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An investigation of the primary immunosuppressive therapy's influence on kidney transplant survival at one month after transplantation

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ABSTRACT

Immunosuppressive therapy is complex and challenging to do correctly due to on-target and off-target side effects. However, it is vital to successful allotransplantation. In this article, we analyzed the critical classes of immunosuppressants used in renal transplantation, highlighting the mechanisms of action and typical clinical applications used to develop predictive models for the diagnosis of various diseases, including the prediction of survival after kidney transplantation. In patients, the authors used a dataset with two immunosuppressants (tacrolimus and cyclosporin). The primary task was investigating critical risk factors associated with early transplant rejection. For this, the censored Kaplan-Meier survival estimation method was used. Our study shows a pairwise correlation between taking and not using a particular immunosuppressant. Therefore, the correct choice of immunosuppressive drugs is necessary to improve the prognosis of transplant survival.

1. Introduction

Studies of organ transplantation show that recipients often do not know all the possibilities of transplantology. There is a need to improve the accumulated clinical and therapeutic data to improve the evidence base for immunosuppressive therapy to prolong graft function. In 2021, more than two hundred kidney transplants were performed in our country, 41.9% of which were from cadaver donors. At the same time, the total estimated need for such transplantation is 13.5 thousand per year. Today, patients with end-stage renal failure undergo hemodialysis, less often peritoneal dialysis, which becomes a life-long procedure for them. The state spends UAH 200–300 thousand on hemodialysis for one patient per year and provides this procedure to 30% of those who need it. In the European Union, most such patients undergo hemodialysis only when finding a donor kidney [1,2].

Immunosuppression is one of the critical factors for a successful transplant and the patient's continued health. Immunosuppressive therapy is complex, challenging, and has on-target and off-target side effects. But it is key to successful allotransplantation. This article analyzed the critical classes of immunosuppressants used in renal transplantation, highlighting mechanisms of action and typical clinical applications [1]. Supportive immunosuppressive therapy after kidney transplantation should last a certain time. If necessary, the appointment of various combinations of drugs and the selection of the optimal protocol of immunosuppression, which considers individual characteristics and accompanying pathological conditions in a specific patient with the appropriate conversion of drugs, are indicated. In medical practice, a combination of drugs of two main classes are used: calcineurin inhibitors (tacrolimus, cyclosporin) and derivatives of mycophenolic acid (cellsept or mifortic). Azathioprine is also included in the second group of drugs of choice, although it is used much less often due to the better effectiveness of mycophenolic acid drugs [3].

The main means of immunosuppressive therapy are calcineurin inhibitors, particularly cyclosporin A. This drug has been an immunosuppressant since 1986 and is usually prescribed twice daily. The mechanism of action of cyclosporin A consists of the reversible inhibition of interleukin-2, which activates T-cells. These characteristics ensure no drug effect at the end of its administration. Because cyclosporine A is nephrotoxic, it is important to monitor creatinine levels during therapy [1].

The following representative of calcineurin inhibitors is tacrolimus, introduced in 1994, and has ten times more pronounced inhibitory effect than cyclosporine A. The drug's mechanism of action is identical - the reverse inhibition of interleukin-2. Tacrolimus has a narrow therapeutic window and nephrotoxicity, so it is indicated for creatinine control. Additionally, while taking tacrolimus, a diabetogenic effect due to

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effects on the islets of Langerhans may be observed. The combination of tacrolimus with corticosteroids has the maximum impact on the glucose level and is the main reason for developing post-transplant diabetes [1,3,4]. The second group of drugs, which is used for immunosuppression, includes two representatives: mycophenolate mofetil, which is mainly adsorbed in the stomach, and mycophenolic acid, which is adsorbed in the small intestine and has advantages in drug exposure compared to gastric adsorption. The primary mechanism of action is the inhibition of purine synthesis, mainly in T- and B-lymphocytes, as well as the inhibition of T-cell response. As a rule, these drugs are prescribed twice a day. The side effects of mycophenolic acid derivatives include leukopenia, thrombocytopenia, anemia, and gastrointestinal disorders [1,4].

