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Survival of living-related kidney graft recipients in the era of modern immunosuppressive treatment

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BACKGROUND AND OBJECTIVES: Currently, there is no consensus about immunosuppressive therapy following kidney transplantation. Acute rejection rates and allograft survival rates are the clinical outcomes traditionally used to compare the efficacy of various immunosuppressive regimens. Therefore, we conducted this study to evaluate whether patient survival rates improved in the era of modern immunosuppressive treatment during living-related kidney transplantation.

DESIGN AND SETTING: Retrospective cohort study in a university-based tertiary internal medicine teaching hospital performed between 1999 and 2009 and patients followed up to 7 years.

PATIENTS AND METHODS: Survival rates were assessed in 38 patients receiving basiliximab and mycophenolate mofetil (regimen A) and 32 patients receiving antithymocyte globulin and azathioprine (regimen B). The rest of the regimen (cyclosporine A and steroids) remained the same. A secondary end point was acute rejection episode.

RESULTS: Seven-year survival rates were 100% and 72% (*P*=.001) and 7-year acute rejection-free survival rates were 82% and 53% (*P*=.03), in groups A and B, respectively.

CONCLUSION: Long-term survival after living-related kidney transplantation has improved in the era of modern immunosuppressive treatment.

Potent immunosuppressive therapy in kidney transplantation has lowered rates of acute rejection,[1] but despite significant reduction in acute rejection rates[2] and improvements in 1-year kidney allograft survival rates,[3] the rates of chronic graft loss after the first year remain substantial and may not have improved over the last decade.[4] Immunosuppressive protocols include induction and maintenance immunosuppressive therapy. Induction immunosuppression is intense prophylactic therapy used at the time of transplantation to prevent acute rejection early. There are two induction strategies. The first one employs high doses of conventional immunosuppressive agents such as a calcineurin inhibitor cyclosporine A (CsA) or tacrolimus; corticosteroids; and antimetabolite mycophenolate mofetil (MMF) or azathioprine (AZA). The second strategy is the newer one and includes antibodies against T-cell antigens in combination with lower

doses of conventional agents. The antibodies are perioperative polyclonal or monoclonal antibodies. Polyclonal antibody is antithymocyte globulin (ATG) obtained by immunization with human thymocytes of horses (ATGAM) or rabbits (thymoglobulin). Monoclonal antibodies are OKT3, which is directed against the CD3 antigen; alemtuzumab (against CD52); and IL-2 receptor antibody (IL2RAb) daclizumab or basiliximab (BX). In 2006 the most frequently used antibody in the USA was thymoglobulin (42%), followed by basiliximab (18%), daclizumab (11%), alemtuzumab (10%), ATGAM (1%), OKT3 (1%) and none (21%).[5]

The optimal maintenance immunosuppressive therapy in renal transplantation is not established either.[6] It includes corticosteroids, AZA, MMF, mycophenolate sodium (myFortic), CsA, tacrolimus, everolimus and rapamycin (sirolimus).[7-9] In the United States, in 2006 corticosteroids were used in 68%, tacrolimus in 82%,

CsA in 12%, MMF in 76%, mycophenolate sodium in 12%, AZA in 0.9%, sirolimus in 8% and everolimus in 0.5% of patients.[10] The antibodies reduced the rate of acute rejection, but they did not improve long-term transplant outcomes.[11] Also, maintenance immunosuppressive regimens improved 1-year allograft survival, but the incidence of allograft loss over time remained significant.[2] IL2R antibodies were associated with higher rates of acute rejection, and the combined end point of graft loss, death and all-cause mortality in comparison with other antibodies, and currently there is no consensus for induction therapy following renal transplantation.[5] Given the currently available evidence, AZA and MMF appear to be similar in terms of acute rejection rates and long-term allograft survival rates, which are the clinical outcomes traditionally used to compare the efficacy of various immunosuppressive regimens.[6] Therefore, we conducted this study to evaluate whether patient survival rates after living-related kidney transplantation improved with an immunosuppressive regimen consisting of the combination of IL2RAb basiliximab and mycophenolate mofetil as opposed to that of antithymocyte globulin and azathioprine.

PATIENTS AND METHODS

We conducted a retrospective cohort study comparing two immunosuppressive regimens in a university-based tertiary internal medicine teaching hospital in the town of Tuzla, Bosnia and Herzegovina. The inclusion criterion was that patients were transplanted in the period from 1999 until 2009, and patients were excluded if donors were deceased. The primary endpoint was patient survival and the secondary endpoint was acute rejection episode.

Regimen A comprised the modern immunosuppressive treatment that involved the introduction of humanized IL2RAb (basiliximab 20 mg IV bolus dose on days 0 and 4) and MMF (2 g/d in divided doses) introduced at our center in September 2002 while regimen B comprised ATGAM (15 mg/kg/d IV within 48 hours of transplant and continued treatment for up to 14 days) and AZA (2 mg/kg), respectively. The rest of the regimen remained the same (CsA and steroids). Immunosuppressive regimens were represented as nominal variables (regimens A and B). Patients on regimen A received their transplants from September 2002 until September 2009; and those on regimen B, from September 1999 until September 2002. Two patients were switched from CsA to tacrolimus 1 month post-transplant, 1 in each group. There were 2 re-transplants and 1 lost to follow-up, both in group A.

