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Effect of rituximab on reducing the panel-reactive antibody in dialysis patients of transplant candidate

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ABSTRACT

Introduction: Based on the evidence, rituximab may be an effective treatment for kidney transplantation for reducing panel-reactive antibody.
Objectives: This study was conducted to investigate the effect of rituximab on reducing the panel in transplant dialysis patients.
Patients and Methods: This is an interventional study that was conducted on 20 dialysis patients who were candidates for kidney transplantation. Patients first had a panel-reactive antibody test and patients with a panel-reactive antibody above the age of 30 were included in the study. First, rituximab was administered at a dose of one gram and then after two weeks, another dose of one gram was administered. Panel-reactive antibody was measured baseline, one and six months later.
Results: One and six months after stopping the drug, we found a significant decrease in the mean amount of reactive antibodies. Additionally, six months after stopping the drug, a significant decrease in the level of patients' reactive antibodies in comparison to one month before taking the drug was detected ($P < 0.05$).
Conclusion: The findings showed that treatment with rituximab is useful for reducing panel-reactive antibody in kidney transplant patients. However, more studies are needed to optimize rituximab injection protocols.

Implication for health policy/practice/research/medical education:
Treatment with rituximab is useful for reducing panel-reactive antibody in kidney transplant patients.
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Original

Introduction

Chronic kidney disease is a clinical condition in which the patient becomes permanently dependent on renal replacement therapy (dialysis or kidney transplant) due to an irreversible decrease in renal function (1). Considering the annual growth of approximately 5 to 6% of terminal kidney failure patients in the world compared to the population growth in the world (1.1%), this disease is one of the most important therapeutic problems in all countries of the world (2). Studies show kidney transplantation constitutes on average about 20% of the treatment of end-stage renal disease (ESRD) patients. Most patients with kidney failure consider kidney transplantation to be the best and greatest treatment to return to a normal life. Generally, the use of transplanted organ from one person to another one will lead to rejection of the transplant unless immunosuppressive drugs are given (3). The recipient must undergo some tests to ensure that the surgery is safe. The type of tests will vary according to age, gender, kidney disease and other medical conditions present (4). Regardless of the type of transplanted kidney-living or deceased donor-special blood tests are needed to determine blood type and tissue. These tests will help find the kidney donor that matches the recipient (5).

Among the various factors involved in the outcome of a transplanted kidney, immunological incompatibility is the most important. Alloantibodies produced in the serum of a transplant recipient against a transplanted human leukocyte antigen are among the most important problems in kidney transplantation. Studies have shown that this factor has a significant inverse effect on the outcome of a transplanted kidney from a living relative or non-relative (6). The process of producing human leukocyte anti-antigen antibodies is called allergenicity,

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and these alloantibodies can be evaluated as panel-reactive antibodies (7). This test screens antibodies against class I and class II human leukocyte antigens in kidney transplant candidates. In this test, the graft of the transplant recipient is assessed against antigen or cells obtained from different donors and the percentage of the panel is expressed based on the positive ratio. Various factors such as previous transplantation, history of blood transfusion, pregnancy and dialysis have been identified as factors influencing panel size.

One of the blood tests for human leukocyte antigen is called a tissue type test. The immune system can employ this indicator to identify which cells belong to a person's body (8). A close match between the leukocyte antigen markers in the donor and the recipient will reduce the risk of the donor's immune cells, which invade the recipient and thus increase the outcome of the transplant. The potential recipient is tested for antibodies through cross-matching before transplantation (9). The presence of antibodies causes the matching test to be positive, which will effectively prevent transplantation. A kidney will be "perfectly matched" when all donors and recipient signs are the same. A fully adapted kidney transplant will give the best results for kidney function for several years (10). In many pre-kidney transplants, rituximab is administered as an intravenous injection of 375 mg/m^2, one or two weeks before transplantation with plasmapheresis and intravenous immunoglobulin to kill all peripheral B cells (11). Vieira et al (12) reported that the administration of rituximab reduced panel-reactive antibody from 87% to 51% by simultaneously reducing the fluorescence intensity.

