Impact Factor: 9.9 ISSN-L: 2544-980X

Effectiveness of Desensitizing Therapy in Kidney Transplantation in Highly Sensitized Patients Before Transplantation

Ismatov Tuychiboy Akhrorkulovich [1]

Resume: This article provides detailed data from the analysis of the results of examination of 27 recipients with a high degree of sensitization to the donor kidney transplant. Considering the identified changes, clinical and laboratory parameters were assessed prior to transplantation, with an emphasis on the changes in sensitization levels to thresholds permissible for surgical interventions, along with a comparison to modern literature sources.

Key words: kidney transplantation, sensitization, treatment of end-stage renal failure.

Relevance

Kidney transplantation is recognized as the most effective treatment option to improve quality of life and survival of patients with end-stage kidney disease, (ESRD) [1,2,18,21,29,30]. However, the kidney transplant waiting list may be long or unproductive for highly sensitized patients who cannot find an immunologically compatible donor [3,10,17,19,22,26,28]. Compared with non-sensitized patients, highly sensitized kidney transplant recipients often have worse clinical allograft outcomes and patient survival [4,7,9,11,16,20,23,32]. The development of alloantibodies against human leukocyte antigens (HLA), generated by blood transfusions, previous transplants, infections, and pregnancy, leads to sensitization. The proliferative reactive antibody (PRA) test is commonly used to determine the degree of sensitization of potential kidney transplant candidates, and candidates with a PRA ≥80% are generally considered highly sensitized [5,12,13,21,25,31], while candidates with a PRA ≥98% are considered very highly sensitized and receive increased priority for allocation [6,14,15,24,30,31]. Although approximately 30% of kidney transplant candidates on the waiting list are sensitized, only 6.5% receive a transplant each year [4,7,19,26,31]. In Europe, approximately 20% of patients awaiting kidney transplantation are sensitized, with 5% being highly sensitized [1,8,13,22,28,31].

Objective: To improve the treatment outcomes of kidney transplantation in highly sensitized recipients by developing an algorithm for a desensitization regimen.

Materials and methods.

The article presents the results of treatment of patients in the Samarkand Regional Multidisciplinary Medical Center, in the Department of Angiosurgery and Transplantation. In patients, the duration of terminal renal failure (TRF) varied from **1 year to more than 10 years** . In most patients (85.2%), the disease lasted more than **4 years** , which indicates the chronic nature of renal pathology and the accumulation of sensitization. The distribution of patients by the duration of the disease is presented in Table 1.

Statistical analysis showed that the average duration of the disease was **7.8 ± 3.2 years** . Long-term ESRD contributes to the development of chronic changes in the kidneys and increases the risk of developing immune complications after transplantation (Abecassis et al ., 2018).

[1] Samarkand Regional Multidisciplinary Medical Center, Department of Angiosurgery and Transplantation

Table 1. Duration of renal failure in patients

Duration of the disease	Absolute number	IN %
Up to 1 year	1	3.7%
1-3 years	3	11.1%
4-5 years	6	22.2%
6-10 years	8	29.7%
More than 10 years	9	33.3%
Total	**27**	**100%**

The average age of patients was **32.0 ± 5.6 years.** (range 18 to 45 years) . The gender distribution was as follows: **18 men (66.7%)** And **9 women (33.3%) ,** which corresponds to a ratio of 2:1 (see Table 2) . This distribution is consistent with data from other studies, which also note a predominance of men among patients with end-stage renal disease (ESRD) (Kasiske et al ., 2018).

Table 2. Demographic characteristics of patients

Parameter	Meaning
Middle age	32.0 ± 5.6 years
Men	18 (66.7%)
Women	9 (33.3%)
Total	**27 (100%)**

In the vast majority of patients, the cause of end-stage renal failure (ESRF) was chronic glomerulonephritis — **26 patients (96.3%) .** In one patient (**3.7%**), the cause of ESRF was interstitial nephritis (see Table 3). This distribution corresponds to data from national registries, where chronic glomerulonephritis is one of the leading causes of ESRF (United States Renal Data System [USRDS], 2020).

Table 3. Etiology of renal failure in patients (n = 27)

Etiology	Number of patients	Percent (%)
Chronic glomerulonephritis	26	96.3%
interstitial nephritis	1	3.7%
Total	**27**	**100%**

Table 3 shows that the main cause of ESRD in the study group is chronic glomerulonephritis. This result is consistent with the data of international and national studies, where chronic glomerulonephritis accounts for a significant share in the structure of causes of chronic renal failure (USRDS, 2020; Nephrology Registry of the Russian Federation, 2019).

