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Management of Highly Sensitized Patients in Renal Transplantation: Prospective Single-Center Study

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Abstract

Background and objectives: In kidney transplantation, immunologic risk assessment was performed through pretransplant measurement of human leukocyte antigen, donor-specific antibodies. The aim of this study was to address the impact of early pre-transplant donor-specific antibodies screening.

Methods: A cross-sectional study was conducted in the Duhok Kidney Center in the Kurdistan region, Iraq. The study started on the 1st of March 2021 till the 1st of July 2023. A convenient nonrandom sampling of 40 pairs of patients and donors was included in this study. a structural close-ended questionnaire prepared. The first part of the questionnaire included the socio demographic characteristics of the studied sample. The age, gender, occupation, and residency of both the recipient and the donor were recorded. The induction immunosuppression and type of transplants were investigated.

Results: Most recipients (70%) were weakly sensitized; the moderate group rated 22.5%, and the strong group rated 7.5%. The mean age of the recipients was 40.02 ± 9.33, and they were followed for 2.05 ±0.84 years. The mean of donor-specific antibodies was compared before and after induction therapy: 4454.02±3227.10 vs 1479.85±1044.12, respectively. The result was highly significant. The history of the previous renal transplants was 17.5%, the blood transfusion was 5%, and the history of pregnancy was 57.5%. The mean difference in glomerular filtration rate was 8 ± 2.6 vs. 81.24 ± 24.06 among the rejected and non-rejected groups. The serum creatine was 6.7 ± 1.01 in the rejected and 1.14 ±1.17 in the non-rejected group.

Conclusion: Multiple plasmapheresis sessions were part of the desensitization protocol, with low-dose immunoglobulin and Rituximab administered simultaneously. Based on these findings, in the future, we anticipate that safe kidney transplantation will be performed even in highly sensitized recipients, thereby actively improving their prognosis**.**

Keywords: Allograft, Cross-sectional study, Donor Specific Antigen Screening, Renal Transplantation

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Introduction

In kidney transplantation, immunologic risk assessment was performed through pretransplant measurement of human leukocyte antigen (HLA)and donor-specific antibodies (DSAs). The newest approach to antibody calculation comprises mixing candidates' sera with HLA peptides linked to polystyrene beads and measuring the antibody binding using the Luminex platform. The method provides complete information on anti-HLA antibodies that could cause rejection. The test demonstrated that not all antibodies are produced equally. Most participants do not develop antibodies-mediated rejection due to the quantity of the antibodies, their binding capability, and their IGg subtype. The test also identifies the change in the immunological pathway through treatment.[1] A study concluded that pretransplant monitoring of DSA through single-antigen bead SPIs could benefit risk stratification.[2] Kidney transplantation (KT) remains associated with suboptimal five (77%) and ten-year graft survival (56%). The long-term survival rate after kidney transplantation has been satisfactory.[3] A mean fluorescence intensity (MFI) of more than 500 was considered positive, and clinical significance was considered at an MFI of more than 1000. [4] A study revealed that for patients with HLA-DSA, high cumulative mean fluorescence intensities of more than 103.000 MFI of all pretransplant HLA antibodies revealed the best sensitivity and specificity to predict an elevated risk for antibody-mediated rejection (AMR)posttransplant.[4] A cumulative MFI value of more than 103 indicated the highest risk for The purpose of desensitization protocols is to achieve negative cross-match by using intravenous immune globulin and plasmapheresis. [5] A study found that the graft survival rate of patients who underwent desensitization and received a kidney from an HLA-incompatible donor could be improved.[5] The commonly used plasmapheresis and Intravenous immunoglobulin IVIg with or without Rituximab, or the more lately initiated complement inhibitor eculizumab, anti-CD20 Obinutuzumab, or IgG cleaving enzyme imlifidase can be used in highly desensitized individuals to overcome the immunological barrier.[6] In the different desensitization methods, removing DSA antibodies is essential. Intravenous immunoglobulin is a vital strategy for desensitization, and it will be more efficient if it is associated with mechanical antibody removal, such as plasmapheresis. DSA-sensitized patients with high MFI levels (> 3000) can receive transplantation across the HLA barrier using intensified posttransplant immunosuppressive therapy.[7] The aim of this study is to address the impact of early pre-transplant DSA screening and to find any association between the levels of MFI and damaging effects on the allograft and to desensitize patients to lower the levels of preformed antibodies to avoid rejection in highly sensitized recipients.

