The long-term outcome of renal transplantation. A 10-year follow-up of 765 recipients

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Short title: The long-term outcome of renal transplantation
Abstract

Introduction. Renal transplantation is a treatment of choice for patients with end stage renal disease. The main goal of the transplant care is to achieve the best long-term patient survival (PS) and graft survival (GS).

Objectives. The impact of various immunosuppression (IS) protocols on PS and GS survival following renal transplantation was investigated.

Patients and methods. This was a retrospective single center cohort study. 765 consecutive adult renal transplant recipients (RTR) transplanted in 1998-2003. Primary endpoints included PS and GS. Secondary endpoints were graft function determined by estimated GFR and the hospitalization length per patient per year.

Results. Ten-year PS and GS rates were 88.6% and 78.7% respectively. The intent-to-treat (ITT) group received IS that was changed later, whereas in the group on randomized therapy (ORT) the same IS protocol was maintained during follow-up. ITT group had significantly better PS and GS than ORT group. ITT patients treated with the combination of tacrolimus (TAC) and azathioprine (AZA), cyclosporine (CSA) and AZA or CSA and mycophenolic acid metabolites (MPA) had significantly better PS than TAC and MPA-treated subgroup. The ORT group receiving AZA in any combination also had significantly better PS than MPA-treated individuals.

Conclusions. Influence of IS protocols on the long-term outcomes vary depending on patient subpopulations. Therefore, treatment recommendations should be individualized. Considering our results and fact that IS solves the rejection-related problems, but nowadays RTR die from cardiovascular diseases, malignancies or infections, thorough internal follow-up is necessary to improve the long-term outcomes of renal transplantation.

Keywords: azathioprine, immunosuppression, internal care, outcome, renal transplantation
Introduction

The main goal of the transplant care is to achieve the best long-term patient survival (PS) and graft survival (GS). Since the clinical application of kidney transplantation in 1954, PS and GS improved thanks to advances in surgical techniques, perioperative and immunosuppression (IS) care [1-4]. However, for the last two decades they have been not improving anymore [4,5]. The growing incidence of IS-related infections, malignancies and cardiovascular comorbidities may explain this. For these reasons the role of IS in the long-term outcome was intensively investigated. On the one hand, the increasing number of renal transplant recipients (RTR) with longer and longer follow-up allow obtaining big data which should enable to identify factors influencing the outcomes [6-8]. On the other hand, many questions as well as many answers still stand out. For example, recommendations of The Kidney Disease: Improving Global Outcomes (KDIGO) related to RTR are supported by level A quality evidence in 2% of them only, while the majority (67%) are graded C or D [9,10]. This is due to a great diversity in relation to donor (eg. extended donor criteria and age), recipient (eg. increasing comorbidities), center experience and protocols of the clinical studies that were included. Nevertheless, many factors affecting the outcomes were established. Some of them, such as age, gender, ethnicity and primary kidney disease cannot be modified at the time of transplantation. In contrast, cold ischemia time (CIT) and renal replacement therapy can be influenced by allocation policies, as can be made the choice of a specific IS scheme by a transplant physician. Therefore, the role of IS in the outcome of today’s renal transplantation is very important. This study aimed to assess the impact of different types of immunosuppressive schemes and other factors on the long-term outcome of single center RTR population.
Patients and methods

This was a single center retrospective study of 765 consecutive adult Caucasian RTR transplanted in 1998-2003. Their follow-up duration was 10 years and their post-transplant care was centralized in one transplant unit [11]. The survival function could not be analyzed in 9 RTR (1.2%), in whom the outcome data were missing (Table 1). In 608 RTR (79.5%), who were followed-up and in 148 patients (19.3%), who were lost to follow-up the Kaplan-Meier estimate with right-censored data was computed.