All patients were tested for pre-existing antibodies using panel reactive antibodies (PRA) and donor-specific antibodies (DSA). PRA levels ranged from 25% to over 80% and DSA levels ranged from 500 to 5000 MFI (Mean Fluorescence Intensity) (see Table 4).

Based on PRA and DSA values, patients were divided into two subgroups:

2A. Moderate sensitization : 17 patients (63.0 %) with PRA from 25% to 40% and DSA from 500 to 3000 MFI.

2B. High degree of sensitization : 10 patients (37.0 %) with PRA more than 40% and DSA more than 3000 MFI.

Table 4. Distribution of patients by degree of sensitization (n = 27)

Degree of sensitization	Number of patients	Percent (%)	PRA (%)	DSA (MFI)
Average	1 7	63.0 %	25–40	500–3000
Tall	1 0	37.0 %	>40	>3000
Total	**27**	**100%**		

The stages of conducting studies concerning sensitization and transplant compatibility are described in detail in Chapter 2 of the study. The indicators of this study will be demonstrated in a clinical example, which provides detailed data on the analysis of the results in the pre-transplant period before and after the course of treatment to eliminate sensitization of the body.

Statistical analysis showed that the average PRA level in the moderate sensitization group was **32.4 ± 4.5%** , and in the high sensitization group it was **65.7 ± 8.9%** . The differences were statistically significant (**p < 0.001**), which justifies dividing patients into subgroups for individualization of therapy.

Table 5. Mean PRA and DSA levels in sensitization subgroups

Indicator	2A. Average sensitization (n = 17)	2B. High sensitization (n = 10)	p-value
PRA (%)	32.4 ± 4.5	65.7 ± 8.9	p <0.001
DSA (MFI)	1,500 ± 500	4,000 ± 800	p <0.001

Note: *p-values are calculated using independent samples t-test. A p-value <0.001 indicates a statistically significant difference between the moderate and high sensitization groups in PRA and DSA with a high degree of confidence.*

Analysis of the mean PRA and DSA levels in the sensitization subgroups (see Table 5) showed that patients with a high degree of sensitization had significantly higher PRA and DSA levels compared with patients with a moderate degree of sensitization (p < 0.001). This statistically significant difference indicates the need for more intensive preoperative preparation in patients with high sensitization to reduce the risk of graft rejection. Our data are consistent with the results of studies by other authors indicating the importance of taking into account the degree of sensitization when planning therapy (Jordan et al ., 2017).

Patients with a high degree of sensitization received intensive preoperative immunomodulatory therapy aimed at reducing the level of circulating antibodies and preventing the risk of acute graft rejection (see Table 6). The therapy regimen included the following components:

- **Human intravenous immunoglobulin (IVIg) : 2 g/kg** , divided into several infusions over 2 weeks. IVIg helps modulate the immune response and reduce antibody levels by blocking Fc receptors and neutralizing complement [Jordan et [al ., 2017].
- **Rituximab : 375 mg/m²** once 7 days before surgery. Rituximab is a monoclonal antibody to the CD20 antigen on B lymphocytes, which results in a decrease in B cell numbers and a decrease in antibody production [Vo et [al ., 2014].
- **Therapeutic plasmapheresis : 3-5 sessions** every other day with removal of 1.5-2 liters of plasma per session. Plasmapheresis allows for effective removal of circulating antibodies and immune complexes from the bloodstream [Stegall et [al ., 2011].
- **Transfusion of albumin solution : 20 g** after each plasmapheresis session to restore the volume of circulating plasma and maintain oncotic pressure.
- **Immunosuppressive therapy : tacrolimus** in dose **0.05 mg/kg/ day** And **mycophenolate mofetil 1 g/ day** 7 days before surgery. This combination of drugs suppresses the activation and proliferation of T- and B-lymphocytes [Clatworthy , 2011].
- **Induction therapy : antithymocyte globulin (ATG) 1.5 mg/kg/ day** for **5 days** , starting on the day of surgery. ATG reduces the number of circulating T-lymphocytes, preventing the development of cellular rejection [Montgomery et [al ., 2018].

Patients with moderate sensitization received less intensive therapy adapted to their antibody levels:

- **Human intravenous immunoglobulin (IVIg) : 1 g/kg** given as a single dose. A lower dose of IVIg is sufficient to modulate the immune response in moderately sensitized patients.

- **Therapeutic plasmapheresis : 2-3 sessions .** A smaller number of sessions effectively reduces the antibody level to acceptable values [Taner et [al ., 2015].
- **Immunosuppressive therapy :** similar to the highly sensitized group, but **without the use of rituximab** and with a shorter duration of **ATG induction therapy (1.5 mg/kg/ day for 3 days)** . This reduces the risk of side effects with sufficient immunosuppressive effect.

