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New Immunosuppressive Therapies and Surgical Complications After Renal Transplantation

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ABSTRACT

Background. To analyze the association between the principal immunosuppressive drugs (mycophenolate mofetil, calcineurin inhibitors and mammalian target of rapamycin [mTOR] inhibitors) used in the routine management of kidney transplant patients and the development of postoperative surgical complications.

Materials and Methods. We analyzed 415 kidney transplants, studying the influence of various immunosuppressive regimens on the main postoperative surgical complications.

Results. The mean follow-up for the entire group was 72.8 months (± 54.2 SD). Patients treated with myeophonolate mofetil (MMF) and cyclosporine ($n = 121$) experienced a higher frequency of wound eventration odds ratio [OR], 5.2; 95% confidence interval [CI], 1.2–23.5; $P = .03$) compared with azathioprine and cyclosporine ($n = 71$). Compared with transplant recipients treated with tacrolimus and MMF ($n = 181$), transplant recipients treated with cyclosporine and MMF ($n = 121$) had a significantly greater frequency of wound eventration (OR, 3.7; 95% CI, 1.5–9.5; $P = .005$), urologic (OR, 2; 95% CI; 1.02–3.9; $P = .04$), wound (OR; 2.2; 95% CI; 1.07–4.6; $P = .03$), late (OR, 1.7; 95% CI; 1.01–3.03; $P = .04$), and Clavien grade 3 surgical complications (OR; 1.9; 95% CI, 1.1–3.37; $P = .01$). Patients treated with mTOR inhibitors ($n = 26$) had higher rates of lymphocele (OR, 3.6; 95% CI, (1.1–11.4; $P = .002$) compared with those who received tacrolimus ($n = 197$).

Conclusions. New immunosuppressive drugs have improved short-term functional results; however, in some cases they seem to increase surgical complications rates.

KIDNEY TRANSPLANTATION improves the survival of patients with end-stage kidney disease compared with those who remain on the waiting list, even after adjusting for age, gender, cause of renal failure, and other comorbidities.[1,2] For this reason, one of the principal objectives in the current kidney transplantation setting is the optimization of graft survival results. However, the main obstacle to this purpose is graft rejection. Both acute and chronic rejection inexorably lead to chronic graft dysfunction and to dialysis, dealing once more with an increased morbidity period.[3]

The modernization of immunosuppressive regimens is a reflection of the attempt to overcome these barriers. The introduction of new immunosuppressive drugs over the last decade has decreased the acute rejection rate and seems to have improved short-term graft survival.[4–8] Nevertheless, these benefits obtained in the immunology field are not free from side effects. A higher incidence of wound infection, eventration and lymphocele related with new immunosuppressive therapies had been described.[4–6] However, limited studies are available about the full effect of these drugs among all the different subtypes of surgical complications (parietal, urologic, or vascular) observed in the context of renal transplantation, and the available information is controversial.

The purpose of this study was to evaluate the effects of the principal immunosuppressive drugs (mycophenolate mofetil [MMF], calcineurin inhibitors, and mammalian target of rapamycin [mTOR] inhibitors) used in the routine management of kidney transplant recipients. We study their

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association with the development of postoperative complications, focusing on surgical events using a validated classification method.[9,10] Finally, we aim to ascertain whether the new immunosuppressive regimens provide a real benefit for graft survival.

MATERIALS AND METHODS

Patients and Data Assessment

We carried out an analytical, observational, retrospective study of 415 consecutive kidney transplantations performed between 1994 and 2010. We studied the influence of various immunosuppressive regimens on the main postoperative medical and surgical complications, and we assessed the impact of these drugs on graft survival. We analyzed 3 different immunosuppressive therapies. First, we compared patients who were treated with azathioprine and cyclosporine with those treated with MMF and cyclosporine. Secondly, we compared patients treated with cyclosporine and MMF with those who received tacrolimus and MMF. Finally, we compared patients treated with mTOR inhibitors and cyclosporine with those who received MMF and cyclosporine.

