Comparison of the Treatment Efficacy of Rituximab and Plasmapheresis/Intravenous Immunoglobulin Combination with Historical Control in Chronic Antibody Mediated Rejection

Kronik Antikor Aracılı Rejeksiyonda Rituksimab ve Plazmaferez/İntravenöz İmmünglobulin Kombinasyonun Tarihsel Kontrol Grubu ile Tedavi Etkinliğinin Karşılaştırması

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ABSTRACT

OBJECTIVE: Chronic antibody mediated rejection (CAMR) is a major therapeutic challenge for achieving long-term graft survival; treatment options are limited to several anti-humoral interventions.

MATERIAL and METHODS: Efficacy of rituximab combination therapy was retrospectively investigated by comparison with a historical control group for allograft function at six month and overall graft survival/dysfunction. The inclusion criterion was biopsy proven chronic AMR according to the Banff 2007 classification. Nineteen patients found eligible, rituximab group had nine patients (rituximab, plasmapheresis and low dose IVIG); control group had ten recipients. Predictive factors for graft failure also investigated according to Banff scores and renal functions.

RESULTS: None of the outcomes were exposed significant efficacy of rituximab, although better treatment response at sixth month (55% vs. 40%, p=0.51), fewer overall graft failures (33% vs. 60%, p=0.25) and dysfunctions (66% vs. 80%, p=0.52). Overall, 47% of patients suffered graft failure. Advanced transplant glomerulopathy was found in 90% of biopsies (all scored ≥2). Peritubular capillaritis score (1.67±0.87 vs. 0.70±0.94, p=0.04) and interstitial inflammation score (1.78±0.44 vs. 1.00±0.47, p=0.004) were significantly higher in recipients who suffered graft failure.

CONCLUSION: Rituximab could not sufficiently prevent further deterioration of allograft and failed to improve allograft survival in CAMR, especially after settlement of the irreversible transplant glomerulopathy.

KEY WORDS: Kidney transplantation, Chronic antibody mediated rejection, Transplant glomerulopathy, Rituximab

ÖZ

AMAÇ: Kronik antikor aracılı rejeksiyon (K-AAR) geç dönem graft disfonksiyonu/kaybının en önemli sebeplerindendir. K-AAR tedavisi zor ve net olarak ortaya konmamış bir klinik/patolojik durumdur.

GEREÇ ve YÖNTEMLER: Rituksimab içeren kombinasyon tedavisinin etkinliği, tarihsel kontrol grubu ile altıncı aydaki allogreft fonksiyonları ve genel allogreft disfonksiyon/kaybı oluşumu karşılaştırılması yapılarak retrospektif olarak değerlendirildi. Çalışmaya dahil edilme kriteri; Banff 2007 sınıflamasına göre değerlendirilmiş, biyopsi kanıtlı K-AAR olmasıydı. Bu kritere göre 19 hasta çalışmaya dahil edildi, Rituksimab kombinasyon grubunda (Rituksimab, plazmaferez, düşük doz IVIG) on hasta bulunurken, tarihsel kontrol grubunda dokuz hasta vardı. Ayrıca çalışmada olası allogreft kaybının tahmini için Banff 2007 parametrelerinin detaylı skorlaması değerlendirildi.

BULGULAR: Rituksimab grubunda; altıncı ayda tedaviye daha iyi yanıt olmasına (% 55'e karşı %40, p=0.51), genel allogreft disfonksiyon (%66'ya karşı %80, p=0.52) ve kaybı (%33'e karşı %60, p=0.25) daha az olmasına rağmen istatistiksel olarak anlamlı etki bulunmadı. Değerlendirilen biyopsilerin %90' da ileri düzeyde transplant glomerülopati saptandı (transplant glomerülopati skor ≥2). Allogreft kaybının tahmininde peritubular kapillerit (1.67±0.87 vs. 0.70±0.94, p=0.04) ve interstisiyel inflamasyon skoru (1.78±0.44 vs. 1.00±0.47, p=0.004) anlamlı olarak allogreft kaybı olanlarda daha yüksek olarak bulundu.

SONUÇ: Özellikle, geri dönüşümsüz transplant glomerülopatinin yerleştiği ilerlemiş kronik AAR varlığında; Rituksimab içeren kombine tedavi, allogreftin ilerleyici bozulmasını engelleyip, allogreft sağ kalımını uzatma açısından yeterli etkinlikte değildir.