Rituximab is a common biological agent that is widely administered to treat B cell lymphoma, lymphoproliferative disorders, rheumatoid arthritis and some vasculitis and other inflammatory conditions (13). Side effects of this drug include; cardiovascular problems, skin, gastrointestinal problems and nervous system complications (14).

Objectives

Studies have reported conflicting results regarding the use of this drug while evidence suggests that rituximab may be an effective and safe treatment for renal impairment and kidney transplantation. However, ideal dosing strategies and combinations with other factors are still debated. Since rituximab is one of the most widely used drugs in various diseases, this study was conducted to determine the effect of rituximab on reducing the panel in dialysis patients who were the candidates for transplantation in Ahvaz, Iran in 2020.

Patients and Methods

Study design

This is an interventional and prospective study, which was conducted in kidney transplant hospitals. The study population included all patients referred for kidney transplantation in the second six months of 2019 and 2020. Using purposive sampling and according to the inclusion and exclusion criteria, 20 people were selected as the research sample. First, rituximab was administered at a dose of one gram and then after two weeks, another dose of one gram was administered.

Inclusion criteria are dialysis patients who are candidates for kidney transplantation who are not prohibited from taking rituximab, their panel reaction antibody test is moderate to severe (panel reaction antibodies less than 10, 10 to 29, 30 to 49 and greater or equal to 50, respectively were considered as negative, positive, mild, moderate and severe). Exclusion criteria included dissatisfaction with the study, patients with heart problems, lung problems, a history of infection, allergies and history of anaphylactic shock and drugs interfering with rituximab. Moreover, all patients were excluded from the study for taking drugs that affect the amount of panel and the activity of the renin-angiotensin system, such as lovastatin, procainamide, alpha-methyldopa and inhibitors of the mentioned system.

Patients were tested for panel-reactive antibodies before the treatment and then treated with rituximab. Then, one and six months after drug administration, they were re-tested for panel-reactive antibodies.

First, rituximab was administered at a dose of one gram, then two weeks later, another dose of one gram was administered. Panel-reactive antibody was measured baseline, one and six months later.

Conditions for prescribing rituximab are as follows;

1. The drug should be administered as an intravenous infusion.
2. To start the administration, the dose can be started from 50 mg/h and in case of no allergic reactions and events during the injection; increase the injection speed must be increased every 50 minutes to a maximum of 400 mg/h.
3. Acetaminophen or diphenhydramine can be administered to reduce allergic reactions such as hypotension, bronchospasm and angioedema before infusion.
4. During the infusion, the patient should be closely monitored and in case of infusion-related symptoms, discontinue the injection and use epinephrine, diphenhydramine and corticosteroids immediately. Once the patient's condition has stabilized, the infusion rate should be reduced by 50%.
5. In case of life-threatening arrhythmias, the infusion should be discontinued.
6. In the case of significant infusion-related symptoms, the patient should be undergone cardiological monitoring.

Statistical analysis

To analyze the data, number and percentage indices were

employed for qualitative variables and for quantitative variables mean, standard deviation, mean and minimum-maximum value indices were utilized. Due to the normal distribution of data, which was confirmed by the Kolmogorov-Smirnov test, the repeated measure ANOVA test was applied to evaluate the effect of drug administration over time since the post hoc Bonferroni test was used to evaluate the two-time test. All descriptive tables and statistical tests were prepared using SPSS software version 21 and the statistical significance level was considered 0.05.

Results

The present study was conducted on 20 dialysis patients who were candidates for kidney transplantation, since 60% of whom were female. Thirty-three points three percent of women had a history of three pregnancies and 25% of them had no history of any pregnancy. Among the study participants, 80% had a history of hypertension, 70% a history of diabetes, 20% had a history of heart disease, 20% had a history of systemic lupus erythematosus (SLE), 5% had a family history of renal diseases, 20% had a history of proteinuria and also 10% had the history of kidney cysts. Fifteen percent had no pre-transplant blood transfusions; however, 40% of patients experienced multiple blood transfusions before transplantation (Table 1).

