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Low-dose Rituximab and Thymoglobulin Induction With Steroid-free Maintenance Immunosuppression and Protocol Biopsies Improves Long-term Patient and Graft Survival After Kidney Transplantation: Survival and Safety Outcomes in More Than 1100 Patients From a Single Center

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Background. Steroid-free maintenance immunosuppression after kidney transplantation provides acceptable patient and graft survival and minimizes steroid-associated side effects among recipients with a low immunological risk. However, the long-term outcomes of such protocols, incorporating low-dose rituximab and thymoglobulin induction along with protocol biopsies, in non-European populations remains underreported. **Methods.** We retrospectively analyzed 1142 consecutive kidney transplantations conducted at our center from July 2005 to October 2017. Immunosuppression protocol included induction with thymoglobulin and low-dose preoperative rituximab. Maintenance immunosuppression consisted of tacrolimus and mycophenolate mofetil; prednisolone was discontinued on postoperative day 5. Protocol biopsies were carried out at 3 months and at 1, 5, and 10 years after transplantation—in addition to the indicated biopsies. The 12-year patient and graft survival and posttransplantation complications were studied. **Results.** The analysis of outcomes was conducted for 1111 transplant recipients. Patients (70.59%) remained steroid-free at 12 years after transplantation. The patient survival rates at 1, 5, and 12 years were 97.7%, 94.8%, and 92.4%, respectively. The corresponding graft survival rates were 97.2%, 90.9%, and 86.1%, respectively. Biopsy-proven acute rejection occurred in 12.7% of recipients, including 3.5% subclinical rejections. The cumulative incidence of graft loss was 6.56% at 12.3 years. The overall incidence of death was 5.3%. **Conclusions.** Steroid-free maintenance immunosuppression was associated with excellent long-term patient and graft survival rates and reduced incidence of prednisolone-related side effects, despite acceptable rejection rates. Low-dose rituximab with thymoglobulin induction with immediate steroid withdrawal and surveillance biopsies resulted in excellent long-term outcomes in our single-center experience.

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Kidney transplantation remains the cornerstone of therapy in patients with end-stage renal disease. Steroid-based immunosuppression has been the mainstay for the prevention and treatment of acute rejection episodes in kidney transplantation for a long time.[1] However, steroids are associated with a myriad of debilitating adverse effects when used as a part of long-term maintenance immunosuppression after transplantation. Some of the reported side effects include new-onset diabetes,[2] mortality from infections,[3] cataract,[4,5] hypertension,[6] dyslipidemia,[7] growth retardation,[8] lowered bone mineral density (BMD),[9] and osteopenia.[10] An important area of interest in research on kidney transplantation is, therefore, the need to address the paradoxical effects of steroids and optimize their usage in the posttransplantation period.

Historically, several attempts were made to test the benefit-risk profile of steroid-sparing regimens. While protocols involving late steroid withdrawal after kidney transplantation have reported an increase in acute rejection episodes[11-13] and poor graft survival rates,[13,14] immediate steroid withdrawal or steroid-free maintenance immunosuppression protocols have yielded promising patient and graft survival outcomes in low-risk, mostly European populations.[15-17] Protocols with complete steroid avoidance have also reported low rejection rates, better graft survival and function, and acceptable tolerability.[18,19] However, these studies involved a limited number of study subjects, thus limiting the generalizability of their findings. Furthermore, studies reporting the benefits of steroid-sparing protocols in the long-term are also limited.

A retrospective study on a steroid-avoidance immunosuppression protocol conducted among kidney transplant recipients reported a 72% graft survival rate at 7 years after transplantation.[20] A prospective, randomized study of 3 maintenance immunosuppression regimens, all with rapid steroid withdrawal, reported comparable and acceptable 10-year outcomes with all the 3 treatments.[21] Favorable 10-year patient and graft survival rates with reduced incidence of side effects have been reported in another study evaluating steroid-free maintenance immunosuppression after kidney transplantation.[22] In another prospective randomized trial, comparing the cessation of corticosteroids 7 days posttransplantation with long-term low-dose corticosteroid therapy, acute rejection rates were higher in the steroid withdrawal group. However, after 5 years of follow-up, the increased acute rejection rate in the steroid withdrawal group did not result in differences in graft loss; even so, concerns remained regarding the long-term effects of this additional acute rejection burden.[23]

In this context, it may be worthwhile mentioning that low-dose rituximab was not included in induction regimens in any of these long-term studies. Furthermore, none of the long-term steroid-sparing protocols tested earlier included protocol biopsies of steroid-sparing regimens for >10 years after kidney transplantation.