The main objective of this study is to use the Kaplan-Meier method to independently confirm key factors of risk associated with early transplant rejection based on changes in the blood concentration of the main immunosuppressive drugs (cyclosporin and tacrolimus) after transplantation. This paper has considered possible transplant rejection tasks within the first 30 days after transplantation.

2. State-of-the-arts

Recently, in many countries, there has been an increase in the use of tacrolimus and mycophenolic acid preparations compared to the use of cyclosporine and azathioprine as the main immunosuppression for the treatment of acute rejection crisis. Monoclonal antibodies (basiliximab) are also preferred over polyclonal antibodies (thyroglobulin) in treating acute rejection. [5].

Improvements in kidney transplant outcomes in recent times have been attributed to more effective immunosuppressive strategies. Thus, the development of experience in treating immunomedicaments is key to the success of organ transplantation. This briefly reviews maintenance immunosuppressants after kidney transplantation. It also presents the most commonly used treatment protocols based on patient and donor risk for health [1,3].

Despite significant improvements in short-term kidney transplant survival over the past 30 years, long-term transplant survival remains virtually unchanged in most recipients, averaging 10–15 years of transplant function. Because calcineurin inhibitors (tacrolimus and cyclosporin) have various side effects, including nephrotoxicity, researchers are working on the development of new protocols that can preserve the function of the renal allograft and minimize the side effect of immunosuppressants, which is associated with an increased risk of transplant rejection.

Modern protocols should have recommendations that avoid the long-term use of glucocorticosteroids and minimize the dose of calcineurin inhibitors, with their subsequent replacement by rapamycin inhibitors and mycophenolic acid drugs. In recent years, it has been determined that chronic alloimmune organ damage, rather than chronic immunosuppressant nephrotoxicity, is the main factor in late renal allograft failure [4,6,7].

Complete abstinence from calcineurin inhibitors (CNI) seems inappropriate now, as other immunosuppressants such as Rituximab are required to prevent rejection, which is often accompanied by higher rates of infection and unacceptably rates of acute rejection transplant when avoiding CNI. In some articles, discontinuing CNI in adults receiving renal allografts with stable or reduced graft function was associated with improvement in renal function; however, this came at the cost of a higher rate of acute rejection in 15% of recipients [8].

The North American Registry of Pediatric Renal Research and Collaborative Research (NAPRTCS) reported the most popular immunosuppressant protocol, which included CNIs in combination with mycophenolate mofetil and glucocorticosteroids: 91.4% and 87.8%, respectively, of patients with a functioning graft after 1 year and 59, 1%; 53.3% through 5 years after kidney transplantation.

Treatment with immunosuppressants without calcineurin inhibitors or induction therapy with mycophenolic acid drugs is not possible. It requires further long-term studies to determine the possible time of transplant rejection and preservation of kidney function in both kidney and extrarenal transplantation. [8]. [9]. As noted above in the review, calcineurin inhibitors reduce the incidence of early acute rejection but do not improve long-term allograft survival. Because of their nephrotoxicity, the research focus has shifted to regimens without calcineurin inhibitors or with minimal calcineurin inhibitor doses. Costimulatory blockade with belatacept, a second-generation CTLA4-Ig variant with higher avidity, has emerged as part of a regimen of non-calcineurin inhibitor protocols. Belatacept has demonstrated a higher glomerular filtration rate than calcineurin inhibitors, albeit with an increased risk of early and histologically severe rejection [7,9].

If patients tolerate conversion from CNI to inhibitors rapamycin, it may be preferred as a maintenance immunosuppressant after renal transplantation. This conversion may be sufficient if used for some time after CNI [10]. It is unknown whether mTOR inhibitors differ in their effects on survival of renal function, as the evidence base is shallow based on a small study with only a three-month follow-up [11].