Table 6. Comparison of preoperative therapy regimens depending on the degree of sensitization

Component of therapy	Average sensitization	High sensitization
IVIg	1 g/kg	2 g/kg
Rituximab	No	375 mg/m² single dose
Plasmapheresis	2-3 sessions	3-5 sessions
Albumen	20 g after plasmapheresis	20 g after plasmapheresis
Tacrolimus	0.05 mg/kg/ day	0.05 mg/kg/ day
Mycophenolate mofetil	1 g/ day	1 g/ day
Induction therapy (ATG)	1.5 mg/kg/ day , 3 days	1.5 mg/kg/ day , 5 days

Patients with a high degree of sensitization received more intensive and prolonged therapy, including the use of rituximab and more plasmapheresis sessions. This approach is aimed at more effectively reducing antibody levels before transplantation, which is supported by data from studies [Vo et al ., 2014; Jordan et al ., 2017]. The use of rituximab in combination with IVIg and plasmapheresis showed high efficiency in desensitization of patients with high levels of PRA and DSA.

After preoperative therapy, a significant decrease in PRA and DSA levels was observed in all patients (see Table 7 and Figure 1).

Table 7.Reduction in PRA and DSA levels after preoperative therapy

Indicator	Before therapy	After therapy	Decrease (%)	p-value
Average sensitization (n = 1 7)				
PRA (%)	32.4 ± 4.5	10.2 ± 3.1	68.5%	p <0.001
DSA (MFI)	1,500 ± 500	400 ± 150	73.3%	p <0.001
High sensitization (n = 10)				
PRA (%)	65.7 ± 8.9	20.5 ± 5.2	68.8%	p <0.001
DSA (MFI)	4,000 ± 800	900 ± 200	77.5%	p <0.001

Note: *p-values were calculated using independent samples t-test. A p-value <0.001 indicates a statistically significant reduction in PRA and DSA levels after preoperative therapy in both sensitization subgroups.*

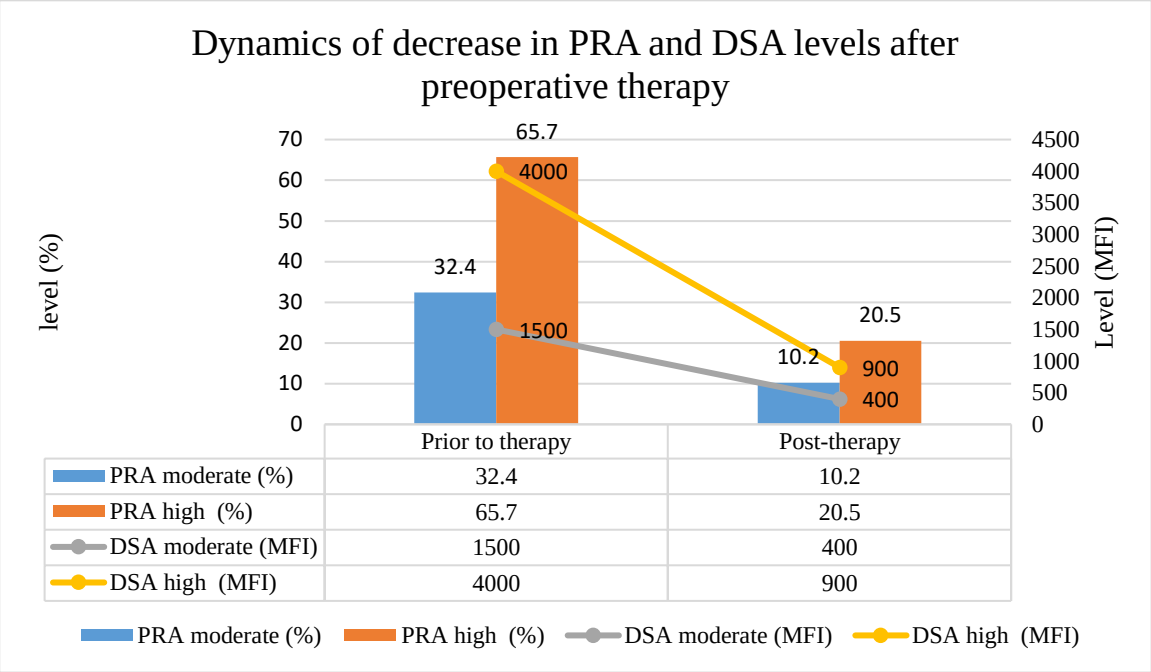

Figure 1. Dynamics of decrease in PRA and DSA levels after preoperative therapy

After preoperative therapy, statistically significant decreases in PRA and DSA levels ($p < 0.001$) were observed in patients of both groups. This indicates the effectiveness of the selected treatment regimens in reducing the degree of sensitization, which allowed kidney transplantation to be performed with a minimal risk of hyperacid rejection (see Figure 1).