To meet the stated research needs, we sought to report the patient and graft survival rates and tolerability outcomes for 12 years with our treatment protocol (comprising low-dose rituximab with thymoglobulin induction, immediate steroid withdrawal, and surveillance biopsies), through a retrospective cohort evaluation of our database of kidney transplant recipients.

MATERIALS AND METHODS

Patients

All consecutive renal transplantations conducted at our center between July 2005 and October 2017 were included, and the pretransplant and posttransplant data from the medical records of all these patients were retrospectively analyzed. All diabetics, long-standing elderly hypertensives (aged >60 y), and patients with suspected or a history of coronary artery disease had undergone pretransplant myocardial perfusion scan and, if required, coronary angiography and revascularization.

Data Collection

Relevant information was extracted from the medical records of patients who had undergone kidney transplantation at our center during the stated period, using the Statistical Package for the Social Sciences software.

Graft loss was defined as retransplantation, return to dialysis, or death with a functioning graft. New-onset diabetes after transplantation (NODAT) was defined as the new requirement of antidiabetic agents in the posttransplantation period. Leucopenia was defined as a white blood cell count of <2500/mL.[3]

Histological Assessment

As per the standard posttransplantation management protocol at our center, all patients underwent protocol biopsies at 3 months and 1, 5, and 10 years after transplantation. Apart from this, indicated biopsies were done in cases of new-onset proteinuria, hematuria, or rise in serum creatinine that exceeded 0.2 mg/dL from the previous baseline.

Immunosuppressive Regimen

Based on a standard protocol employed at our center, all transplant recipients received a consistent immunosuppression regimen. Thymoglobulin was administered intravenously for induction at a dose of 1.5 mg/kg/day for the first 2 days; the first dose was given intraoperatively. The third dose was given on the fifth or sixth postoperative day when the CD3 count had started rising; the CD3 count was kept below 25/μL in the first week posttransplantation. The dosage range of thymoglobulin (Thymoglobulin, Sanofi) used was 1.5–8 mg/kg/day (mean dose was 4.5 mg/kg). Elderly patients were given a lower dose (≤3 mg/kg/day). Injection rituximab 200 mg intravenous was administered before transplantation to patients at high risk for rejection, such as those with a history of multiple blood transfusions and parous women; and 500 mg intravenous was administered to patients who exhibited donor-specific antibodies (DSA) on single-bead testing and second transplants (retransplantation). However, owing to the favorable outcomes with low-dose rituximab induction, injection rituximab was given before transplantation to all kidney transplant recipients over the past 4 years; overall, 60%–65% of the study cohort received the rituximab injection. Intravenous methylprednisolone was administered at a dose of 500 mg on day 0 followed by intravenous dexamethasone 0.25 mg/kg on day 1 and then reduced by 25% every day till it was rapidly discontinued by postoperative day 5. Maintenance immunosuppression was given using tacrolimus (PanGraf—Panacea) and mycophenolate mofetil (MMF) (CellCept—Roche or Myfortic—Novartis). Tacrolimus trough levels were kept at 8–10 ng/mL in the first

3 months which was gradually reduced to 7.5–8.5 ng/mL by 6 months and maintained at 6–7.5 ng/mL by the end of one year. The target level was slightly higher for patients who were treated for acute rejection. The tacrolimus dose was reduced and everolimus added whenever calcineurin inhibitor (CNI) toxicity was suspected. The target trough levels of tacrolimus were around 3.5–4.5 ng/mL, and everolimus was 4.5–5.5 ng/mL. The dose of MMF was 500 mg twice daily for most of the patients. This was increased to 750 mg twice daily if the weight of the patient was ≥70 kg. However, in patients receiving 750 mg twice daily dose, the dose was reduced to 500 mg twice daily in case of leucopenia.

All rejections were biopsy-proven and treated with 500 mg pulse intravenous methylprednisolone daily for 3 days along with an increased dose of tacrolimus and additional dose of thymoglobulin (1–1.5 mg/kg). Following subclinical or clinical acute rejections, steroids were generally added at a dose of 2.5–5 mg to the immunosuppressive regimen. Antibody therapy, plasmapheresis, and intravenous immunoglobulin were incorporated into the treatment regimen for refractory rejections whenever indicated. Valganciclovir was administered for 60 days for prophylaxis against cytomegalovirus (CMV) infection in all CMV D+/R+ patients. For CMV D+/R– patients, prophylaxis was given for 6 months (1% of patients).

Outcomes

The primary outcomes analyzed in this study included patient and graft survival. The secondary outcomes included graft loss; NODAT; rate of infections, including tuberculosis, BK virus, and parvovirus infections; rate of bone loss; posttransplant malignancy; need for antihypertensives; cardiovascular mortality; and mortality due to infections.

Statistical Analysis

Baseline demographic information has been presented as mean ± SD. Patient and graft survival and overall survival were examined using the Kaplan–Meier (KM) method.