ANAHTAR SÖZCÜKLER: Böbrek nakli, Kronik antikor aracılı rejeksiyon, Transplant glomerülopati, Rituksimab

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INTRODUCTION

In the modern transplantation era, potent immunosuppression with calcineurine inhibitors and mycophenolic acid successfully overcome T-cell mediated allograft injury and rejections. However, antibody mediated injury to kidney allograft is still a problem for achieving long-term graft survival (1,2). A recent prospective study stated that chronic antibody mediated rejection (AMR) is the leading cause of late graft dysfunction and responsible for 64% of graft failures (3).

Chronic AMR is a challenging situation and resistant to treatment because of ongoing antibody mediated injury and chronic/irreversible pathological structural damage on the allograft (4,5). The pathological hallmark of chronic AMR is transplant glomerulopathy (TG) that consists of double layering of glomerular basement membrane due to continuous endothelial injury with donor specific mainly HLA Class II antibodies and microcirculation inflammation that resembled as peritubular capillaritis and glomerulitis (6,7). Anti-HLA Class II antibodies reported to be strongly related to development of TG in a large cohort of kidney transplant recipients (8). Regarding the chronic AMR, the presence of transplant glomerulopathy has been shown to be inversely correlated with allograft survival and treatment response (8-10).

Thus, there are no well-established guidelines or approved treatment for chronic AMR, recently a numerous of studies have been published about the influence of rituximab (a monoclonal anti-CD 20 antibody) alone or combination with intravenous immunoglobulin G (IVIG) on progression and outcomes of chronic AMR with inconsistent results (4,9-13). These studies were mostly retrospective, and have distinct inclusion criteria and end points for evaluation of response. Additionally, most of the studies did not have control groups due to ethical considerations.

In the present study, we aimed to investigate the efficacy of rituximab containing combined treatment modalities in chronic AMR by comparison with a historical control group for allograft functions and graft survival. Moreover, another aim of the study was to investigate the predictive value of clinical factors and histopathologic features of chronic antibody mediated rejection on estimation of allograft failure risk.

MATERIAL and METHODS

Patient Selection and Clinical Features

The study design was retrospective cohort and approved by the local ethics committee. The inclusion criterion for the study was the diagnosis of biopsy proven chronic AMR. Clinical and pathological records of kidney allograft recipients were retrospectively reviewed and eligible 19 patients enrolled in the study. Other pathologic diagnosis such as acute cellular rejection, acute antibody mediated rejection, de novo or recurrent glomerular diseases were excluded. All of the allograft biopsies were indication biopsy due to unexplained elevation of serum creatinine at least greater than 20% of baseline or appearance of proteinuria more than 1 gr/day in the 24-hour urine sample. Same transplant pathologist evaluated the pathological specimens according to Banff 2007 criteria (14). The medical data of these patients further evaluated for immunologic features, treatment interventions, allograft functions and graft survival. The initial maintenance immunosuppressive protocol consisted of prednisone (tapered to 5 mg by six months post-transplant), mycophenolate mofetil (MMF; 2 gr/day), and calcineurine inhibitors (with dose adjustment according to through blood levels) in all recipients.

Treatment Groups and Evaluation of Treatment Response

Two groups were formed according to the treatment interventions; Group 1 (Rituximab group, n=9) had combination therapy of rituximab, plasmapheresis (TPE) and low dose IVIG. Rituximab has begun to use for the treatment of CAMR since 2011 in our clinic, the kidney transplant recipients who had a diagnosis and treatment of CAMR before this date, was reflecting the historical control (Group 2, n=10). The treatment interventions in the control group were low dose IVIG and TPE for six recipients, and methyl prednisolone pulses (500 mg intravenous three days) for four patients. The IVIG dose was 200 mg/kg after the each plasmapheresis session for both groups. TPE was performed daily, total at least five sessions with one and half exchange of total plasma volume and administration of 5% albumin for replacement. Rituximab was administered as a single dose (375mg/m^2) after completion of TPE sessions.