In most patients a standard triple calcineurin inhibitor (CNI) based IS consisting of tacrolimus (TAC) or cyclosporine (CSA), steroids and one of the antimetabolites: azathioprine (AZA) or mycophenolic acid metabolite (MPA) was administered. Only 1% of RTR did not receive CNI, 3.8% received no steroids and 12.9% were antimetabolite free. Proliferation signal inhibitors were used in 8.8% of RTR: everolimus in 14 RTR (1 in combination with TAC and 13 with CSA), sirolimus in 53 RTR (31 in combination with TAC, 13 with CSA and 3 with MPA). Induction therapy with anti-thymocyte globulin (rabbit-ATG) or anti-CD25 antibodies (daclizumab or basiliximab) were used in 15.9% of patients. Demographic data, laboratory results and adverse events were analyzed based on patients’ medical records. For this type of retrospective study formal consent and the institutional research committee was not required.

At first, all consecutive RTR were evaluated. Then, we divided them in two groups: 1) patients without induction, and 2) patients, who received induction therapy, to separate high immunological risk individuals including second or third RTR. Double organ transplant recipients were excluded. In all RTR and no induction RTR group, two subgroups were defined: 1) intent-to-treat (ITT), and 2) on randomized therapy (ORT). Patients who received transplanted organ and at least one dose of intended IS, but this therapy was changed at some point of the follow-up were ITT group. RTR in whom initial IS was maintained throughout the
entire follow-up period were ORT group. The number of patients in the subgroups is presented in table 2.

Primary endpoints were PS and GS. Secondary endpoints included graft function, assessed by estimated glomerular filtration rate (eGFR, calculated with CKD-EPI equation) at every post-transplant year; and the length of the hospitalization per patient per year, as an indirect measure of the adverse events (AE) [12]. The influence of the IS on the primary and secondary endpoints was analyzed. Firstly, by comparing the outcomes in patients treated with one of the four pairs of immunosuppressive drugs: CSA+AZA vs. CSA+MPA vs. TAC+AZA vs. TAC+MPA. Secondly, by comparison of patients treated with AZA to those receiving MPA (regardless the type of CNI used), as well as patients treated with CSA to those receiving TAC (regardless the type of antimetabolite used).

The relationship of the demographic parameters, age, gender, primary kidney disease, dialysis vintage, HLA mis-match number, use of machine perfusion (MP) and cold ischemia time (CIT) to the primary and secondary endpoints were also studied.

Statistical Analysis

The survival function was computed using the Kaplan-Meier estimate with right-censored data. The survival functions were compared using the log-rank test. To verify if it can be expected that average population results for primary and secondary endpoints (dependent variables) vary between the groups (divided by gender, MP used, CIT or dialysis vintage) the Welch t-test was used. Pearson $\chi^2$ test was used to determine the effect of variables such as immunosuppressive drugs, causes of end-stage renal disease (ESRD), gender or MP on the outcomes. The strength of the association of the variables with graft function and length of hospitalization was expressed by the Pearson correlation coefficient $R$. Significance test for Pearson’s correlation coefficient was performed to assess whether there is a linear relationship between pair of
variables. ANOVA was used to study the association between the groups of patients treated with different immunosuppressive drugs or with different causes of ESRD to renal function. If the result of the variance analysis was significant, then groups were compared using the set of post-hoc Tukey HSD type tests. The differences were considered statistically significant if the p value <0.05.

Results

All 765 RTR were Caucasians in the mean (SD) age of 41.9 (12.8) years at the time of transplantation. Their baseline demographic data, average 10-year serum creatinine and eGFR are summarized in Table 2. As many as 702 RTR (91.7%) received their first transplant and the remaining 63 individuals (8.3%) had prior history of renal transplantation. 718 transplantations were cadaveric (93.9%) and 47 were living related (6.1%). The primary kidney disease was unknown in 447 RTR (58.4%). In the remaining 318 subjects, the leading causes of transplantation were: tubulointerstitial nephritis (9.8%), biopsy proven glomerulonephritis (9.5%), autosomal dominant polycystic kidney disease (9.5%) and diabetic nephropathy (5.1%). The mean CIT (SD) was 25.06 (9.5) hours. 554 kidneys were machine perfused prior to transplantation. The IS changed during 10-year follow-up in 42.2% of all RTR (Table 2). Only 51.2% of patients assigned CSA+MPA remained ORT, in contrast to other subgroups: CSA+AZA 62%; TAC+MPA 57.9%; and TAC+AZA 72.3%, respectively.