Ethical Considerations

The procedures used for data collection from the kidney transplant recipients' database and measures taken to maintain data confidentiality were reviewed and approved by the Hospital Ethics Committee.

RESULTS

Demographics and Transplant Characteristics

One thousand one hundred forty-two patients underwent live kidney transplantations at our center during the study period. About 2.5% of patients were lost to follow-up. The remaining 1111 transplant recipients were considered for the analysis. The mean follow-up duration was 5.8 years. The baseline characteristics of all the kidney transplant recipients along with human leukocyte antigen matching data are presented in Table 1.

Figure 1 shows the percentage of patients on prednisolone-free treatment for 1–12 years. Patients who required steroids were given a low dose of prednisolone of 2.5–5 mg/day. Steroids were included in the treatment, owing to acute rejections; change from MMF to azathioprine due to intolerability; CNI toxicity; continuation of prednisolone from previous transplantation or prior disease (eg, lupus nephritis); recurrent disease in allograft; posttransplant acute kidney injury; progressive worsening of interstitial fibrosis (IF)/tubular atrophy (TA) in serial protocol biopsies; and pure red cell aplasia.

TABLE 1.

Pretransplant patient characteristics and HLA matching data

General characteristics	Total, n = 1142
Age range, y	5–72
Mean age, y	43
Male, n (%)	919 (80.4)
Female, n (%)	223 (19.5)
Prior medical history	
Diabetes, %	30.96
Tuberculosis, %	6.1
Confirmed coronary artery disease, % (underwent revascularization)	4
Causes of ESRD (all data represented as n [%])	
Chronic glomerulonephritis	
Biopsy-proven	190 (16.63)
Presumed (clinical features)	292 (25.5)
Focal segmental glomerulosclerosis	69 (6)
Chronic IgAN	165 (14.4)
Others (membranous nephropathy, DDD, lupus nephritis, anti-GBM antibody, HSP, etc)	17 (1.48)
Chronic interstitial nephritis (biopsy-proven and presumed)	175 (15.3)
Diabetic nephropathy	199 (17.42)
Miscellaneous (eg, ADPKD, Alport syndrome)	35 (3)
HLA matching, n (%)	
1 HAPLO	258 (21.6)
2 HAPLO	96 (8.04)
1/4 antigen match	42 (3.52)
3/4 antigen match	38 (3.18)
4/6 antigen match	1 (0.08)
5/6 antigen match	20 (1.66)
No HLA match	192 (16.8)
Not done[a]	495 (43.3)

[a]Presumed to be nil match because genetically unrelated (eg, spousal transplants).
ADPKD, autosomal dominant polycystic kidney disease; DDD, dense-deposit disease; ESRD, end-stage renal disease; GBM, glomerular basement membrane; HSP, Henoch-Schönlein Purpura; IgAN, immunoglobulin A nephropathy.

Out of 1142 patients, 1103 patients were biopsied. A total of 4258 biopsies were conducted, including both protocol and indicated biopsies. Donor-specific antibodies test was not routinely done preoperatively till 5 years before, due to unavailability of single-bead technology for DSA detection. Over the past 5 years, panel-reactive antibody test was done for all patients, and those with positive results were confirmed by DSA on single-bead technology.

Survival Rate

The patient survival rates at 1, 5, and 12 years were 97.7%, 94.8%, and 92.4%, respectively. The overall survival rate was 92%. Figure 2 shows the KM plot for the overall survival.

The graft survival rates at 1, 5, and 12 years were 97.2%, 90.9%, and 86.1%, respectively. The corresponding death-censored graft survival rates were 99.4%, 95.9%, and 93.4%, respectively. Figures 3 and 4 show the KM plots for graft survival and death-censored graft survival, respectively. The incidence of death was 5.3% for the entire observational period.