These two treatment groups were compared in terms of allograft function after six months of therapy, and overall severe graft dysfunction and graft survival rates. Moreover, the clinical and pathologic features of rituximab responder and non-responders were evaluated to reveal the prediction of rituximab response. Graft functions were evaluated with serum creatinine and 24-hour urine collection for calculation of glomerular filtration rate (GFR) and proteinuria. Response to treatment was defined as stabilization of creatinine or elevation of serum creatinine not exceeds 10% of baseline after six months of therapy. Severe graft dysfunction was defined as GFR lower than 20 ml/min (without dialysis) and graft failure as initiation of dialysis.

Immunologic/Pathologic Evaluation and Prediction of Graft Failure

Complement dependent cytotoxicity (CDC) and flow cytometric cross match (FCCM) tests were negative in all recipients prior to transplantation. Immunologic evaluation was performed with flow cytometric panel reactive antibody (PRA) test with single antigen assay for identification of donor specific antibody (DSA), PRA was considered positive if any detectable antibody determined (PRA>0%) at the diagnosis of chronic AMR.

The allograft biopsy specimens of the study cohort were evaluated again for confirmation of diagnosis and the staining pattern/power of the glomerular or peritubular C4d. A detailed re-evaluation and scoring also performed for the histopathologic indicators of antibody mediated injury that are transplant glomerulopathy (TG), peritubular capillaritis, glomerulitis, interstitial inflammation and tubular atrophy according to Banff 2007 criteria (14).

For the prediction of the graft failure risk, allograft recipients who suffered graft failure were compared to recipients with functioning graft in terms of renal functions and pathologic features/Banff scoring.

Statistics

The results were analyzed with an IBM SPSS 20.0 for Windows statistical package. Continuous variables were expressed as the median (range) or mean (± SD), and categorical variables as a proportion (%). Comparisons between the groups were performed using non-parametric Mann-Whitney U test. Kaplan-Meier estimation was used for predicting graft survival with log-rank analysis for the comparison. The p value <0.05 (two-sided) was considered as significant.

RESULTS

Clinical-Immunologic Features

In our series, 19 Ktx recipients (15 male/ 4 female) had chronic antibody mediated rejection. The average age was 39.1±11.7 years, 84% had living donor kidney transplantation. The median time for occurrence of chronic AMR was 71months (range; 7-210 months). The mean total HLA mismatch was 2.75±1.4 and was not associated with severe graft dysfunction or graft failure (p=0.59 and p=0.56, respectively). Both, HLA Class I and Class II antibodies were detected in all patients by flow cytometric PRA test. Median HLA Class I antibody level was 2.5% (range 0.45% to 25%). The HLA Class II antibodies have predominance and detected higher level (median 27.3%; range 0.5% to 68%). Moreover, the Class II antibody level was more than 5% in three quarters of patients. Single antigen assay for identification of donor specific antibodies were available for nine patients; the Class I antibody was detected in two; Class II in five patients, two patients had both Class I+II donor specific antibodies. There were nine graft failures (47%) and fourteen severe graft dysfunctions (74%) during the observed period.

The maintenance immunosuppressive protocol was prednisone, MMF and tacrolimus (n=16) or cyclosporine (n=3). The cyclosporine (C_0) median through blood level was 74 ng/ml (21-84 ng/ml). The median tacrolimus trough blood level was 3.4 ng/ml (2-6.4 ng/ml) and 57% of recipients had a trough blood level <3.4 ng/ml . Six months before the diagnosis of chronic AMR, both serum creatinine (1.80±0.5 mg/dl vs. 3.3±2.4 mg/dl, p<0.001) and GFR (49.1±20.2 ml/min vs. 28.8±15 ml/min, p<0.001) were significantly better than the creatinine and GFR at diagnosis.

The Comparison of the Groups for Treatment Response and Graft Survival

The mean observation period after treatment intervention was 13±8.7 months. The comparison of the treatment response at the sixth month revealed no differences among the groups (5/9 responders in rituximab vs. 4/10 responders in the control group, p=0. 51). At the end of the observation period, there were three graft failures and six graft dysfunctions in rituximab and, six graft failures and eight severe graft dysfunctions in the control group. All of the non-responders suffered from graft failure except one patient in the rituximab group who had a measurable functioning graft. Although there were less graft failures and dysfunctions in the rituximab group, none of the outcomes exposed significant efficacy of rituximab (p=0.25 and p=0. 52 respectively). The creatinine, GFR and proteinuria were not significantly different for both groups at the diagnosis of chronic AMR and during the follow up period of treatment. Table I shows the comparison of the rituximab versus control group in terms of clinical features and treatment response. The analysis for responders and non-responders to rituximab therapy did not reveal any statistical significant clinical/pathologic difference as presented in Table II. Kaplan-Meier estimated one-year graft survival after treatment was 62.2% in rituximab and 46.7% in the control group (log-rank p=0. 46) (Figure 1).