Patients and methods

A prospective cross-sectional study was conducted in the Dohuk Kidney Center in the Kurdistan region. The study started on the 1st of March 2021 till the 1st of July 2023. The first part of the questionnaire included the sociodemographic characteristics of the studied sample. The age, gender, occupation, and residency of both the recipient and the donor were recorded. A convenient nonrandom sampling of 40 pairs of patients and donors was included in this study. The inclusion criteria were chronic renal disease patients with high sensitization who need renal transplantation, and patients with risk factors that elevate sensitization, like history of previous renal transplantation, blood transfusion, and pregnancy. The exclusion criteria are severe cardiac or pulmonary disease, active malignancy, active infection,

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active drug abuse, and uncontrolled psychiatric disease.Each individual's serum was tested with LIFECODES LifeScreen Deluxe-LMX (Gen-Probe-Immucor, Stanford, CT, USA). According to the manufacturer's directions, centrifugation was used to obtain serum from every individual. The whole blood was incubated with beads for 30 minutes to facilitate antigen-antibody binding. To remove any unbound material, the samples were washed with phosphate-buffered saline. A second antibody, immunoglobulin G, was later conjugated with a fluorophoresis. Phycoerythrin was added to allow the Luminex system to detect the antigen-antibody complex. The induction immunosuppression and type of transplants were investigated. The MFI was decreased to weak or negative values before KT by performing pretransplant desensitization. The desensitization protocol in these hospitals was as follows: if the DSA is 1000-5000 (mild cases), then a Rituximab vial 375mg/m2 is given on the first day. The second dose of Rituximab is given on day 14. On days 15 and 18, the plasmapheresis session with low-dose IVIG (100mg/kg) is performed. After that, the cross-match will be repeated, and after the negative results, the transplantation will proceed. The positive cases require further (2) doses of Rituximab and two sessions of plasmapheresis. In moderate cases (DSA 5000-10000), on day 1, Rituximab vial 373mg/m^2 will be given, and the second dose will be given on day 14 of the cycle. Plasmapheresis will be started on day 15 and repeated on days 18, 21, and 24. The low IVIG dose will be given simultaneously (4 plasmapheresis sessions and four IVIG doses). On day 26, the Rituximab vial(373mg) will be given as a third dose, and the fourth dose will be given on day 40 of the cycle. The cross-match should be repeated, and if negative, renal transplantation will be performed. The high results of MFI require repeating the protocol. In severe cases, with DSA class II MFI values more than 10,000, require on day 1 Rituximab vial 373mg/m2, and the second dose will be given on day 14. The cycle will be continued with four plasmapheresis sessions and four IVIG doses (100mg/kg) on days 15,18, 21, and 24, respectively. The third dose of Rituximab (373mg/m^2) will be given on day 26 and the 4^{th} one on day 40. The cross-match will be repeated, and the transplant will be performed if negative. The positive cases require further treatment. Two doses of Tocilizumab (400mg) will be added, the first dose on day 50, and the same dose will be repeated on day 64. Then, continue the cycle with 4 sessions of plasmapheresis and low-dose IVIG on days 66,69,72, and 75. The transplantation will be performed for negative cases, and the live donor will be changed for positive cases. The 40 cases were divided into three groups according to baseline mean fluorescence intensity (MFI) HLA-DSA: strong more than 10,000, moderate=5000-10000, and weak=1000-5000. Graft loss was defined as the return to dialysis, transplantation, or patient death. The data was entered into an Excel sheet and then transferred to SPSS (version 27). Descriptive and inferential statistical analyses will be accomplished. The Categorical data were tested using the Chi-square test, and numerical data were tested using the t-test. Graft and patient survival rates were evaluated using the Kaplan-Meier analysis with the log-rank test. A p-value less than 0.05 was considered statistically significant. The ethics committee of the Kurdistan Higher Council for Medical Specialties approved the study. The investigator approached each patient separately. Written informed consent was obtained from the patients after they had been told about the nature of the study. Confidentiality was assured, Table (2).

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Results:

The mean age of the recipients was 40.02 ± 9.33, and they were followed for 2.05 ±0.84 years. Two-thirds were females, and only one-third were males. Those who had an occupation were 60%, and those who had no occupation were 40%. More than half live in rural areas, and only 47% live in urban areas. The mean age of the donor was 31 ±22; 70% were males, and 30% were females, Table (1). Less than 30 means severely decreased; 5% were between 30 and 44 (moderately to severely reduced), 7% were between 45 and 59(mildly to moderately reduced), and 78% were more than 60 (mildly reduced) as shown in Figure (1). The distribution of the rejected transplants was 7.5%, and non-rejected transplants were 92.5% and were accepted. The history of the previous renal transplant was 17.5%, the blood transfusion was 5%, and the history of pregnancy was 57.5%. 14.3% of deaths had a history of previous renal transplant, and 13% had a history of pregnancy. The result was not statistically different (p-values were more than 0.05).

Table (1): Shows the distribution of the studied sample by sociodemographic characteristics.