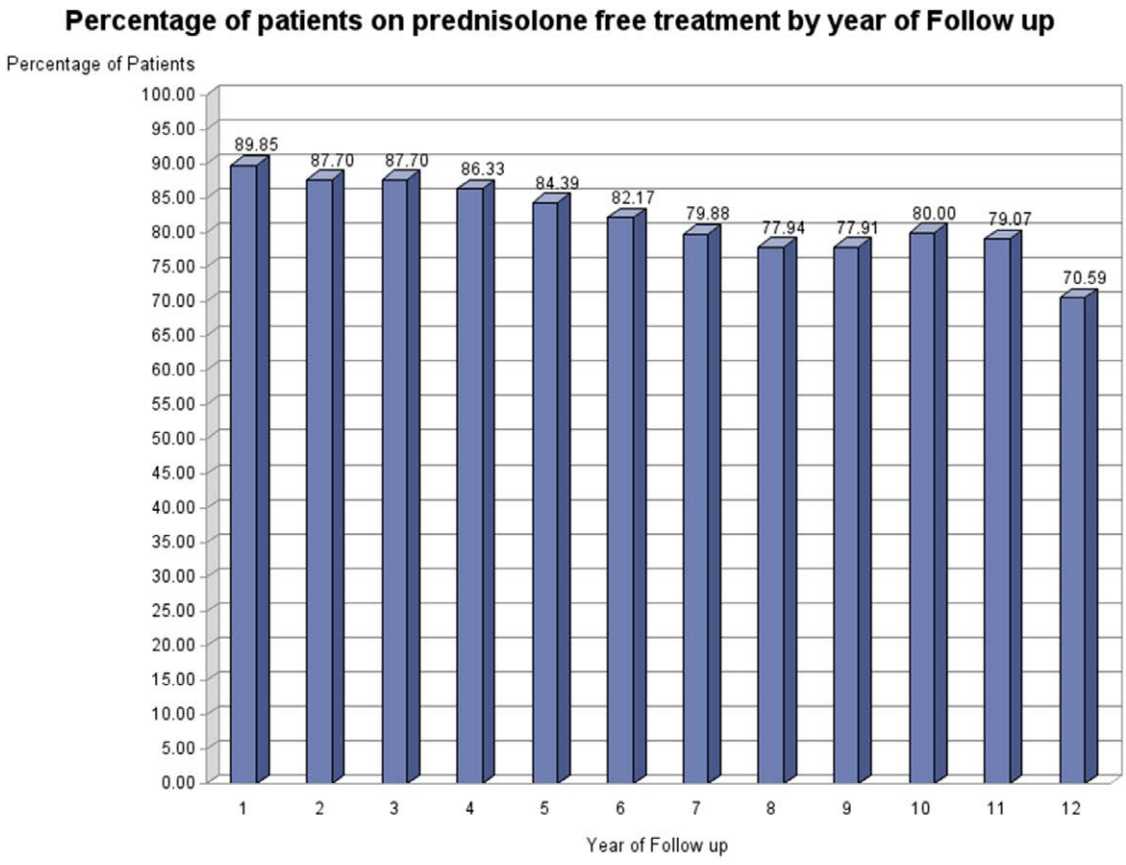

FIGURE 1. Percentage of patients on prednisolone-free treatment by y of follow-up.

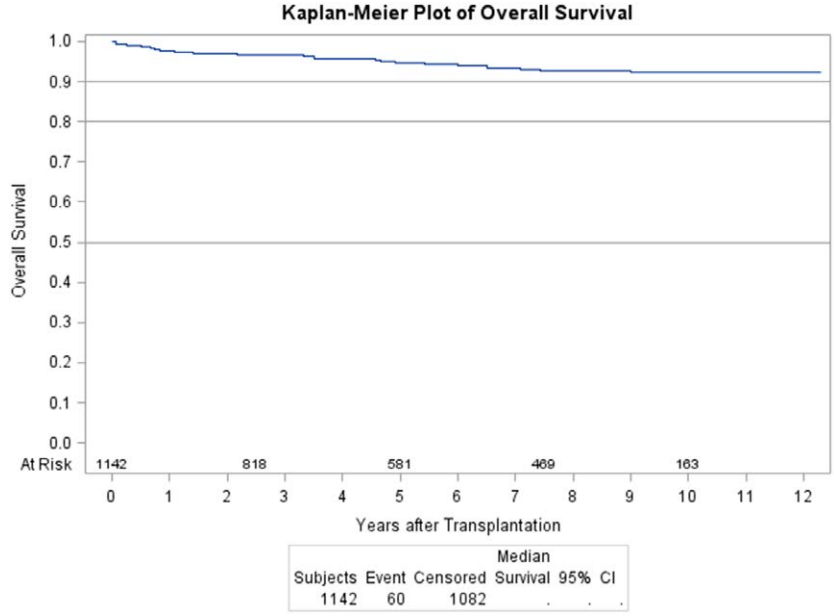

FIGURE 2. Kaplan–Meier plot for overall survival. CI, confidence interval.

Acute Rejection and Graft Loss

The mean serum creatinine levels at 1, 5, and 12 years in steroid-free patients were 1.2, 1.3, and 1.5 mg/dL, respectively. Patients (9.2%) experienced early acute rejection and 3.5% of patients experienced subclinical rejection, and overall the biopsy-proven acute rejection-free survival at 12 years was 83%. All rejections were biopsy-proven. IF/TA was seen in 8.5% biopsies out of 4258 biopsies by 10 years.