Most often, CNI is combined with corticosteroids and a proliferation inhibitor, mycophenolic acid (MPA), either less often azathioprine (AZA), because MPA is believed to have a more substantial immunosuppressive effect than AZA and a lower risk of acute rejection and side effects compared to AZA. Still, treatment with MPA is more expensive [10]. Registry data show that the frequency of acute rejection is steadily decreasing. Approximately 10% to 35% of kidney recipients will experience at least one acute rejection episode during the first year after transplantation. Treatment options include using a polyclonal and monoclonal antibody, pulse steroid therapy, modification of background immunosuppression, or a combination of these options.

As shown above, current immunosuppressive protocols used in renal transplantation are sometimes ineffective and pose significant mortality risks. Cell therapy is a promising alternative for prolonging graft survival while minimizing the toxicity of immunosuppressant treatment. Regulatory T cells and macrophages were added to the induction regimen, allowing lower doses of immunosuppressive drugs to be used without increasing graft rejection risk [10]. Induction of tolerance during transplantation can avoid the long-term side effects of immunosuppressive treatment.

But tolerance induction is not used in standard clinical practice due to the high cost of the study [11,12]. However, in the future, mathematical prediction of transplant survival remains one of the high levels of evidence. In addition to the classical method of predicting transplant rejection, newer and more accurate methods for predicting transplant rejection have been developed [13,14].

The year 2020 presented significant challenges to the field of kidney transplantation. After increasing each year since 2015 and reaching the highest annual count in 2019, the total number of kidney transplants decreased slightly, to 23,642, in 2020. The decrease in whole kidney transplants was due to a reduction in living donor transplants; the number of deceased donor transplants rose in 2020. The number of patients waiting for a kidney transplant in the United States declined slightly in 2020, driven by a slight drop in the number of new candidates added in 2020 and an increase in patients removed from the waiting list owing to death-important patterns that correlated with the COVID-19 pandemic. Due to the pandemic-related disruption of living donations in the spring of 2020, the number of living donor transplants in 2020 declined below annual counts over the last decade. In this context, only a small proportion of the waiting list receives living donor transplants each year, and racial disparities in living donor transplant access persist. As graft and patient survival continue to improve incrementally, the total number of living kidney transplant recipients with a functioning graft exceeded 250,000 in 2020. Graft survival continues to improve, with superior survival for living donor recipients versus deceased donor recipients [15].

3. Materials and methods

This study used data from a retrospective review of 152 disease hystories of recipients who were in an inpatient or outpatient treatment after the first kidney transplant in the Nephrology and Dialysis Department of the Lviv Regional Clinical Hospital from 1992 to 2020 year. The collected data included information on basic clinical and laboratory parameters and methods of immunosuppressive therapy in these recipients 30 days after kidney transplantation. The retrospective analysis of the report was carried out through the analysis of the recipient's disease history from the department of nephrology and dialysis in the archive of Lviv Regional Clinical Hospital during the first trimester of 2021.

Laboratory examination methods for determining the concentration in the blood of the main immunosuppressive drugs (cyclosporine and tacrolimus) were performed in the central laboratory of the KNP "Lviv Regional Clinical Hospital." It was conducted 24 h before and after transplantation using Abbott reagents (ARCHITECT Whole Blood Precipitation Reagent) to the corresponding above-specified immunosuppressants.

3.1. Statistical processing of results

We have created analysis tables in the Statistica 6.1 and Excel (Microsoft Office 2016) programs to conduct [16,17] a statistical analysis of the results of our study. We entered the collected primary data on the reception of immunosuppressants by recipients within 30 days after transplantation. The software R-studio v.1.1.442 was used to process these obtained statistical data. First, we determined the normality of the distribution in the obtained sample populations using the Shapiro-Francia test. The results obtained by us were depicted in the form:

- values of the average and their standard deviations (M ± SD) - with a Gaussian distribution,
- sample medians, 25th, and 75th percentiles: Me [25%; 75%] - in a non-Gaussian distribution,
- sample share (%).

In order to evaluate the probability of the difference in the obtained results in the comparison groups, the following was used:

- odd *t*-test - for two groups with Gaussian distribution;- Mann-Whitney *U* test – for two groups with a non-Gaussian distribution;
- criterion χ^2 (chi-square) – when comparing sample proportions.