The 10-year PS and GS were 88.6% and 78.7% respectively (Figure 1 A, B). The RTR in whom IS changed during follow-up (ITT group) had significantly better PS and GS (Figure 1 C, D). The female gender was also associated with superior PS, when all RTR were evaluated (Figure 1 E). Other variables, such as age, primary reason for ESRD, dialysis vintage, HLA matching, use of MP, CIT or IS protocol had no influence on the primary end points. Renal function was
affected by use of steroids, by the type of antimetabolite used, and correlated with the hospitalization length (Figure S1). The average hospitalization length varied in each consecutive year. It was longest in the first year (37.3 days) and reduced gradually year by year to 1.7 days in the 10th year. All patients had at least one hospitalization related to the post-operative care. Other studied factors did not influence significantly the secondary outcomes.

Patients without induction therapy

After exclusion of patients who received induction therapy 643 RTR were available for analysis. They were all recipients of their first graft, 59.9% of them remained ORT, 17.9% were lost to follow-up and for 0.9% of them the outcome data were missing (Table 2).

The 10-year PS and GS were 87.7% and 78.3% respectively (Figure 2 A, B). Interestingly, the only variable impacting significantly the primary endpoints was the immunosuppression change. Both PS and GS were significantly better in ITT than ORT group (Figure 2 C, D). On the contrary, renal function was significantly better in ORT group (Figure S2 C). Additionally, it was affected by use of steroids, was significantly better in MPA than AZA-treated patients and correlated significantly with the hospitalization length (Figure S2 A, B, D). Other factors such as age, primary cause of ESRD, dialysis vintage, HLA matching, MP or CIT use did not influence significantly primary and secondary outcomes.

ITT subgroup analysis

No induction ITT patients treated with TAC+AZA or CSA+AZA, as well as those on CSA+MPA had significantly better PS than TAC+MPA subgroup (Figure S3 A). Moreover, PS in ITT patients was significantly better in females (Figure S3 B). Other variables had no significant influence on PS and GS in the ITTgroup.
Renal function was significantly better in the steroid-free ITT recipients than in patients receiving steroids and was correlated with the hospitalization length (Figure S3 C, D). The remaining variables had no significant influence on renal function and hospitalizations.

ORT subgroup analysis

The choice of specific IS protocol had no significant influence on patient survival in ORT group (Figure S4 A). However, ORT patients who received AZA (regardless the type of CNI used), had significantly better PS than MPA-treated individuals (Figure S4 B). GS of ORT patients was not associated significantly with any of the studied parameters, whereas graft function was significantly better in these ORT recipients, who received no steroids and correlated significantly with the hospitalization time (Figure S4 C, D).