Recipient group	Mean ±SD
Age	40.02 ± 9.33
Follow-up in years	2.05 ±0.84
Follow-up in months	24.75 ± 9.82
	No (%)
Gender	
Male	13 (32.5)
Female	27 (67.5)
Have occupation	24 (60)
No-occupation	16 (40)
Urban	19 (47.5)
Rural	21(52.5)

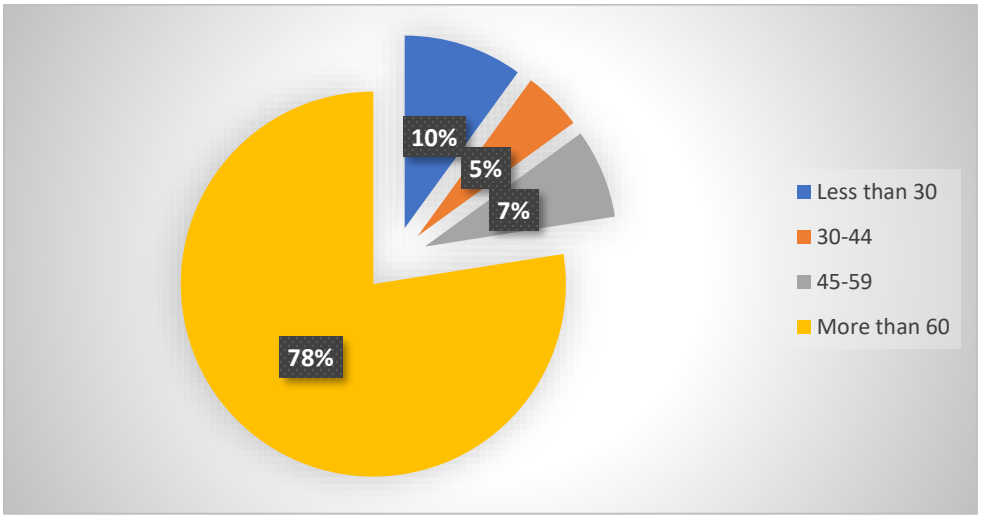

Figure (1): the proportion of patients with GFR levels.

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Table (2): shows the immunological characteristics of the studied sample

Number of patients	Group	The DSA level at baseline	Desensitisation
1	strong	14450	PP/IVIG/Rituximab/tocilizumab
2	strong	14150	PP/IVIG/Rituximab/tocilizumab
3	strong	11644	PP/IVIG/Rituximab/tocilizumab
4	moderate	8288	PP/IVIG/Rituximab
5	moderate	7447	PP/IVIG/Rituximab
6	moderate	7149	PP/IVIG/Rituximab
7	moderate	6620	PP/IVIG/Rituximab
8	moderate	6500	PP/IVIG/Rituximab
9	moderate	6300	PP/IVIG/Rituximab
10	moderate	5850	PP/IVIG/Rituximab
11	moderate	5600	PP/IVIG/Rituximab
12	moderate	5500	PP/IVIG/Rituximab
13	weak	4800	PP/IVIG/Rituximab
14	weak	4730	PP/IVIG/Rituximab
15	weak	4720	PP/IVIG/Rituximab
16	weak	4700	PP/IVIG/Rituximab
17	weak	4600	PP/IVIG/Rituximab
18	weak	4500	PP/IVIG/Rituximab
19	weak	3900	PP/IVIG/Rituximab
20	weak	3857	PP/IVIG/Rituximab
21	weak	2980	PP/IVIG/Rituximab
22	weak	2908	PP/IVIG/Rituximab
23	weak	2890	PP/IVIG/Rituximab
24	weak	2880	PP/IVIG/Rituximab
25	weak	2600	PP/IVIG/Rituximab
26	weak	2350	PP/IVIG/Rituximab
27	weak	2300	PP/IVIG/Rituximab
28	weak	2300	PP/IVIG/Rituximab
29	weak	2160	PP/IVIG/Rituximab
30	weak	2108	PP/IVIG/Rituximab
31	weak	2060	PP/IVIG/Rituximab
32	weak	2010	PP/IVIG/Rituximab
33	weak	2000	PP/IVIG/Rituximab
34	weak	1990	PP/IVIG/Rituximab
35	weak	1950	PP/IVIG/Rituximab
36	weak	1620	PP/IVIG/Rituximab
37	weak	1600	PP/IVIG/Rituximab
38	weak	1500	PP/IVIG/Rituximab
39	weak	1350	PP/IVIG/Rituximab
40	weak	1300	PP/IVIG/Rituximab

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Discussion:

The current study included 40 patients; the mean age of the recipients was 40.02 ± 9.33, and the follow-up in months was 24.75 ± 9.82. A study was conducted in Turkey; the mean age was 43.7 ± 12.5 years, and the mean follow-up time was 26.1 ± 17.7 months.[8] The findings of this study were consistent with that of Sinangil. [8] In the current study, all desensitized patients were positive for DSA, and treatment with PP/IVIG more effectively eliminated preexisting DSAs. Graft survival was 92% in all desensitized patients. This result was in line with a study by Sharma.[9] The immunomodulatory treatments were used in this study to eliminate DSAs or prevent their production. This transplant center used a modified desensitization protocol by the Renal Transplant Unit, National Institute of Solid Organ and Tissue Transplantation, in Dow University Hospital, Karachi, Pakistan.[10] According to the British Transplant Society, DSAs with MFI value <5000 and negative CDC cross-match for T and B lymphocytes are associated with lower susceptibility to allograft rejection. There was no statistical difference between groups for history of blood transfusion, history of pregnancy, or history of dialysis in Sinangil study. [8] The result of the current study was consistent with this finding. Living kidney transplant recipients were treated with Plasmapheresis, low-dose IVIG, and Rituximab until the CDC cross-match became negative and measured DSA was below the 1,000 MFI threshold. Chung Studie showed that the presence of preexisting DSA leads to poor posttransplant outcomes. DSA strength specifically correlates with AMR and graft loss.[11] In the Chung study, 24% of the sample was categorized as strongly sensitized (the DSA was more than 10,000), 32% were among the moderately sensitized group, and 44% were weakly sensitized.[11] In the current study, the strong, moderate, and weak groups rated 7.5%, 22.5%, and 70%, respectively. The majority were weakly sensitized, and this result was consistent with that of Chung study.[11] The treatment approach used in the current study was a stratified desensitization therapy that depended on HLA-DSA strength at the baseline. The investigator used a more potent therapeutic regimen in the strong group and started the treatment earlier. The cycle was repeated if the HLA-DSA did not decrease to a weak or negative level. The current study also investigated the incidence of death among the recipients and the association of baseline DSA with the outcome of KT. The three deaths (rejected group) were among the moderate group, and the mean difference was significant compared to the other two groups (4986.66±2450.00) and (4410.83±3305.00). The current study used GFR and S.Cr to monitor impaired renal function. The mean difference in GFR was 8 ± 2.6 vs. 81.24 ± 24.06 among the rejected and non-rejected groups. The S.Cr was 6.7 ± 1.01 in the rejected and 1.14 ±1.17 in the non-rejected group. The p-value was highly significant ($p < 0.001$). Kannapiran Studies revealed that both indicators are essential in predicting renal failure. [12] Glomerular filtration rates (GFR) are considered the best index of graft function.[13] In Santos study in Portugal, patients were divided according to DSA strength (MFI <15, 000 vs.≥ 15, 000) and C1q-binding ability. AMR frequency was high (30%), and it increased with DSA strength ($P = 0.002$) and C1q+ DSA ($P < 0.001$). Both the strength and binding ability of DSA were essential for improving the risk assessment pretransplant.[14] A cross-sectional study by Ali was conducted at the nephrology and renal transplant center.[15] Those who had transplant procedures underwent desensitization by intravenous immunoglobulins, plasmapheresis, and Rituximab. The graft survival rate of

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sensitized patients was 61.1%, and the death rate was 2/63 (3.17%). The study revealed that pretransplant testing for anti-HLA antibodies helps assess patients' risk, make decisions regarding patient and donor selection, and plan treatment strategies.[15] This supports the current study findings. A study was conducted to evaluate the experience of a kidney transplant program in a single center in Erbil, Iraq. The result revealed a patient survival rate of 90% and an acute rejection rate of 5.3%.[16]

Conclusion:

The transplant center successfully desensitized and transplanted 40 HLA-sensitized kidney transplant candidates with moderate to high DSAs. The desensitization protocol comprised multiple plasmapheresis sessions with simultaneous low-dose IVIG, Rituximab, and Tocilizumab. Upon follow-up, we did not notice any significant transplant-related events, such as allograft dysfunction or rejection among the majority of our patients, and the mortality rate was shallow. The DSA was a significant predictor of the outcome of renal transplant.

Limitations

The current study's limitation was the small number of patients with high HLA-DSA values in the strong group. Therefore, further studies with a larger sample size are recommended. The second limitation affecting clinical inference is the lack of protocol biopsies, which is considered an essential approach in managing susceptible individuals. The third limitation was the non-homogeneity in the desensitization therapy between the groups. This study's strength: it is the first to cover this issue and show the relation of DSA strength with graft survival. This result is essential for centers that perform HLA-incompatibility renal transplants and helps to decide which individual is suitable for renal transplant and desensitization therapy.

Recommendation:

Further studies are to be conducted with a larger sample size. The clinical relevance of the present study remains to be validated in future studies.

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Conflicts of interest

No conflict of interest to report.

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