The difference between the groups was considered reliable at $p < 0.05$.

The censored Kaplan-Meier method [13] was used to study cumulative graft survival among patients. Determination of the significance of the difference in the difference in survival levels in individual groups was carried out using the logarithmic rank coefficient [18].

4. Results and discussion

The results of the evaluation of clinical and laboratory data are described in our previous work [14]. These recipients received HLA-compatible kidney allografts from donors, their first- and second-line relatives in Ukraine. Among the 152 recipients, there were 64 (42.1%) female recipients and 88 (57.9%) male recipients with an average age of 32.6 ± 8.7 years (minimum and maximum age range was 18–60 years) at the time of kidney transplantation.

Kidney transplantation was performed in 6 transplantation centers of Ukraine in 79.6% of patients and in other countries of Europe and Asia in 20.4% of recipients. 86.2% of patients received a kidney from a family donor; all donors were from Ukraine, 13.8% of recipients received a cadaver kidney. An acute rejection crisis occurred in 13.2% of patients, with cessation of graft function during the perioperative period. Patients after transplantation were observed in the department of nephrology and hemodialysis of the Lviv Regional Clinical Hospital.

All patients with a kidney transplant from a relative had stage V chronic kidney disease. The causes of end-stage renal failure were:

- chronic glomerulonephritis - 99 (65.1%) patients,
- malformations of the urinary system - 23 (15.1%) patients,
- systemic connective tissue disease - 9 (5.9%) patients (systemic lupus erythematosus - 4, systemic scleroderma - 1, Sharp's disease - 1 and rheumatoid arthritis – 1, systemic vasculitis −1),
- type 1 diabetes - 9 (5.9%) patients,
- chronic pyelonephritis - 12 (7.9%) patients.

Among 152 primary transplant patients: I (0) blood group was 48 (31.6%) patients, II (A) group - 9 (44.1%) patients, III (B) - 26 (17.2%), IV (AB) - 11 (7.2%). Rhesus factor was positive - 137 (90.2%) patients. 93 (61.2%) were on chronic dialysis, 14 (9.2%) on peritoneal dialysis, and 59 (38.8%) were without dialysis.

All studied patients received immunosuppressive therapy. Among this group of patients, 30 (19.7%) patients had a low immunological risk of transplant rejection. It is due to first transplantation, lack of hemodialysis before transplantation, young age, body weight matching of the donor organ with the recipient organ, negative cross matches, and a small number of match cities, etc. Therefore, induction immunosuppressive therapy in the form of basiliximab, thyroglobulin, and solumedrol was not used for these recipients. According to the protocol, the other 122 (80.3%) recipients received this immunosuppressive therapy. The risk of not having induction immunosuppression far outweighs the risks associated with its administration and is desirable even in patients at low immunological risk. Induction immunosuppression should be individualized and thus vary from patient to patient [19].

Medrol, tacrolimus, cyclosporine, myfortic or mycophenolic acid, everolimus, and azathioprine were used among the supportive immunosuppressive therapy in these recipients. The most used triple maintenance immunosuppressive treatment protocols within 30 days after transplantation in these patients were medrol+tacrolimus+myfortic - 100 (65.7%) and medrol+cyclosporine+myfortic - 52 (34.3%) recipients. Other drugs in the protocols were used in isolated cases due to low efficiency and many side effects. The concentration of drugs between the C0 and C2 periods in the blood after transplantation was determined for cyclosporine and tacrolimus since, among other immunosuppressants, there are no significant fluctuations in the concentration of the drug between the C0 and C2 periods. A wide range of immunosuppressive therapy and protocols allows individual planning of the initial regimen according to the immunological risk status of individual patients. Pre-transplant risk assessment can include many factors, but there is no clear consensus on which parameters to consider and their relative importance. In general, younger patients are known to have a higher risk of acute rejection, compounded by a higher rate of nonadherence in adolescents [20].