Acute rejection was confirmed through biopsy and by the improvement of renal function after the administration of corticosteroids. Delayed onset of kidney function was defined by a patient's need for dialysis within the first postoperative week. Glomerular filtration rates were calculated with the 4-variable Modification of Diet in Renal Disease (MDRD) formula. The clinical information shown in Table 1 was obtained from hospital records. Kidney transplantation was performed by the same 4 surgeons throughout the study period using a previously described surgical technique.[11]

Immunosuppression

Recipients adhered to the immunosuppressive regimens for ≥1 year after transplantation. These therapies evolved over the study period. Modern therapies involve tacrolimus and MMF, whereas older approaches included cyclosporine and azathioprine. In addition, all patients received 5 mg/kg methylprednisolone intraoperatively. This dose was increased to 20 mg/d during the first month after surgery. After this period, the dose was decreased, in an effort to wean the patient off corticosteroids. The different immunosuppressive regimens are listed in Table 1.

Surgical Complications

Surgical complications were categorized as early (≤30 days after transplantation) or late complications (>30 days after transplantation). Wound complications included wound infections and wound eventrations. Collections consisted of lymphoceles and perirenal hematomas. Urologic complications included hydronephrosis with deterioration in renal function, urinary fistulas, ureterovesical junction stenosis, vesicoureteral reflux, and graft lithiasis. Vascular complications consisted of postoperative hemorrhage, renal vein thrombosis, renal artery thrombosis, and renal artery stenosis. All surgical complications were recorded and classified according to the modified Clavien classification (Table 2).

Statistical Analyses

Data analysis was performed using statistical software (SPSS, version 15.0, SPSS Inc., Chicago, Il). Comparisons were made using the *t*-test for continuous variables and the chi-square test for categorical variables. The risk of developing surgical complications was calculated with binary logistic regression analysis. The Kaplan–Meier method and the log-rank test were used to evaluate graft survival. The primary endpoint of the study was graft failure, defined as the recurrence of end-stage renal failure (after transplantation) necessitating dialysis. Continuous data were reported as mean values ± SD and categorical data as number (%). Statistically significant differences were defined by $P \leq .05$.

RESULTS

The study group consisted of 415 renal allografts, mainly obtained from cadaveric donors (97.1%). The mean follow-up for the entire group was 72.8 months (± 54.2 SD). The other clinical characteristics are listed in Table 1.

Comparison of Azathioprine ($n = 71$) Versus MMF ($n = 121$)

Patients treated with azathioprine and cyclosporine were significantly younger (47.1 vs 51.7 years), had a greater frequency of first-year acute rejection odds ratio ([OR], 2.3; 95% confidence interval [CI], 1.2–3.2; $P < .006$), overall acute rejection (OR; 3.1; 95% CI; 1.6–5.9; $P < .001$), and chronic rejection (OR; 3.3; 95% CI; 1.5–7.2; $P < .002$) than patients treated with MMF and cyclosporine. On the other hand, the MMF group experienced a greater frequency of wound eventration (OR, 5.2; 95% CI; 1.2–23.5; $P = .03$) and hospitalization related with digestive disease (OR; 2.5; 95% CI; 1.1–6.1; $P = .03$) even after adjusting for recipient age. The rest of the clinical and pathologic variables summarized in Table 3 were homogeneously distributed between the groups.

The graft survival analysis revealed no differences between groups ($P > .05$). Patients treated with azathioprine had 3- and 5-year survival rates of 88% (95% CI, 85%–91%) and 85% (95% CI; 81%–89%), compared with 93% (95% CI; 91%–95%) and 86% (95% CI, 83%–89%) in those treated with MMF.

Comparison of Cyclosporine ($n = 121$) and Tacrolimus ($n = 181$)

Compared with transplant recipients treated with tacrolimus and MMF, transplant recipients treated with cyclosporine and MMF had significantly greater frequency of wound eventration (OR; 3.7; 95% CI; 1.5–9.5; $P = .005$). When analyzing surgical complications types, a significant greater incidence of urologic (OR; 2; 95% CI; 1.02–3.9; $P = .04$), wound (OR; 2.2; 95% CI; 1.07–4.6; $P = .03$), and late (OR; 1.7; 95% CI; 1.01–3.03; $P = .04$) surgical complications was found. The acute rejection episodes were also more frequent in this group (OR; 2.1; 95% CI; 1.3–3.5; $P = .0002$).

