensitization of human leukocyte antigen-sensitive and ABO-incompatible patients and treatment of antibody-mediated rejection and post-transplant lymphoproliferative disease [4]. Rituximab inhibits B-cell proliferation and causes apoptosis and lysis by

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Table 1. Demographic Parameters and Laboratory Results of the Patients

	Treatment Group (n = 27)	Control Group (n = 13)	*P* Value
Age, mean ± SD, y	43 ± 13	43 ± 15	.623
Sex, No. (%)			
Female	10 (37)	5 (38.5)	.931
Male	17 (63)	8 (61.5)	
Etiology of CKD, No. (%)			
Chronic glomerulonephritis	7 (26)	3 (23.3)	.882
Hypertensive nephrosclerosis	4 (15)	2 (15)	
CAKUT	4 (15)	2 (15)	
Unknown	9 (33)	3 (23.3)	
Others	3 (11)	3 (23.3)	
Previous renal replacement history			
Hemodialysis, No. (%)	13 (48)	11 (85)	.027*
Peritoneal dialysis, No. (%)	3 (11)	1 (8)	.736
Duration of dialysis. mean ± SD, y	4 ± 4	5 ± 4	.427

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; SD, standard deviation.
*Significant.

complement-dependent and antibody-dependent cellular cytotoxicity [4,5]. Rituximab may inhibit some cytokines and antibodies that may play an active role in the atherosclerotic process. There are few reports of the relationship between rituximab and the atherosclerotic process in rheumatologic disorders [5–7]. The aim of the study was to evaluate the efficacy of rituximab on atherosclerosis biomarkers in kidney transplant recipients.

METHODS

Study Population

All patients, 18 years of age and older, who underwent kidney transplantation and received at least 1 dose of 375 mg/m^2 rituximab were considered for participation in this study. Patients with a history of cardiovascular disease or diabetes mellitus were excluded from the study. A signed consent form was obtained from all patients who agreed to participate in the study. A total of 27 patients treated with rituximab and 13 historical control patients not treated with rituximab enrolled in the study. Demographic and clinical data included age at kidney transplant, gender, the cause of the end-stage renal disease, and prior renal replacement treatment history. Biomarkers associated with atherosclerosis measured in both groups included the following: interleukin 10 (IL-10), tumor necrosis factor α, transforming growth factor β, anti–oxidized low-density lipoprotein (anti-oxLDL) antibody, CD19$^+$ B lymphocytes, CD3$^+$ and CD45$^+$ T lymphocytes, and CD16$^+$ and CD56$^+$ natural killer cells. The study was approved by the local ethics committee.

Study Endpoints

The primary study endpoint was the development of cardiovascular disease after rituximab therapy. The secondary endpoint was the onset of cytomegalovirus (CMV) disease or biopsy-confirmed BK virus nephropathy. In addition, comparison of atherosclerosis biomarkers was performed between study and control groups.

Table 2. Post-transplant Complications and Laboratory Results of Patients

	Treatment Group (n = 27)	Control Group (n = 13)	*P* Value
Post-transplant complications, No. (%)			
BK virus nephropathy	5 (19)	1 (8)	.369
CMV viremia	8 (30)	0 (0)	.028*
Acute rejection	10 (37)	1 (8)	.052
Laboratory results, mean ± SD			
CD19$^+$ B lymphocyte count, cells/μL	27.4 ± 50.2	145.5 ± 149.9	.001*
CD19$^+$ B lymphocyte, %	1.9 ± 2.5	5.7 ± 4.8	.002*
CD3$^+$ T lymphocyte count, cells/μL	1175 ± 700	1908 ± 622	.008*
CD3$^+$ T lymphocyte, %	89.6 ± 7.6	86.9 ± 6.6	.141
CD16$^+$ 56$^+$ natural killer cell count, cells/μL	94.6 ± 90.0	713.9 ± 1996.2	.049*
CD16$^+$ 56$^+$ natural killer cell, %	7.6 ± 6.4	6.8 ± 5.1	.988
CD45$^+$ T lymphocyte count, cells/μL	1333 ± 777	2219 ± 781	.005*
Serum level of IL-10, pg/mL	6.1 ± 2.4	4.6 ± 0.9	.043*
Serum level of TNF-α, pg/mL	58.3 ± 111.1	10.5 ± 3.4	.112
Serum level of TGF-β, ng/L	465.6 ± 395.7	613.1 ± 496.7	.254
Anti-oxLDL antibody level, ng/L	3845 ± 3386	4597 ± 4167	.634