Discussion

In a large single center RTR population we found that 10-year PS and GS were significantly influenced by the type of IS, but not in the entire patient population. It is the subgroup analysis that revealed the differences. ITT group had significantly higher patient and graft survival rates than ORT patients. Furthermore, subgroup analysis revealed that AZA was superior to MPA as adjunct to CNI-based IS schemes. The significance of the outcome difference between ITT and ORT group was found in both, the entire RTR population and the group, who received no induction therapy. We demonstrated previously that separation of ITT and ORT patients can cause differences in the results, particularly when the follow-up duration was longer [13,14]. Therefore, we suggest that every analysis of the transplant outcome data should include ITT vs ORT comparisons. Moreover, we believe that subgroups identification may help establishing better treatment options and agree with recent opinions concerning patient selection from a position statement paper by O’Connell and colleagues [15]. Our findings did not show superiority of any specific IS combination in the entire RTR population. However, selection of
the patients who received no induction and were ITT revealed significant outcome differences. The ITT subgroups treated TAC+AZA or CSA+AZA or CSA+MPA had significantly better PS than TAC+MPA subgroup, independent from the gender. Moreover, the ORT patients who received AZA had significantly better PS than MPA-treated individuals. Of course, understanding of these phenomena would be better if the events leading to IS conversion were known. Nevertheless, these results indicate that subgroups analysis may lead to different conclusions resulting in more personalized medicine. There is no “one fits all” IS in renal transplantation and it is not surprising that large cohort results do not favor specific drug combinations. Previously, the Collaborative Transplant Study (CTS) registry data analysis revealed no PS and GS differences of RTR treated with any of the four standard IS regimens [6]. Meta-analyses of the randomized trials also did not show superiority of any specific IS protocols [9]. However, it should be underlined that meta-analyses have certain drawbacks. For example, in many studies the long-term outcome data are missing. The enrollment criteria select patients and preclude generalization of conclusions. Furthermore, the outcome reporting quality is debatable. A search for randomized trials of primary IS in kidney transplantation in the Cochrane Renal Group’s Specialized Register 2000–2012 yielded a conclusion that outcome reporting is inconsistent and frequently incomplete. Therefore, published estimates of treatment effects should be evaluated with caution [16]. Our study was retrospective, with all design’s limitations, but population was uniform in ethnicity, single center procedures, post-transplant care and data collection. Moreover, all consecutive RTR were assessed and the lost-to-follow-up rate was low. These factors contribute to the data quality, but also make the results difficult to be translated into general population.

According to the CTS [6] and OPTN/SRTR [7] reports, present RTR receive CNI mostly with MPA, whereas AZA is disappearing from the standard IS protocols. Our results highlighted that still high proportion of RTR may remain on the therapies assigned years ago (CSA+AZA - 62%
and TAC+AZA – 72.3%). Moreover, some RTR may benefit from them. Therefore, AZA deserves reappraisal in the context of long-term outcomes. Good example is an extended 15-year follow-up of a randomized trial, which's short-term results contributed to the shift from AZA to MPA in the late nineties [17]. Authors found no statistically significant differences between the AZA and MPA groups in long-term PS and GS [18]. Moreover, in a recent meta-analysis involving 2987 participants of 16 studies no statistically significant difference for MPA vs AZA treatment was found for all-cause RTR mortality [19]. Given these results, our data and particularly the costs of AZA vs MPA based IS it is reasonable to reconsider old AZA in the modern era of transplantation.