In our study, the Kapplan-Meier survival curves in the perioperative period (0–30 days) were as follows. In the group of patients (65.7%), who took tacrolimus after transplantation, the survival results were worse ($p = 0.5$) but without significant difference than in the group of patients (34.3%), who did not take tacrolimus (Fig. 1). There was also no significant difference between the indicators of age and gender ($p > 0.05$).

According to the blood cyclosporine concentration indicators, a significant difference ($p = 0.048$) was established between the groups of patients who took cyclosporine (33.6%) and the group of patients who did not take cyclosporin (66.4%) due to better survival results in the first group (Fig. 2).

No significant difference ($p > 0.05$) was established between the transplantation in Ukraine and in other countries of the basic metabolic

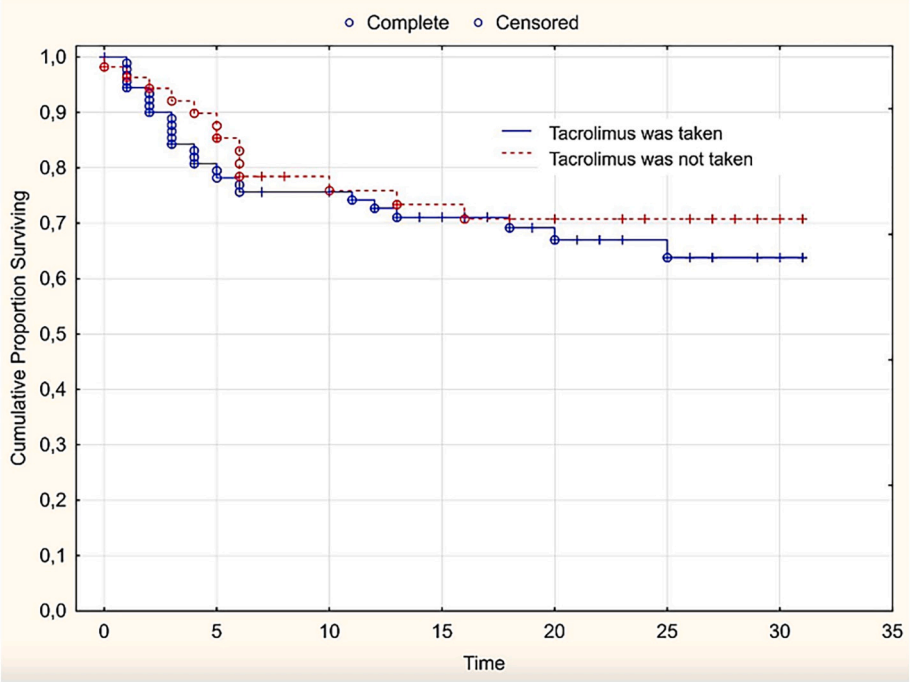

Fig. 1. Assessment of graft function depending on the use of tacrolimus in the group of patients with primary transplantation.