About 88% and 85% of biopsies were normal at 5 and 10 years, respectively. The cumulative incidence of graft loss was 6.56% at 12.3 years. The causes of graft loss are listed in Table 2. Retransplantation was done in 4.0% of patients; 45

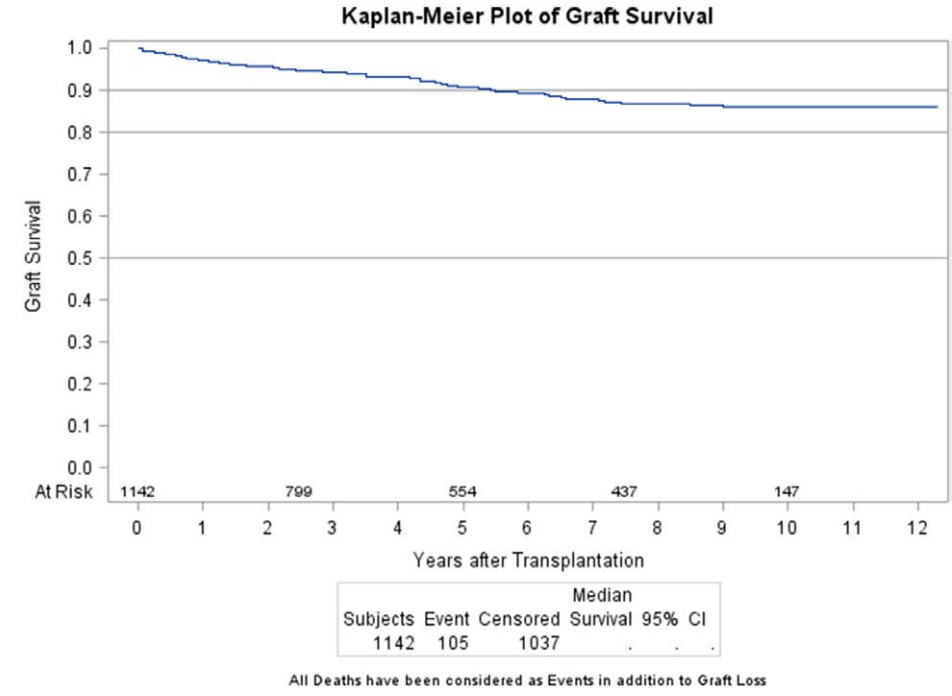

FIGURE 3. Kaplan–Meier plot for graft survival. CI, confidence interval.

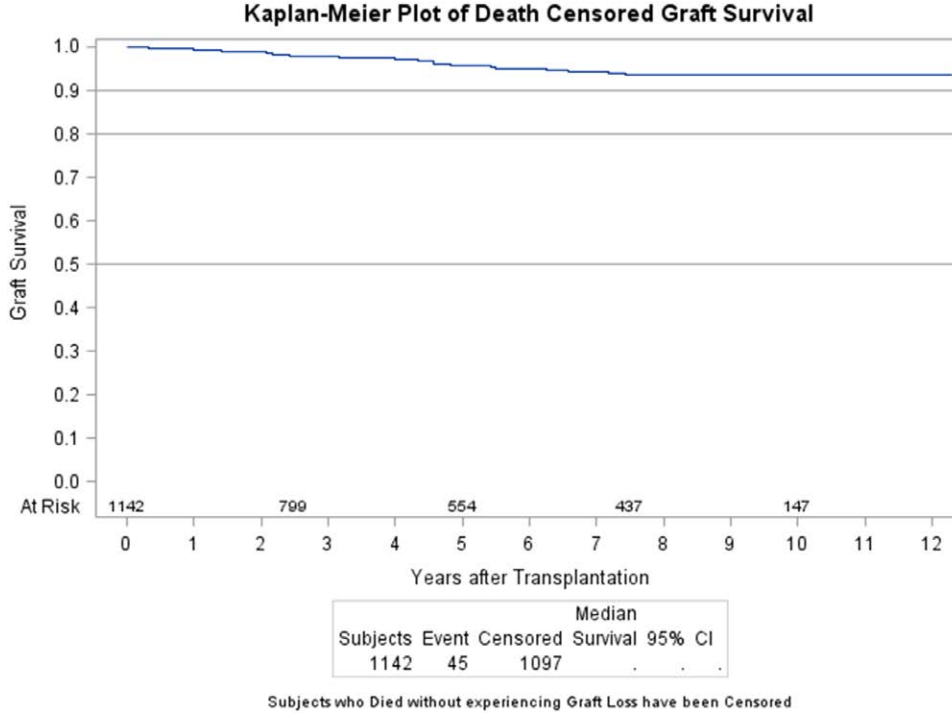

FIGURE 4. Kaplan–Meier plot for death-censored graft survival. CI, confidence interval.

patients received a second transplant and 2 patients received a third transplant. Hemodialysis was required in 23 (2.0%) patients, due to acute kidney injury; one patient developed primary nonfunction of the graft.