However, immunosuppressive drugs solve the rejection-related problems [20], but it is known from previous reports that nowadays patients die from cardiovascular diseases, malignancies or infections. All mentioned post-transplant problems are in the scope of internal medicine. We think that the structure of the post-transplant care may have even bigger impact on survival, and it is an internal medicine that is the mainstay of the post-transplant care. Internists provide continuous and long-term care for renal transplant recipients. It was previously reported, that the post-transplant outcomes may vary between the countries because of allocation policies, cultural differences influencing preferences for living versus deceased donation, and government-funded health care [4]. For example, Ojo and colleagues found that the adjusted 10-year patient survival after deceased donor kidney transplant was 86% in Spain in contrast to 67% in the United States [21]. Using the CTS database, Gondos and others showed that 10-year unadjusted deceased donor allograft survival rates were superior in Europe (56.5%) compared with the United States (46%, 48% and 34% for whites, Hispanic and African American, respectively) [22]. This can be explained by the fact that in the United States patients lose coverage for IS three years after transplantation, leading to nonadherence in some cases and late allograft loss [23]. In Poland, the IS costs are covered as long it is necessary. In our center
RTR remain long-term under medical care of the same transplant team. In the outpatient clinic patients are routinely consulted by a transplant physician with internal medicine background 4 times per year and additionally in urgent medical conditions. Each patient is assigned to one transplant specialist, who is also involved in their hospital care [11]. It was reported by others that very close life-long follow-up and adequate care delivery to RTR could improve the outcomes [24]. We believe that over 50 years of transplant experience and developing our local care system contributed to the results of renal transplantation. Of course, one must not forget medical reasons for the outcome differences between the countries. For example, diabetes mellitus, one of the diseases most adversely influencing the outcomes. Multiple studies have shown a higher prevalence of recipient ESRD from diabetic nephropathy (DN) in the US than in other countries [4]. Ojo and colleagues reported 24.1% of ESRD from DN among RTR transplanted in US vs 5.6% in Spain [21]. Respectively, Gondos and others found 26.0% in US vs 8.3% in Europe [22]. Our results (5.1%) are comparable to the Spanish data. Given that DN is associated with increased cardiovascular morbidity and mortality, this may help explain better long-term patient survival in our and other European centers.

Gender plays a role in the incidence and progression of a wide variety of diseases and conditions related to transplantation including the pharmacokinetics and the pharmacodynamics of IS [25]. Therefore, its influence on the renal transplantation outcomes was studied. We found that recipients’ female gender is an independent predictor of superior PS both in population of all RTR, as well as in the ITT subgroup. This is an interesting observation, since previous studies revealed no influence on PS and GS rates, when donor or recipient genders were evaluated separately [26]. Only the combination between donor-recipient genders could determine GS and male to female transplantation was better than female to male [27]. Such approach is more practical and could determine allocation of organs for transplantation, whereas our observation has limited predictive use only.
We are aware that our study has several other limitations. The study design was retrospective. The IS modifications details are lacking: how many times the drug protocols were changed, which drug conversions were performed and what exactly the indications for the drug changes were. The data on comorbidities, medicines other than IS and their influence on outcomes was not analyzed, either. Another limitation concerns the possible learning curve for MPA and TAC use. Both drugs were introduced in Poland in the late nineties, so our patient population was probably the first to be treated with these agents. In our opinion, this fact could have influenced the outcomes. Furthermore, our observation that treatment with TAC+MPA in ITT population was associated with the inferior outcomes is limited by a small patient number. Moreover, the cohort in our center is 100% Caucasian and is comprised of most recipients undergoing cadaveric transplantation. As such, it may be difficult to compare it to the non-homogenous e.g. US population, where most of the transplantations are from the living donors.

In conclusion, we confirmed that the influence of IS protocols on the long-term outcomes vary depending on the patient subpopulations. As an example, our results indicated that azathioprine was superior to MPA as adjunct to CNI-based IS in ORT group and to TAC-based IS in ITT group. We suggest reconsidering its return to IS protocols, especially in the economic context. Considering the results of our study, the fact that immunosuppressive drugs solve the rejection-related problems, and previous reports showing that nowadays patients die from cardiovascular diseases, malignancies or infections, thorough internal follow-up is necessary to improve the long-term outcomes of renal transplantation.
Contribution statement

B.F. and K.M. participated in study concept and design, in acquisition, analysis and interpretation of data, in preparing the article and submitting its final version. Both authors equally contributed to this study.

M.F., A.S., M.C., M.D., A.G., R.K., M.K., S.N. and Z.G. participated in the acquisition of data, in revising the article for intellectual content and approved its final version.

L.P. participated in study concept, contributed to data analysis and interpretation, participated in revising the article for intellectual content and approved its final version.

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2. Funders: None.


Conflict of Interest Statement

None declared
References


Table 1. Patients numbers in studied RTR populations.