Timely correction of immunosuppressive therapy based on laboratory data improved treatment outcomes in patients.

Conclusions

The study showed that the use of preoperative immunomodulatory therapy, including plasmapheresis, immunoglobulins and rituximab, effectively reduces PRA and DSA levels. This allows kidney transplantation to be performed with a minimal risk of acute rejection.

Individualized therapy based on the degree of sensitization and response to treatment improves transplant outcomes and preserves graft function. This confirms the need for personalized treatment regimens and careful monitoring of highly sensitized patients.

Thus, the results of the study of this group of patients showed that kidney transplantation in patients with high sensitization expands the possibilities, since the tactics of patient management in the pre- and postoperative period developed by the dissertation candidate sharply reduces the sensitization of this category of patients and thereby contributes to a sharp reduction in the number of patients with high sensitization on the “waiting list”, and accordingly to an increase in the frequency of transplant survival and an improvement in the percentage of postoperative complications.

BIBLIOGRAPHY

1. Abramowicz D., Cochat P., Claas F.H., et al. European Renal Best Practice Guideline on kidney donor and recipient evaluation and perioperative care. Nephrology Dialysis Transplantation, 2018; 33(8): 1291-1302.
2. Barba A., Romagnoli J., Piras A., et al. Ultrasonographic evaluation in kidney transplantation: a case study review. Journal of Transplantation, 2019; 16(2): 48-59.
3. Chipman V, Cooper M, Thomas AG, Ronin M, Lee B, Flechner S, et al. Motivations and outcomes of compatible living donor-recipient pairs in paired exchange. Am J Transplant (2021). doi : 10.1111/ajt.16821.

4. Clayton PA, McDonald SP, Russ GR, et al. Long-term outcomes in kidney transplantation. Nephrology, 2017; 22(1): 11-21.
5. Cole EH, Nickerson P, Campbell P, Yetzer K, Lahaie N, Zaltzman J, et al. The Canadian kidney paired donation program: a national program to increase living donor transplantation. Transplantation (2015) 99:985–90. doi : 10.1097/TP.0000000000000455.
6. De Klerk M, Kal -van Gestel JA, van de Wetering J, Kho ML, Middel - de Sterke S, Betjes MGH, et al. Creating options for difficult to match kidney transplant candidates. Transplantation (2021) 105:240–8. doi : 10.1097/TP.0000000000003203.
7. Delmonico FL, Morrissey PE, Lipkowitz GS, Stoff JS, Himmelfarb J, Harmon W, et al. Donor kidney exchanges. Am J Transplant (2004); 4:1628-34. doi : 10.1111/j.1600-6143.2004.00572.x.
8. Djamali A., Vidovich M., Jain A., et al. Vascular disease in kidney transplantation. Journal of the American Society of Nephrology, 2016; 27(7): 2102-2112.
9. Ferrari P, Hughes PD, Cohney SJ, Woodroffe C, Fidler S, D'Orsogna L. ABOincompatible matching significantly enhances transplant rates in kidney paired donation. Transplantation (2013) 96:821–6. doi : 10.1097/TP.0b013e3182a01311.
10. Halloran PF, Reeve J, Koo DDH, et al. Molecular assessment of rejection and injury in kidney transplants. American Journal of Transplantation, 2019; 19(9): 2574-2585
11. Halloran P.F., Schinstock C., Einecke G., et al. The Banff classification of renal allograft pathology: Update and future directions. American Journal of Transplantation, 2020; 20(9): 2080-2085.
12. Himmelfarb J, Ikizler TA, Hakim RM, et al. The uremic syndrome: Pathophysiology of uremia. Kidney International, 2019; 95(4): 753-764.
13. Karami F. Optimal integration of desensitization protocols into kidney paired donation programs. Operations Research for Health Care (2019) 32:100198. https://doi.org/10.1016/j.orhc.2019.100198 [Accessed 24 September 2021].
14. Kasiske BL, Zeier MG, Chapman JR, et al. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients: a summary. Kidney International, 2018; 86(1): 1120-1130.
15. Koh YT, Shah KV, Miller B., et al. Donor-specific antibodies in renal transplantation: diagnostic and therapeutic implications. Journal of Nephrology, 2018; 31(4): 549-561.
16. Leichtman AB, Cohen DJ, Keith DS, et al. The impact of aging on kidney transplant outcomes. American Journal of Transplantation, 2018; 18(2): 470-479.
17. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2019 Annual Data Report: Kidney. American Journal of Transplantation, 2019; 20(S1): 20-120.
18. Montgomery RA, Lonze BE, King KE, Kraus ES, Kucirka LM, Locke JE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med (2011) 365:318–26. doi : 10.1056/NEJMoa1012376.
19. Mostafa D., Wahba GG, Ammar MI Ultrasound and Doppler evaluation of transplanted kidneys: morphology, vascularity, and function. Journal of Radiology Research, 2020; 12(4): 215-222.
20. Nephrol Dial Transplant. Cardiovascular disease in dialysis and kidney transplantation. Nephrol Dial Transplant, 2021; 36(2): 215-220.
21. Orandi BJ, Luo X, King EA, Garonzik -Wang JM, Bae S, Montgomery RA, et al. Hospital readmissions following HLA-incompatible live donor kidney transplantation: a multi-center study. Am J Transplant (2018) 18:650–8. doi : 10.1111/ajt.14472.