Table 2 shows that the mean pre-reaction antibody of rituximab was 59.5 units with a standard deviation of 17.84 units ranging from 30 to 100 units. Mean panel reactive antibody one month after rituximab was 26.0 ± 19.30 units ranging from 10 to 70 units. The mean panel reactive antibodies six-month after taking rituximab was 20.94 ± 19.59 units ranging from 10 to 70 units.

Complications in dialysis patients who are candidates for kidney transplantation and took rituximab for six months include infection in 15%, catheter infection in 5% and lack of response to treatment in 5% of patients. In this study, 10% of patients died and 90% of them recovered (Table 3, Figure 1).

The results of Table 4 show that rituximab significantly reduced the mean of panel reactive antibodies in patients over a period of six months ($P < 0.001$). We found a significant difference of panel reactive antibodies between the first and six months after the study ($P < 0.001$; post hoc test). In other words, with the administration of rituximab one month after taking the drug, a significant decrease in the average level of reactive antibodies was observed and also six months after taking the drug, a significant decrease in the average level of reactive antibodies in patients compared to one month before taking the drug was observed. Figure 2 clearly shows the trend of this decrease.

Discussion

The results showed that with the administration of rituximab after one month, a significant decrease in the

Table 1. Summary of demographic information and disease history

Variable		Frequency	Percent
Gender	Male	8	40
	Female	12	60
Pregnancy history	None	3	25
	Once	2	16.7
	Twice	2	16.7
	Three times	4	33.3
	More than 3 times	1	8.3
History of blood pressure	Yes	16	80
	No	4	20
History of diabetes	Yes	14	70
	No	6	30
History of heart disease	Yes	4	20
	No	16	80
Proteinuria	Yes	4	20
	No	16	80
SLE	Yes	4	20
	No	16	80
Positive family history	Yes	1	5
	No	19	95
Kidney cyst	Yes	2	10
	No	18	90
Frequent dialysis	6-month before transplantation	2	10
	1	6	30
	2	3	15
	3	6	30
	5	3	15
Number of blood transfusions before transplantation	None	3	15
	Once	1	5
	Twice	4	20
	Three times	2	10
	Five times	1	5
	Six times	1	5
	Several times	8	40

Table 2. Summary of reactive antibody information before drug administration

Reactive antibodies	Mean	SD	Min.	Max.
Before taking the drug	59.5	17.84	10	75
One month after taking the drug	26	19.30	10	70
Six months after taking the drug	20.94	19.59	10	70

Table 3. Complications after six months of drug administration

Complications		Frequency	Percent
Infection	Yes	3	15
	No	17	85
Catheter infection	Yes	1	5
	No	19	95
Lack of response to treatment	Yes	1	5
	No	19	95
Final status	Deceased	2	10
	Improved	18	90

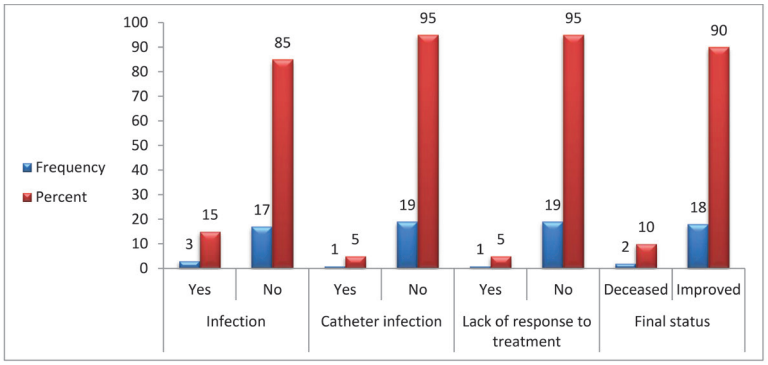

Figure 1. Complications after six months of drug administration.

mean rate of reactive antibodies was seen. Furthermore, six months after taking the drug, a significant decrease in the average amount of reactive antibodies in patients compared to one month before taking the drug was detected too. Studies have shown that one of the first-line treatments for kidney transplant patients is rituximab, which should be given as an intravenous injection of 375 mg/m^2 (11, 15-18).