Complications After Transplantation

NODAT was observed in 1.5% at 1 year and 6.1% at 12 years. Cataract surgery was not needed in patients aged below 40 years in our study.

Leucopenia was seen in 34.4% of patients. Patients (72 [6.3%]) had pretransplant hepatitis, and 36 (3%) patients had new-onset or relapsed hepatitis following transplantation. The graft and overall survival rates were significantly lower in patients with hepatitis after transplantation compared with patients without hepatitis.

Routine screening was not conducted for detection of BK virus in most patients. Screening was done only in case of any suspicious histological findings from protocol or indicated

TABLE 2.
Causes of graft loss

Cause	Patients, n (%) ([a]N = 44)
Antibody-mediated rejection	6 (13.6)
Noncompliant with therapy	7 (15.9)
Recurrent IgAN	4 (9.1)
Recurrent FSGS	5 (11.4)
BK virus	2 (4.5)
Calcineurin inhibitor toxicity	1 (2.3)
Chronic allograft nephropathy	18 (40.9)
Tuberculosis of the transplanted kidney	1 (2.3)

[a]Patients died not included in this count.
FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy.

biopsies, in which case a BK virus polymerase chain reaction test was done to detect BK viremia. BK virus infection was seen in 17 (1.4%) patients, of whom 2 patients lost the graft. Immunosuppression was reduced in patients detected with BK viremia. Testing for parvovirus was done only for those patients who had anemia due to pure red cell aplasia. Two patients were positive for parvovirus infection, and they responded well to intravenous immunoglobulin. Tuberculosis was detected in 44 (3.8%) patients after transplantation. There were 4 patients (0.3%) with invasive fungal infections, of whom 2 had mucormycosis: one survived following treatment, while the other died. Cryptococcal meningitis and pulmonary aspergillosis resulted in the death of 2 patients.

There were no new fractures in the patients who remained steroid-free for the duration of follow-up, while there were 3 hip fractures among patients who required steroids. The BMD values of the spine and hip at baseline were compared to the values at 5 years after transplantation in 571 patients. There was no significant improvement in BMD in our subjects.

Posttransplant malignancy was seen in 15 patients. Posttransplant lymphoproliferative disease (PTLD) was observed in 7 (0.60%) (3 treated and in complete remission, remaining 4 died) out of 15 patients. Native renal cell carcinoma was seen in 5 patients, all of whom underwent nephrectomies.

About 61% of patients did not require antihypertensive medications at the end of the first year, and 34.8% did not require antihypertensive medications at the end of the fifth year after transplantation.

Incidence of Death

Sixty patients (5.2%) died during the study period. Infection was the leading cause of death, followed by stroke, chronic hepatitis, and noncompliance with therapy (Figure 5).

DISCUSSION

In the current retrospective analysis, we found that a systematic approach to immunosuppression with low-dose preoperative rituximab and thymoglobulin induction and steroid-free maintenance after the first week of kidney transplantation along with incorporating protocol biopsies resulted in favorable patient and graft survival with acceptable rates of acute rejection and reduced incidence of steroid-related complications.

There was no control group in this analysis. This study was started as a pilot project and we found there was no NODAT in first 25 patients at 4 weeks. NODAT in historical cohort (no thymoglobulin induction) who received prednisolone in addition to MMF and tacrolimus was 43% at 1 month and 24.5% at 1 year, so we thought it would be improper to keep control group. Other long-term studies involving steroid-free maintenance immunosuppression, and rapid discontinuation of prednisone (RDP) protocols have also not reported the use of a control group.[20,21]

In our study, a comparative analysis of the results between living donor (LD) and deceased donor (DD) transplant recipients was not conducted, as the proportion of patients in both the categories was not balanced, with about 95.4% LD transplant recipients.

The patient survival rates in our study were 97.7%, 94.8%, and 92.4% at 1, 5, and 12 years, respectively. In an earlier study by Rizzari et al[22] in transplant recipients (64% LD and 36% DD), treated with RDP protocol, the patient survival rates at 1, 5, and 10 years were 98%, 90%, and 71% for LD transplant recipients and 95%, 86%, and 62% for DD recipients, respectively. Another prospective randomized study by Suszynski et al[21] evaluated an RDP protocol and compared 3 different maintenance immunosuppression regimens. The 10-year patient survival rate was comparable across the 3 regimens and was ≈70%.