Abbreviations: CMV, cytomegalovirus; IL-10, interleukin 10; oxLDL, oxidized low-density lipoprotein; SD, standard deviation; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.
*Significant.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (version 21.0; SPSS, Chicago, IL, United States). Results are reported as mean ± standard deviation when normally distributed or as median (interquartile range [IQR]). Comparisons of continuous variables between the 2 groups were assessed by using the unpaired t test or the Mann-Whitney U test, where appropriate. Pearson's χ^2 was used to test for differences among categorical variables. Univariate survival comparisons were made by using the log-rank test.

RESULTS

Demographic characteristics of study and control groups are shown in Table 1. The study and control groups were matched with regard to age, gender, and etiology of chronic kidney disease ($P = .623$, $P = .931$, and $P = .882$, respectively). Patient and control groups were followed up for 26 (IQR 1–96) months after rituximab therapy.

Fifteen patients received rituximab therapy because of antibody-mediated rejection, 6 patients for desensitization, and 4 patients for membranous glomerulonephritis. There were no cardiovascular events observed during follow up. Only 8 patients in the study group suffered from CMV disease during follow up ($P = .028$). One patient in the control group and 5 patients in the study group developed BK virus nephropathy ($P = .369$).

Post-transplant complications and laboratory results of patients were demonstrated in Table 2. Counts of $CD19^+$ B lymphocytes, $CD3^+$ and $CD45^+$ T lymphocytes, and $CD16^+$ and $CD56^+$ natural killer cells were significantly lower in the rituximab group compared with the control group. Serum IL-10 (6.1 ± 2.4 pg/mL vs 4.6 ± 0.9 pg/mL, $P = .043$) levels were significantly higher in the rituximab group compared with the control group, although anti-oxLDL levels were lower in the rituximab group compared with the control group (3845 ± 3386 vs 4597 ± 4167, $P = .634$), though this did not achieve statistical significance.

DISCUSSION

Twenty-seven patients treated with rituximab and 13 historical controls were enrolled in the study. Patient and control groups were followed up for 26 (IQR 1–96) months after rituximab therapy. Cardiovascular events were not observed during the follow-up period. Only 8 patients in the study group suffered from CMV disease and 1 patient in the control group. Five patients in the study group developed BK virus nephropathy. Serum IL-10 levels were significantly higher and anti-oxLDL levels were lower in the rituximab group compared with the control group.

There are limited data about the association between rituximab and cardiovascular events. They described that rituximab therapy decreased systemic inflammation, improved lipid profile and the atherogenicity index, and ameliorated elastic properties of the arterial walls in patients with rheumatoid arthritis [6,7]. In our study, we did not show this effect in all biomarkers probably because of the short follow-up period and because our patient's cardiovascular risk was higher than that of rheumatoid arthritis patients.

The relationship between rituximab and CMV reactivation is not well known. This effect can be explained by a difficult recovery of T-helper lymphocytes and an altered viral antigen presentation because of the lack of regulatory B cells [8]. However, we believe that CMV reactivation is not associated only with rituximab therapy; rituximab may increase the risk of infection. We think that prophylaxis against CMV is an appropriate approach in patients receiving rituximab therapy.

There are important limiting factors in our study. Our study population is very small to obtain accurate results. In addition, our study could not demonstrate the clinical efficacy of rituximab because of the short follow-up period.

In conclusion, rituximab treatment may increase the risk of CMV reactivation and decrease lymphocyte counts and IL-10 levels; however, significant decreases in all atherosclerotic-related biomarkers have not been shown in our study.

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