The study by Pathak et al (19), showed that steroid-suppressed immune suppression after kidney transplantation provides acceptable survival of the patient transplant. The results of their study showed that induction of low-dose rituximab and induction of thymoglobulin can be effective in patient survival. Additionally, Querido et al (20), found that immunosuppressive therapy with intravenous immunoglobulin and rituximab is effective.

In our study, the side effects of drug use include infection in 15% of patients, catheter infection in 5% of patients, and lack of response to treatment in 5% of patients. In our study also, 10% of patients died and 90% of them recovered. Schrezenmeier et al (21), to find the prevalence of infectious diseases and malignancies after rituximab treatment in kidney transplants, while the median time between the first injection of rituximab and the first infection was four months. They found, out of 88 general infections, 74 cases of severe bacterial infections, five cases of severe viral infections, three cases of severe fungal infections; two cases of severe bacterial and fungal infections and four cases of severe viral, fungal and bacterial infections were observed. Macklin et al (22) showed that a high prevalence of infection was observed in renal transplant recipients after rituximab treatment and most infections occurred within six months after administering rituximab.

Barnett et al (23), also stated that rituximab (in multiple doses or combined with other monoclonal antibodies and/or other immunosuppressants) may increase the risk of infectious complications, although no conclusive evidence is available and, rarely, can it cause the syndrome cytokine secretion, thrombocytopenia, and neutropenia. It should also be noted that in his study, Song et al (18) stated that no side effects from rituximab were observed in kidney transplant patients.

Conclusion

According to the findings of the study, the administration of rituximab during the six months had a significant decrease in the average level of panel reactive antibodies

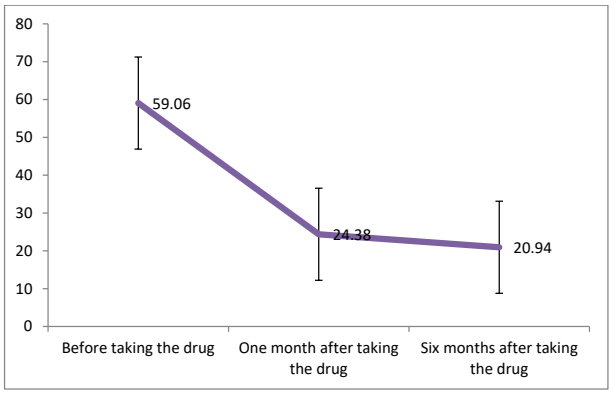

Figure 2. Trend of antibodies before and after drug administration up to six months.

Table 4. Summary of the effects of drug use over a period of six months

Taking medication	Mean	SD	*P* value*	Pairwise comparison**
Before taking the drug	59.06	15.08	F=102.70 *P*<0.001	*P*<0.001
One month after taking the drug	24.38	19.05		
Six months after taking the drug	20.94	19.59		

*Repeated Measure ANOVA, ** Post hoc Bonferroni test.

in kidney transplant patients compared to one month before taking the drug. Physicians may consider treatment with rituximab in specific clinical cases, especially when conventional treatment fails. Controlled studies with new and different designs are also needed to optimize rituximab injection protocols to get more effective results.

Limitations of the study

Lack of cooperation of some patients to collect information.

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Authors' contribution

Conceptualization: AA.
Methodology: AA and ST.
Validation: AA.
Formal analysis: ST.
Investigation: ST.
Resources: ST.
Data curation: AA and ST.
Writing—original draft preparation: ST.
Writing—review and editing: AA, ST, HS and AG
Visualization: AA and ST.
Supervision: AA, ST, HS and AG.
Project administration: ST

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The study was conducted based on the Declaration of Helsinki. The Ethical Committee of the Ahvaz Jundishapur University of Medical Sciences approved the protocol of this study (#IR.AJUMS.HGOLESTAN.REC.1399.065). This study was taken from nephrology fellowship of Samaneh Tirom (#330097572). All participants agreed to take part in the study and signed a declaration of informed consent. Accordingly, ethical issues (including plagiarism, double publication) have been completely observed by the authors.

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