Pathologic Features of Chronic AMR and Prediction of Graft Failure

The pathologic evaluation revealed that glomerular strong diffuse or linear C4d staining found 84% and peritubular strong diffuse or linear CD4 staining found in 53% of biopsies. Transplant glomerulopathy was found 90% of biopsies and TG score was ≥2 in all of these allografts. The comparison of the pathological features of recipients who had graft failure and non-graft failure revealed that especially the peritubular capillaritis score (1.67±0.87 vs. 0.70±0.94, p=0.04) and, interstitial inflammation score (1.78±0.44 vs. 1.00±0.47, p=0.004) were significantly higher in recipients who suffered graft failure. Additionally, there was a statistical trend that revealed a higher tubular atrophy score (1.91±0.6 vs. 1.3±0.82, p=0. 07). The other parameters for Banff 2007 criteria did not show a significant difference for graft failure. Other significant parameters that predicts graft failure risk were higher creatinine (p=0.027) and proteinuria (p=0.016), lower GFR (p=0.034) at the diagnosis of chronic AMR and lower GFR six months before the diagnosis (p=0.034) (Table III).

DISCUSSION

Chronic antibody mediated rejection is a major therapeutic challenge and the leading cause of late graft failure (2, 3). In our series, we found that nearly half of the patients suffered graft failure and three quarters had severe graft dysfunction during the follow up period despite several treatment interventions. The combination therapy that consisted of rituximab, IVIG and

plasmapheresis could not significantly improve the allograft outcomes as compared with the historical control group.

The most accused mechanism for development of chronic AMR is under immunosuppression. By the latter period of transplantation, patients' tendency to non-adherence with increased number of missed visits and clinicians' concerns about the long-term calcineurine toxicity or post-transplant malignancy risk are the main causes of under

Table I: Rituximab and control group in terms of demographic characteristics, treatment response, allograft functions, and survival.

	Rituximab Group (n=9)	**Control Group (n=10)**	**P**
Gender (Male)	78%	80%	0.91
Age (Years)	37±12.7	43.1±11.3	0.19
Donor Source (Living/Deceased)	78%/22%	80%/20%	0.71
Duration between Tx and CAMR (Months)	55.8±51	92.5±63.8	0.18
PRA positivity at diagnosis	100%	80%	0.17
Treatment Response	55%	40%	0.51
Severe Graft Dysfunction	66%	80%	0.52
Graft Failure	33%	60%	0.25
sCr at diagnosis (mg/dl)	3.62±3.56	2.99±0.93	0.62
GFR at diagnosis (ml/min)	30.86±16.74	27.00±13.90	0.59
Proteinuria at diagnosis (mg/day)	2246±2259	3924±2334	0.14
sCr sixth month (mg/dl)	3.50±1.88	4.61±2.52	0.28
GFR sixth month (ml/min)	28.33±20.37	19.40±15.10	0.30
Proteinuria sixth month (mg/day)	2778±2035	3230±2920	0.72
Kaplan-Meier Estimated One-Year Graft Survival	62.2%	46.7%	0.46

Cr: Creatinine, **GFR:** Glomerular filtration rate, **Tx:** Transplantation, **CAMR:** Chronic antibody mediated rejection

Table II: The comparison of the clinical/pathologic features of responder and non-responders to rituximab treatment.