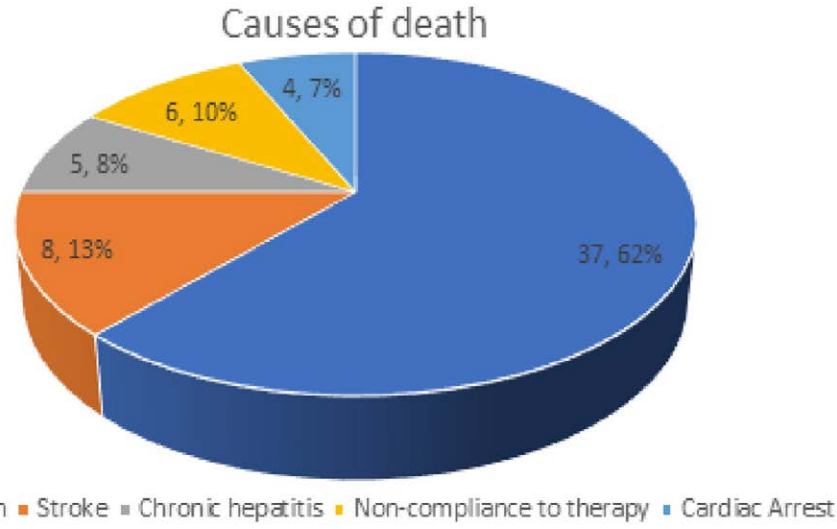

FIGURE 5. Causes of death.

The graft survival rate at 1, 5, and 12 years in our study was 97.2%, 90.9%, and 86.1%, respectively; and death-censored graft survival was 93.5% at 12 years. The graft survival rates reported by Rizzari et al[22] were 96%, 82%, and 61% for LD recipients and 94%, 77%, and 51% for DD recipients at 1, 5, and 10 years, respectively. In the study by Suszynski et al,[21] the overall 10-year graft survival and death-censored graft survival rates were ≈60% and 80%, respectively. In another retrospective study by El-Faramawi et al[20] evaluating the outcomes of complete steroid-avoidance immunosuppression, the graft survival rates at 1, 5, and 7 years posttransplantation were 95%, 77%, and 72%, respectively.

In the organ procurement and transplantation network (OPTN) report published in 2016, the 5- and 10-year all-cause graft failure was 26.5% and >50% in DD transplant recipients and 14.3% and >35% in LD transplant recipients, respectively.[24] These graft failure rates are higher than the graft loss of 6.56% noted in our study at 12.3 years. All-cause graft failure in our study was 11.6% at 12 years.

The reasons for the improved patient and graft survival rates in our study could have been the addition of low-dose preoperative rituximab to thymoglobulin induction (a novel induction method rarely cited in the literature), aggressive cardiovascular screening (resulting in low posttransplant mortality due to ischemic heart disease), lowered infection rate due to steroid withdrawal, and aggressive biopsy procedure—which included protocol biopsies. The utility of protocol biopsies in detecting multiple problems, including subclinical acute rejection, BK viremia, CNI toxicity, and IF/TA among others, remains proven in earlier studies.[25-29] Protocol biopsies have also been found to guide early treatment, lower the graft loss, and improve functional outcomes after kidney transplantation.[25,26]

The early acute rejection rate in our study was 12.7%, which included 3.5% subclinical rejection. In the study by El-Faramawi et al,[20] the acute rejection rate with a complete steroid-avoidance protocol within the first year of transplantation was 19%. The 10-year biopsy-proven acute rejection rate with an RDP protocol in the study by Suszynski et al[21] was in the range of 20%–30%.

The lower rates of acute rejection in our study may be due to thymoglobulin induction, regular use of preoperative low-dose rituximab, and consistent use of tacrolimus-based immunosuppression in all study patients; everolimus was administered only in cases of suspected CNI toxicity. Induction with thymoglobulin and tacrolimus-based immunosuppression has been proposed to lower acute rejection in earlier studies.[30] In a recent study that randomized de novo kidney transplant recipients to convert to everolimus or remain on standard CNI therapy at 10–14 weeks after transplantation, the rates of biopsy-proven acute rejection were lower in the group that continued to receive tacrolimus compared to the group that received everolimus. Furthermore, discontinuation due to adverse events was more in the everolimus group compared to the CNI group.[31] A recent meta-analysis by Zhao et al[32] demonstrated significantly lower rates of acute rejection in sensitized patients treated with rituximab before renal transplantation. Furthermore, induction with low-dose rituximab has been found to result in low acute antibody-mediated rejection rates and high patient and graft survival rates in ABO-incompatible kidney transplantations as well.[33]

The use of protocol biopsies may be a plausible explanation for the lower rates of graft loss in our study. Literature stands proof of the potential role of protocol biopsies in detecting subclinical acute rejection,[34] chronic allograft nephropathy,[35] and inflammation after renal transplantation.[36] Early detection and management of these conditions may help lower the graft loss and prevent the decline in graft function and survival.[25,37,38] Aggressive use of biopsies avoided the unnecessary use of steroid pulse therapy for the treatment of acute rejection empirically.