In terms of severity, cyclosporine was related to Clavien grade 3 complications (OR; 1.9; 95% CI, 1.1–3.37; $P = .01$) requiring treatment with invasive procedures involving surgery, endoscopy, or endoradiology. In contrast, the frequency of posttransplant diabetes mellitus was significantly higher in the tacrolimus group (OR; 3.1; 95% CI, 1.3–6.8; $P = .007$); (Table 4).

Table 1. Demographic and Clinical Characteristics of the Study Group

	n	Mean ± SD
Recipient age (ys)	415	49.9 ± 13.9
Donor age (ys)	413	48.1 ± 18.3
Recipient BMI (kg/m^2)	371	25 ± 4
Donor BMI (kg/m^2)	119	25.4 ± 3.9
Donor ICU stay (d)	212	2.7 ± 3.2
Residual diuresis (cc)	286	840 ± 719.1
Pretransplant dialysis duration (mos)	414	31.7 ± 44.2
HLA matches	403	2.2 ± 0.9
Cold ischemia time (h)	409	14.5 ± 7.3
Time to first acute rejection episode (d)	415	201.8 ± 510.8
Follow-up time (d)	419	2175 ± 1625
	N	*N*%
Males	415	252/60.7
Smokers	414	71/17.1
Recipient arterial hypertension	415	328/79
Recipient dyslipidemia	415	122/29.4
X-ray vascular calcifications	415	83/20
Ventricular hypertrophy	415	134/32.3
Acute rejection episodes	415	179/43.1
Delayed graft function	415	87/21
Functioning grafts	415	326/78.6
Dialysis type	415	
Predialysis		23/5.5
CAPD		72/17.3
Hemodialysis		303/73.1
CAPD + Hemodialysis		17/4.1
Immunosuppression therapies	415	
Cyclosporine + MMF		121/29.1
Cyclosporine + azathioprine		71/17.1
Tacrolimus + MMF		181/43.6
Cyclosporine + sirolimus		12/2.9
Cyclosporine + everolimus		10/2.4
Sirolimus + MMF		4/1
Tacrolimus		7/1.7
Tacrolimus + azathioprine		9/2.2
Monoclonal antibody induction		29/7
Original renal disease	415	
Polycystic kidney disease		81/19.5
Glomerulonephritis		97/23.4
Diabetic nephropathy		31/7.5
Obstructive uropathy		18/4.3
Autoimmune disease		12/2.9
Chronic pyelonephritis		35/8.4
Nephroangiosclerosis		43/10.4
Tubulointerstitial nephritis		26/6.3
Idiopathic		53/12.8
Other		19/4.5
Postoperative complications	415	
Overall surgical complications		145/34.9
Vascular complications		38/9.1
Wound complications		45/10.8
Urologic complications		55/13.2
Early complications		52/12.5
Late complications		97/23.3
Collections		52/12.5
Immediate surgical reinterventions		41/9.9
Wound eventrations		34/8.1
Wound infection		21/5.1
Lymphoceles		30/7.2
Postoperative hemorrhage		22/5.3
Perirenal hematoma		21/5.1

Abbreviations: BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; ICU, intensive care unit.

No differences were found between groups in the graft survival analysis ($P > .05$). Patients treated with cyclosporine had 3- and 5-year graft survivals of 93% (95% CI, 91%–95%) and 86% (95% CI; 83%–89%), compared with 88% (95% CI; 86%–90%) and 85% (95% CI; 82%–88%) among those treated with tacrolimus.

Comparison of mTOR Inhibitors ($n = 22$) and MMF ($n = 121$)

Patients who followed immunosuppressive treatments based on mTOR inhibitors presented a greater incidence of overall surgical complications (15/68.2 vs 45/37.2; $P = .007$; OR; 3.6; 95% CI, 1.3–9.5; $P = .0009$) and chronic rejection (6/27.3 vs 13/10.7; $P = .04$; OR; 3.1; 95% CI, 1.04–9.3; $P = .04$) than patients treated with MMF and cyclosporine. The rest of the clinical and pathologic variables summarized in Table 1 were homogeneously distributed between the groups.