	Rituximab Responder (n=5)	**Rituximab Non-Responder (n=4)**	P
C4d Staining **(+/-)**	100%	100%	1
Glomerulitis	0.8±1.1	0.75±0.95	1
Peritubular capillaritis	1.40±0.89	1±1.5	0.58
Transplant Glomerulopathy Score	1.8±1.1	1.75±1.3	1
Transplant Glomerulopathy Presence	80%	75%	0.87
Interstitial Inflammation	1.2±0.44	1.75±0.50	0.12
Tubulitis Score	0.60±0.55	0.75±0.96	0.89
Interstitial Fibrosis	0.80±0.45	1.5±0.57	0.08
Tubular Atrophy	1.2±0.45	1.5±0.57	0.37
Proteinuria at Diagnosis	2310±2730 mg/dl	2140±1710 mg/dl	0.45
Cr at diagnosis	3.6±2.37 mg/dl	2.45±0.5 mg/dl	0.62
GFR at diagnosis	36 ±17 ml/min	24±15.8 ml/min	0.46

immunosuppression. Non-adherence has found to be strongly associated with the development of de-novo DSA and up to 10-fold increase in the graft failure risk (3, 15). In our series, patients received prednisone 5 mg every other day, mycophenolic acid approximately one-gram/day, the median tacrolimus blood level was 3.4 ng/ml and 36% of patients had tacrolimus blood level lower than 3 ng/ml. Although under immunosuppression could be considered in our patient cohort, detailed information could not be obtained for non-adherence and there was no control group for absolute conclusion.

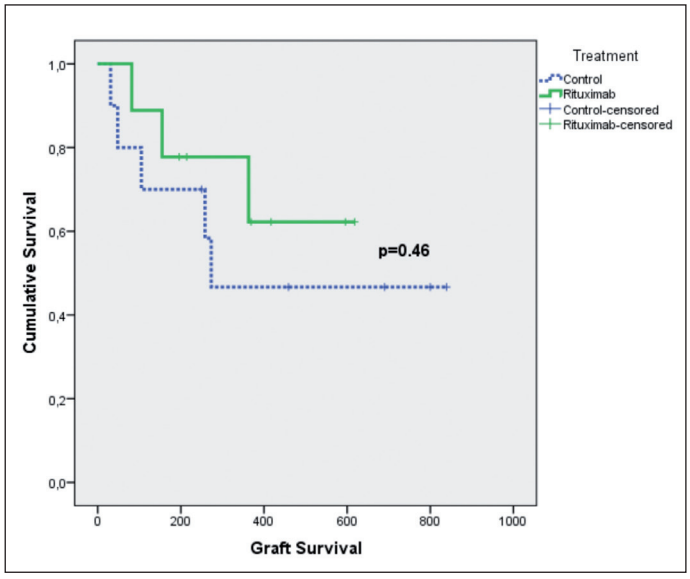

Figure 1: *Kaplan Meier estimation of one-year graft survival for rituximab and control groups.*

De-novo or pre-existing donor specific, especially Class II HLA antibodies have proven to be responsible for the late immune response and chronic antibody mediated injury that leads to graft failure (8, 15-19). In harmony with these data, we found that all of our recipients had flow cytometric panel reactive test positive, particularly for anti-HLA Class II antibody and seven of the nine patients had donor specific Class II antibody. Unfortunately, as a limitation of our study, we did not have the donor specific antibody test with mean fluorescence intensity for all recipients; only nine patient's serum could be examined for single antigen identification.

Regarding the efficiency of rituximab in chronic AMR, no significant difference observed with the historical control group in response rates during six months of treatment. Even though, the rituximab group had a better overall graft survival, lower severe graft dysfunction and graft failure rates, none of the outcomes had statistical significance. Several studies that have been investigated the efficiency of rituximab either alone or in combination concluded inconsistent outcomes probably due to distinct treatment response targets and endpoints.

Table III: The comparison of the clinical and pathological features of graft failure and non-graft failure patients.

	Graft Failure (n=9)	Non Graft Failure (n=10)	P
C4d Staining **(+/-)**	89%	90%	0.94
Glomerulitis	0.33±0.70	0.40±0.84	1
Peritubular capillaritis	1.67±0.87	0.70±0.94	**0.04**
G+PTC Score ≥2	67%	30%	0.12
Transplant Glomerulopathy Score	2.22±0.97	2.30±0.94	0.82
Transplant Glomerulopathy Presence	89%	90%	0.94
Interstitial Inflammation	1.78±0.44	1.00±0.47	**0.004**
Tubulitis Score	0.67±0.70	0.60±0.96	0.58
Interstitial Fibrosis	1.56±0.72	1.20±0.63	0.33
Tubular Atrophy	1.91±0.6	1.3±0.82	**0.07**
Cr six month before diagnosis	2.0±0.3 mg/dl	1.6±0.6 mg/dl	0.19
GFR six month before diagnosis	36.7 ±9.5ml/min	60±21 ml/min	**0.034**
Proteinuria at Diagnosis	2063±2218 mg/dl	4572±2031mg/dl	**0.016**
Cr at diagnosis	4.2±3.4 mg/dl	2.4±0.6 mg/dl	**0.027**
GFR at diagnosis	22 ±13 ml/min	35±14.6 ml/min	**0.034**