22. Orandi BJ, Luo X, Massie AB, Garonzik -Wang JM, Lonze BE, Ahmed R, et al. Survival benefit with kidney transplants from HLA-incompatible live donors. N Engl J Med (2016) 374:940–50. doi : 10.1056/NEJMoa1508380.
23. Rakhimov A.Ya. Studying The Activity Of In Vitro Antiseptics Decasan , Furacillin and Chlorhexidine Bigluconate Against Hospital Strains of S. Aureus, E. Coli, Klebsiella Spp., P. Melaninogenica Separated from the Bed of the Soleus Muscle Texas Journal of Medical Science ISSN NO: 2770-2936, https://zienjournals.com Date of Publication:26-07-2022
24. Rakhimov A.Ya. The Effectiveness of Traditional the Method of Amputation and Treatment at the Lower Leg Level of Patients with Diabetic Foot Syndrome with Critical Lower Limb Ischemia. European Journal of Life Safety and Stability (EJLSS) ISSN2660-9630. www.ejlss.indexedresearch.org Volume 19, July-2022
25. Rakhimov A.Ya. , O.M. Kurbanov , Sh. G.Mirsoliev . The influence of diabetes mellitus on the course of purulent thoracic surgical pathologies. World Bulletin of Public Health (WBPH)Available Online at: https://www.scholarexpress.netVolume-15, October 2022ISSN: 2749-3644
26. Rakhimov A.Ya ., Qurbonov OM, Sagdullayeva GU, Safoyev BB, Latipov OZ Transcutaneous oximetry as the choice of the research for determining the level of amputation of the crus at critical ischemia of the lower extremities at patients with the diabetes mellitus. Asian Journal of Multidimensional Research. AJMR, Vol 8, Issue 12, December 2019, p. 120-125. Impact Factor: SJIF 2018 = 6.053
27. Schinstock CA, Smith BH, Montgomery RA, Jordan SC, Bentall AJ, Mai M, et al. Managing highly sensitized renal transplant candidates in the era of kidney paired donation and the new kidney allocation system: is there still a role for desensitization? Clin Transplant (2019) 33:e 13751. doi : 10.1111/ctr.13751.
28. Terasaki PI, Cai J. The humorous theory of transplantation: mechanisms and treatment strategies. American Journal of Transplantation, 2017; 15(2): 363-371.
29. Torres AM, Wong F, Pearson S, Weinberg S, Roberts JP, Ascher NL, et al. Bi-organ paired exchange-Sentinel case of a liver-kidney swap. Am J Transplant (2019) 19:2646–9. doi : 10.1111/ajt.15386.
30. Vanholder R., Massy ZA, Argilés Á., et al. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrology Dialysis Transplantation, 2020; 35(6): 917-939.
31. Veale JL, Nassiri N, Capron AM, Danovitch GM, Gritsch HA, Cooper M, et al. Voucher-based kidney donation and redemption for future transplant. JAMA Surg (2021) 156:812–7. doi : 10.1001/jamasurg.2021.2375.
32. Viklicky O, Krivanec S, Vavrinova H, Berlakovich G, Marada T, Slatinska J, et al. Crossing borders to facilitate live donor kidney transplantation: the Czech-Austrian kidney paired donation program - a retrospective study. Transpl Int (2020) 33:1199– 210. doi : 10.1111/tri.13668.