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<th>ORT</th>
<th>ITT</th>
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<th>Male</th>
<th>No induction</th>
<th>No induction + ORT</th>
<th>No induction + ITT</th>
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<td>n</td>
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<td>%</td>
<td>n</td>
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<td>21.6</td>
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<td>51.4</td>
<td>181</td>
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<td>TOTAL</td>
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<td>422</td>
<td>308</td>
<td>302</td>
<td>463</td>
<td>643</td>
<td>355</td>
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Abbreviations: ITT, intent-to-treat group; ORT, on randomized therapy group.
Table 2. Baseline demographic data and average 10-year renal function in patients’ subgroups.

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<th></th>
<th>All</th>
<th>ORT (55.2)</th>
<th>ITT (40.3)</th>
<th>Induction</th>
<th>No induction</th>
<th>No induction + ORT</th>
<th>No induction + ITT</th>
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<td>Number of patients (%)</td>
<td>765 (100)</td>
<td>422 (55.2)</td>
<td>308 (40.3)</td>
<td>122 (15.9)</td>
<td>643 (84.1)</td>
<td>355 (55.2)</td>
<td>258 (40.1)</td>
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<td>Missing data on ORT / ITT (%)</td>
<td>35 (4.6)</td>
<td></td>
<td></td>
<td>5 (4.1)</td>
<td>30 (4.7)</td>
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<tr>
<td>Sex, male / female</td>
<td>463 / 302</td>
<td>268 / 154</td>
<td>177 / 131</td>
<td>67 / 55</td>
<td>396 / 247</td>
<td>227 / 128</td>
<td>155 / 103</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>42 (12.7)</td>
<td>42.5 (13.1)</td>
<td>41 (12.4)</td>
<td>41 (11.9)</td>
<td>42.2 (12.8)</td>
<td>42.6 (13.1)</td>
<td>41.4 (12.4)</td>
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<td>CIT, hours (SD)</td>
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<td>2.9 (1.2)</td>
<td>3 (1.2)</td>
<td>2.9 (1.3)</td>
<td>3.1 (1.3)</td>
<td>2.9 (1.2)</td>
<td>3 (1.2)</td>
<td>2.8 (1.2)</td>
</tr>
<tr>
<td>Average 10-year eGFR, ml/min (SD)</td>
<td>51.3 (19.1)</td>
<td>52.4 (19.8)</td>
<td>49.7 (16.2)</td>
<td>54.6 (22.3)</td>
<td>50.6 (18.3)</td>
<td>52.1 (19.8)</td>
<td>48.9 (16.2)</td>
</tr>
<tr>
<td>Average 10-year serum creatinine, mg/dl (SD)</td>
<td>1.7 (0.8)</td>
<td>1.7 (0.9)</td>
<td>1.7 (0.8)</td>
<td>1.6 (0.7)</td>
<td>1.8 (0.8)</td>
<td>1.7 (0.9)</td>
<td>1.8 (0.8)</td>
</tr>
<tr>
<td>Machine perfusion, Yes / No</td>
<td>554 / 211</td>
<td>316 / 106</td>
<td>205 / 103</td>
<td>75 / 47</td>
<td>479 / 164</td>
<td>273 / 82</td>
<td>177 / 81</td>
</tr>
</tbody>
</table>

Abbreviations: CIT, cold ischemia time; ITT, intent-to-treat group; MM, mismatch number; ORT, on randomized therapy group. Conversion factor to SI units for creatinine (µmol/l) is: 88.42.
Figure 1. Kaplan-Meier estimates of 10-year patient and graft survival in the entire studied population: cumulatively - A, B; comparison of intent-to-treat vs on randomized therapy - C, D; male to female comparison of patient survival - E.

Abbreviations: see Table 1 and 2.
Figure 2. Kaplan-Meier estimates of 10-year patient and graft survival in patients who received no induction therapy: cumulatively - A, B; comparison of intent-to-treat vs on randomized therapy - C, D.

**Abbreviations:** see Table 1 and 2.