Cr: Creatinine, **GFR:** Glomerular filtration rate, **G:** Glomerulitis, **PTC:** Peritubular capillaritis

Gupta et al. were defined response as improvement of serum creatinine, histological improvement, decline in DSA, and reported that in a series of 23 patients' cohort, 65% did not achieve any improvement (4). Contrary, Billing et al. were defined treatment response as reduction of the rate of eGFR loss at least 30% when compared six months before and after the therapy. Their conclusion was rituximab in combination with IVIG efficiently provide stabilization of graft functions in 14 of 20 pediatric patients, and both Class I and Class II HLA antibodies were significantly declined after 12 months of intervention however 20% of patients suffered graft failure (9).

The other possible cause of the distinct outcomes of rituximab therapy may be inclusion of patients in different pathologic stages of chronic allograft injury. Transplant glomerulopathy is the hallmark pathological finding of chronic AMR, and has shown to be related to poor treatment response and increased risk of graft failure (8-10, 17). In our study cohort, 90% of patients had TG and all of them scored ≥2 according to Banff 2007. Our high graft lost and lower treatment response rates could be explained by the presence of advanced transplant glomerulopathy. Similar to our findings in a recent study, Bachelet et al. compared the efficiency of rituximab with the historical control group who had high TG score and stated that rituximab could not efficiently control the progression of chronic AMR and failed to improve graft survival (12). Furthermore, Billing et al. also reported in their prospective series that TG is an important indicator for treatment response to rituximab; without TG treatment response was found to be 100%; however, the response rate decreased to 35% in patients with TG. They concluded that rituximab/IVIG combination not able to reverse advanced CAMR (9). We can speculate that rituximab can only suppress the further production of anti HLA antibodies, however, it could not reverse the present and on-going pathological process of the allograft that reflected by transplant glomerulopathy.

Another aim of this study was to reveal the clinical and pathologic factors for prediction of graft failure risk in chronic AMR. In our series, all of the non-responders except one patient in the rituximab group suffered graft failure; because of this, graft failure risk may also reflect the factors affecting the treatment response. We found that higher serum creatinine and proteinuria, lower GFR at diagnosis and lower GFR six month before the diagnosis were significantly related to graft failure. Same relation between declined allograft survival and higher creatinine and/or proteinuria levels at diagnosis was mentioned previously in a numerous studies (10, 12, 20). The pathologic evaluation revealed that graft failure was strongly correlated with peritubular capillaritis, interstitial inflammation score and showed a somewhat weaker correlation with tubular atrophy. Our results were in concordance with studies that reported the similar pathologic features that can predict graft failure or response to rituximab (9, 19, 20). Thus, Immenschuh et al. reported that tubulitis and intense inflammation were negative predictors for responsiveness to rituximab (20). Similarly, Billing et al. stated that degree of TG and interstitial inflammation were significantly related to treatment resistance to rituximab (9).

The main limitations of this study are its retrospective design and low patient numbers that can prohibit the statistical difference and significance among the treatment and historical control group in terms of improved allograft outcomes. Larger scale, prospective studies are warranted for treatment of chronic antibody mediated rejection to provide longer functioning kidney allografts.

In conclusion, chronic antibody mediated rejection is still a major therapeutic challenge for achieving long-term allograft survival. Although rituximab can be efficient in early stages of the process, it is probably inefficient later, especially when irreversible transplant glomerulopathy is settled in the allograft. Peritubular capillaritis and intense inflammation with the accompanying severe decline of renal functions can predict resistance to the treatment and increased risk of graft failure. Close follow-up of patients in the latter period of transplantation and immediate pathologic and immunologic evaluations in suspicious cases, may provide early diagnosis of chronic AMR and prevention of allograft with anti-humoral treatment especially with rituximab.

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