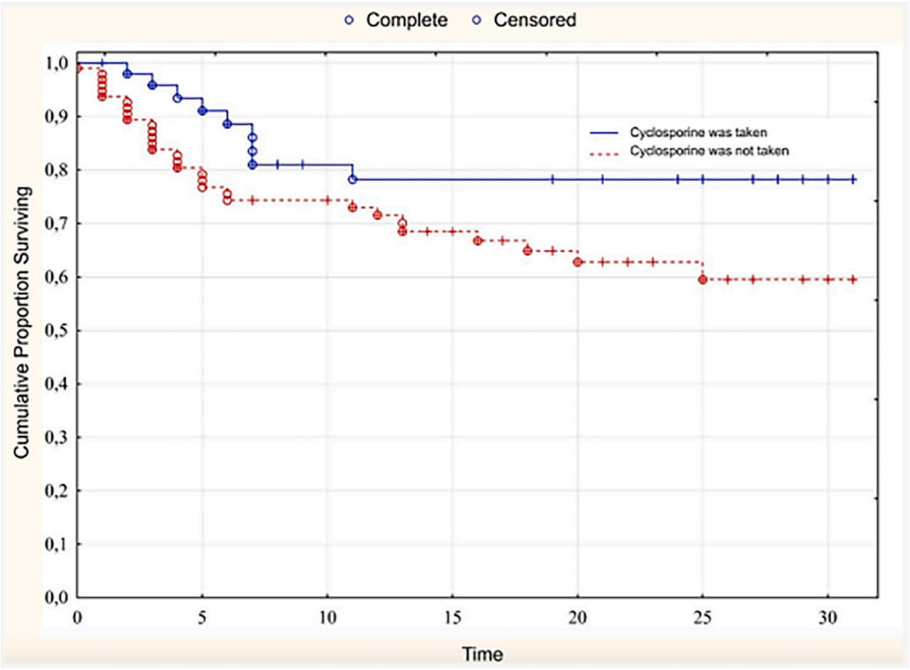

Fig. 2. Assessment of graft function depending on the use of cyclosporine in the group of patients with primary transplantation.

panel analysis. In addition, no significant difference was found between cadaveric and family material in the results of transplant survival ($p > 0.05$).

Also, graft survival at 1-month post-transplant is dependent on donor-related, recipient-related, donor-recipient compatibility, and *peri* – and post-operative factors [18].

T-cellular mediated response (TCMR), Donor Specific Antibody (dnDSA) - and Antibody-mediated response (AMR) is on the continuum of the alloimmune response. T-cellular mediated response frequently precedes the development of Donor Specific Antibodies. Furthermore, reports have documented that dnDSA-associated AMR occurs later, has a higher rate of graft loss, and is frequently manifested as a mixed TCMR/AMR rejection. Compared to memory-associated AMR, it is typically show a pure AMR phenotype, occurs early posttransplant, and is more responsive to therapy [21]. Thus, the alloimmune response cannot be separated into cellular or antibody-mediated but should be considered a continuous process with the dominance of different components at various time points post-transplant.

Immunosuppressive medication nonadherence has emerged as the primary cause of dnDSA formation. Maintaining adequate baseline

immunosuppression, particularly a calcineurin inhibitor (CNI), is key to preventing dnDSA formation. When comparing CNIs, recipients treated with cyclosporin-based therapy have a 2.7-fold higher incidence of dnDSA development than tacrolimus-based therapy [22].

Alternatives to CNI-based therapy are being sought to eliminate its side effects for kidney transplantation recipients (e.g., nephrotoxicity and neurotoxicity). A recent randomized control trial comparing belatacept with cyclosporine and tacrolimus showed no difference in dnDSA formation or AMR rates at 1 year [23,24]. The estimated glomerular filtration rate (eGFR) was significantly higher with belatacept compared with tacrolimus, but so was the incidence of biopsy-proven TCMR. However, the short-term follow-up may limit any conclusive interpretation concerning dnDSA development or long-term outcomes, and a follow-up of at least 5 years may be needed [25].

Future research will be conducted to create accurate prediction models based on machine learning algorithms or artificial neural networks. We have plans to use SGTM neural-like structure and its modifications to solve this problem. For example, using the input-doubling methods [26] based on SGTM with rbf input extension or some modifications of the GRNN-based approaches [27] is logical. Also, future investigations will focus on patients' long-term outcomes and graft survival at 1, 3, 5- years after transplantation.

5. Conclusions

This paper substantiates the choice of optimal immunosuppression schemes and a transplanted kidney survival prognosis within a month after transplantation. We apply the Kaplan-Meier method when using one or another triple immunosuppressive therapy.

We have established that in the perioperative period, the concentration in the blood of two key immunosuppressants, which affect the survival of the kidney transplant, are calcineurin inhibitors: cyclosporin and tacrolimus. Thus, based on the concentration of these drugs in the blood, it is possible to predict the first signs of possible rejection by performing these tests.

Our study shows a pairwise correlation between groups of recipients who did and did not take the corresponding immunosuppressant. Therefore, to improve the quality of the prediction model, it is necessary to choose the right immunosuppressant, dosage, and concentration in the blood.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Dataset is available on https://figshare.com/articles/dataset/Organ_transplantation/14906241 (accessed on Aug 06 2022).

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