Outcome variables were patient survival and rejection-free survival expressed as continuous variables of the time to reach the events. Statistical analysis was performed using StatsDirect statistical software, version 2.7.2 (StatsDirect Ltd., Cheshire, UK). To test the differences in quantitative variables between the independent groups with normal distribution, independent sample t tests were done. To test the differences in discrete variables between the independent groups, chi-squared and the Fisher exact tests were done. Patient survival and rejection-free survival rates were assessed by Kaplan-Meier analysis using the log-rank test. P values <.05 were taken as the level of statistical significance and were reported using one-sided and two-sided tests to estimate whether the newer regimen was better or whether the two regimens differed, respectively.

RESULTS

During the study period, 9 patients died—2 of myocardial infarction, 1 of dissecans aneurysm, 2 of bleeding from renal arteries, 2 of liver cirrhosis, 1 of sepsis from endocarditis and 1 of acute pancreatitis (participants flow chart) (**Figure 1**). Patients survival rates (in %) after 1, 2, 3, 4, 5, 6 and 7 years were 96%, 96%, 96%, 89%, 87%, 87% and 83%, respectively. Seven-year survival rates in patients on two immunosuppressive regimens are shown in **Figure 2**. Patients survival rates for various periods (in years) with various immunosuppressive regimens are listed in **Table 1**. Risk factors for death that are not influenced by IL2RAb and MMF are listed in **Table 2**. Seven-year rejection-free survival rates in patients on two immunosuppressive
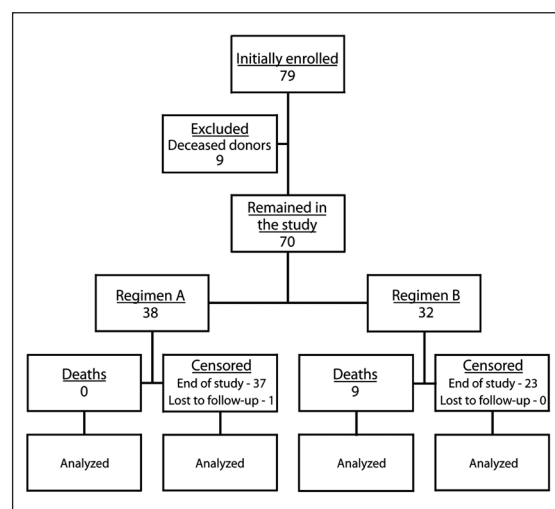

Figure 1. Flow of participants through study.
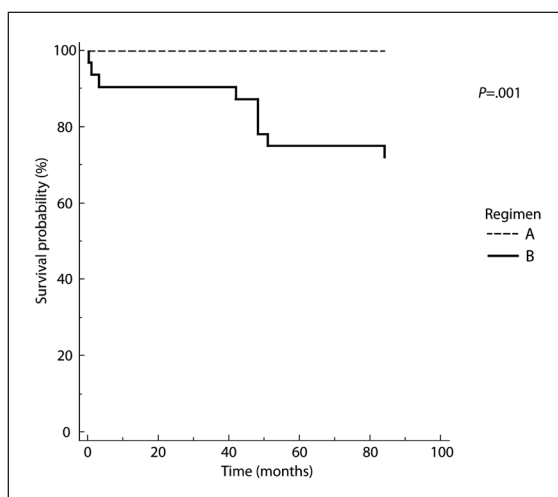
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Figure 2. Seven-year survival rates in patients on two different immunosuppressive regimens. Regimen A — IL-2 receptor antibodies, mycophenolate mofetil, cyclosporine A and steroids; regimen B — antithymocyte globulin, azathioprine, cyclosporine A and steroids.

regimens are shown in **Figure 3**. Rejection-free survival rates for various periods (in years) with various immunosuppressive regimens are listed in **Table 3**.

DISCUSSION

Our results show that long-term survival rates and rejection-free survival rates were better in the group receiving combination of IL2RAb and MMF, as opposed to the group receiving ATG and AZA, unlike the studies reporting no benefit of separate effects of other antibodies as compared to IL2RAb,[5,12] which may be due to paucity of reports on the effects of MMF and AZA on patient survival rate.[6]

Our sample comprised patients from a single center, resulting in our study being carried out with a limited number of participants. Given this limitation, we focused our attention on tight control of all known risk factors that could have possibly biased the results obtained. Patient survival after renal transplantation varies depending upon the source of the allograft, patient age and the presence and degree of severity of comorbid conditions.[4] Comorbid conditions are coronary disease prior to transplantation,[13,14] diabetes mellitus,[15,16] hypertension and hyperlipidemia,[4] and obesity.[17,18] Other possible contributing factors include gender, race and degree of immunosuppression. The level of overall immunosuppression used for induction therapy, maintenance therapy and the treatment of acute rejection episodes is a major risk factor for post-transplant infection, rather than the use of a specific immunosuppres-

Table 1. Survival rates for various periods according to immunosuppressive regimens.