The low dose of rituximab used in our study is aligned with the doses used in other studies for the prevention of antibody-mediated acute rejection in ABO-incompatible kidney transplantations.[33,39-41] The dose of thymoglobulin used for induction is also in line with the dose used in other long-term kidney transplantation studies with RDP protocol.[21] Detection of peripheral CD20/CD19 levels to assess the effect of rituximab was not done in our study, as several studies have proven the efficacy of rituximab in lowering the CD20/CD19 levels, when used at doses similar to that used in this study.[39-41]

The NODAT rates in our study were very low, which are 1.5% at 1 year and 6.1% at 12 years. Similar results were reported by Rizzari et al,[22] with 10-year NODAT rates of 7% and 11% in LD and DD recipients, respectively. Furthermore, the NODAT results in our cohort are comparable to the figures mentioned in the OPTN report.[24]

Cataract surgery was not required in patients aged below 40 years. Rizzari et al[22] also reported a significantly lower incidence of cataract complications with the RDP protocol compared to historical controls.

In our study, graft and overall survival rates were significantly lower in patients with hepatitis virus infection. Recent studies reveal a significant association between hepatitis B virus infection and poor patient and graft survival in kidney transplant recipients.[42,43] A significant association between hepatitis C virus infection and decreased graft survival and increased rate of acute rejection has also been reported.[43]

The incidence of BK viremia noted in our study (1.4%) is less than that reported with prednisone-based immunosuppression (13%) in previous studies.[44] Furthermore, steroid maintenance therapy has also been reported to increase the risk of BK virus replication by about 38%.[45]

Prednisolone avoidance decreased the risk of fractures in our study; 4 fractures were noted in patients who received low-dose prednisolone versus no fractures in patients in the prednisolone-free group. Rizzari et al[22] also reported a lower incidence of fractures in RDP-treated DD nondiabetic recipients.

The incidence of PTLD (0.60%) in our study is relatively lower than the 10-year PTLD noted in the study by Rizzari et al[22] (0.3% and 2% in LD recipients with and without diabetes, and 6% and 1% in DD recipients with and without diabetes, respectively). Our rates are also aligned with the incidence of PTLD at 5 years in the OPTN report (1.7% and 0.5% for patients who were Epstein-Barr virus-negative and virus-positive at the time of transplant, respectively).[24]

Fewer patients needed antihypertensive treatment and coupled with less NODAT after transplantation in our study also probably improved survival. A meta-analysis by Knight and Morris[46] reported a significantly reduced incidence of hypertension after renal transplantation with steroid avoidance or withdrawal strategies.

The overall incidence of death was low in our study (5.21%). This could be attributed to the aggressive cardiovascular screening and treatment before transplantation, resulting in reduced cardiovascular mortality. Furthermore, the incidence of fatal infections was low in our study (3.5%), which may be due to rapid steroid withdrawal. The rates of fatal infections in studies using steroid-based immunosuppression are much higher (10.5%)[47] than those noted in our study. Pretransplant hepatitis B and C in our study were treated to reduce postoperative mortality resulting from hepatic failure.

Our study is most likely the first to report 12-year outcomes in a substantial cohort of kidney transplant patients treated with a new induction protocol comprising low-dose preoperative rituximab and perioperative and postoperative thymoglobulin and steroid-free maintenance immunosuppression along with protocol biopsies. Our study demonstrated excellent short-term and long-term patient and graft survival; the results are significantly better than the figures published in the literature. The all-cause graft failure in our study was better than that noted in the OPTN data published in 2016, wherein most of the kidney transplant recipients were on steroid-based maintenance immunosuppression. Rapid withdrawal of prednisolone lowered the rate of steroid-related side effects and did not increase acute rejection rates and graft loss due to IF/TA. Optimal blood pressure control and reduction in NODAT with our regimen may have beneficial cardiovascular effects. The mortality rate was also low in our study, which could be majorly attributed to mean age of transplant patients, which was lesser in our study compared to general transplant population in other parts of world, the aggressive preoperative cardiovascular screening and treatment. Reduction in death allowed a higher patient and graft survival rate. An aggressive biopsy policy allowed us to identify and treat recurrent glomerulonephritis and thus reduce graft loss, as compared to the published literature.

The use of a systematic steroid-free maintenance immunosuppression strategy including low-dose preoperative rituximab and perioperative and postoperative thymoglobulin induction, tacrolimus–MMF maintenance, use of everolimus in case of tacrolimus toxicity, and the use of protocol biopsies to periodically assess graft function formed the key strength of our study; it allowed us to individualize therapy and optimize survival outcomes.

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