Periods (years)	Regimen A (%)	Regimen B (%)	*P* (one-sided)
1	100	90.6	.04
2	100	90.6	.04
3	100	90.6	.04
4	100	78.1	.003
5	100	75	.002
6	100	75	.002
7	100	72	.001

Regimen A — IL-2 receptor antibodies, mycophenolate mofetil, cyclosporine A and steroids; regimen B — antithymocyte globulin, azathioprine, cyclosporine A and steroids.

Table 2. Distribution of risk factors for death among the groups on different immunosuppressive regimens.

Risk factors	Regimen A	Regimen B	*P* (two-sided)
Recipient age, mean (SD) (years)	29.8 (9.3)	33.2 (8.1)	.10
Recipient sex, males/females	23/15	23/9	.45
Diabetes mellitus, yes/no	3/35	2/30	>.95
Coronary heart disease, yes/no	2/36	3/29	.65
Body mass index, mean (SD) (kg/m²)	20.4 (3.5)	20.9 (3.2)	.62

Table 3. Acute rejection-free survival rates for various periods according to immunosuppressive regimens.

Periods (years)	Regimen A (%)	Regimen B (%)	*P* (one-sided)
1	86	80	.23
2	82	62	.05
3	82	58	.04
4	82	58	.04
5	82	53	.03
6	82	53	.03
7	82	53	.03

Regimen A — IL-2 receptor antibodies, mycophenolate mofetil, cyclosporine A and steroids; regimen B — antithymocyte globulin, azathioprine, cyclosporine A and steroids.

sive agent.[4] However, in our study, the use of a specific immunosuppressive agent proved significant.

Due to the limited number of deaths (n=9), we were unable to adjust the survival analysis for all risk factors, because for every variable included in a multi-

variable Cox model, a minimum of 10 (better, 20) events should have been observed.[19] However, the nature of the relationship between the explanatory variables and the outcome in our study hardly necessitated adjustments, because immunosuppressive therapy had an influence on a number of widely known risk factors. Confounders should not be adjusted for in a multivariate analysis as long as they are on a causal pathway between the predictor and the outcome.[20] Thus, immunosuppressive therapy influences acute rejection episodes, hypertension, hyperlipidemia and infection. Since infections are the leading cause of mortality in the early post-transplant period, infection and allograft dysfunction caused by rejection are closely interrelated through the use of immunosuppressive therapy.[21,22] Therefore, these factors should not have been adjusted for.

Risk factors for death that are not influenced by immunosuppressive treatment and that necessitate consideration of adjustment are listed in Table 2. These factors were equally distributed between the groups of participants, hence they were unlikely to have confounded the result obtained. The source of the allograft was controlled for by excluding deceased donors from the analysis; race was controlled for by including white participants only; and 'medical center' factor was controlled for by reporting the results of a single center. The incidence of acute rejection and the time of its occurrence varied with the therapy used for immunosuppression,[23] so no adjustment was necessary.

This study is further strengthened by the fact that there was only one patient lost to follow-up. However, since this was a single-center study, and the number of participants was small, which seems to be a limitation. However, this limitation was to a certain extent nullified by analyzing the patients coming from a single transplant center, thereby minimizing inter-program variability. Another limitation is that the two immunosuppressive
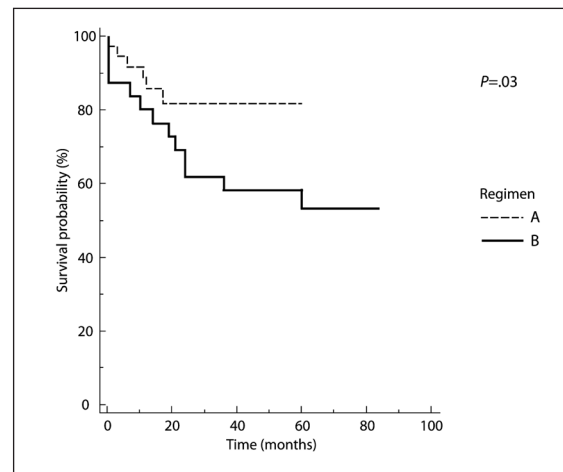

Figure 3. Seven-year acute rejection-free survival rates in patients on two different immunosuppressive regimens. Regimen A — IL-2 receptor antibodies, mycophenolate mofetil, cyclosporine A and steroids; regimen B — antithymocyte globulin, azathioprine, cyclosporine A and steroids.

regimens were not applied concurrently until the introduction of regimen A, so until that time, the unidentified confounders possibly influencing results could not be adjusted for. In general, health management may have improved between the two periods, which could be responsible in part for the differences in survival rates (although only 3 years had passed until the introduction of the new regimen). However, it would have been unethical to try to set up a blind trial as there was already some evidence that the newer method was better.

In conclusion, there is a trend of improvement in patient survival after living-related kidney transplantation in the era of modern immunosuppressive treatment. Larger-scale studies addressing limitations discussed above are needed to establish the association between modern immunosuppressive treatment and improved survival.

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