In this subanalysis, we also studied the incidence of lymphocele for all the different immunosuppressive therapies. We only found significant differences when comparing the group of patients treated with mTOR inhibitors ($n = 26$) with those who received tacrolimus ($n = 197$). The incidence was greater in the mTOR inhibitor group (5/19.2% vs 12/6.1%; $P = .048$; OR, 3.6; 95% CI, 1.1–11.4; $P = .002$).

Once more, graft survival analysis revealed no difference between groups ($P > .05$). Patients who were treated with mTOR inhibitors had 3- and 5-year survival rates of 95% (95% CI; 91%–95%) and 90% (95% CI; 84%–96%), compared with 93% (95% CI; 91%–95%) and 86% (95% CI, 83%–89%) in those treated with MMF.

DISCUSSION

New immunosuppressive drugs have improved short-term functional results, but they also have a negative effect on traditional risk factors. In some cases, they seem to increase the incidence of posttransplantation surgical complications.[12] The present study provided a broader description of different surgical complications related with new immunosuppressive drugs than previously available. Previous studies typically had evaluated only 1 type of complication, such as wound, urologic, or vascular complications, or reported data on overall surgical survival rates, but no previous studies had reported severity of complications with a standardized classification system such as the Clavien sys-

Table 2. Classification of Surgical Complications in 415 Consecutive Kidney Transplant Recipients*

Grade	Effects of Complication	Observed Complications	No (%) Patients With Complications
I	Alteration of the ideal postoperative course No threat to patient's life No reoperation; only bedside procedures necessary No increase in the hospital stay	Surgical wound infection	21 (5.1)
II	More medical treatment with drugs required (including transfusions and parenteral nutrition) No reoperation Potentially life threatening Limited residual disability	Perirenal hematoma	21 (5.1)
III	Surgery, endoscopy, or radiology required†	Wound eventration Lymphocele Hydronephrosis Vesicoureteral reflux Graft lithiasis Urinary fistula Vesicoureteral junction stenosis	109 (26.3)
IV	Life threatening Residual long term disability (including resection of the organ transplant or persistence of life threatening condition)	Renal vein thrombosis Arterial thrombosis Postoperative bleeding	33 (8)
V	Death	None	0 (0)

Adapted and modified from Clavien PA, et al. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 111:518, 1992.
*In all, 145 (34.9%) transplant recipients had 184 surgical complications.
†Different subtypes according to the type of anesthesia were not recorded.

tem.[9,10] Furthermore, conflicting data had previously been reported about new immunosuppressive drugs and surgical complications rates.

This is the case of mTOR inhibitors. A greater incidence of lymphocele has been described with the use of sirolimus, especially in combination with MMF. Of these drugs used in combination, the mTOR inhibitor seems to contribute most to lymphocele development.[13–17] However, other studies show that when surgical technique is correct (careful bench surgery, as well as correct dissection of the recipient perivascular lymphatic tissue), the rate of lymphoceles with sirolimus is not higher than with other immunosuppressive regimens.[16] Nevertheless, although some studies did not demonstrate differences in the surgical complications rates between mTOR inhibitors and other immunosuppressive therapies, the present study confirms the results of others that lymphocele rate are greater in the group treated with mTOR inhibitors and when compared with tacrolimus.

The introduction of tacrolimus, a new calcineurin inhibitor, seems to improve short-term graft survival rates and prevent acute rejection episodes when compared with cyclosporine. On the other hand, major incidences of post-transplantation diabetes and gastrointestinal and neurologic complications have been described.[18–20] When focusing on surgical complication rates, cyclosporine is related with greater postoperative bruises and bleeding rates.[13] Otherwise, there are no more rigorous studies comparing surgical side effects of both calcinerurin-inhibitors.

In our cohort, wound eventration incidence was greater in cyclosporine group, which was translated into an increase of late and wound complications rates. Furthermore, urologic complications incidence was elevated in this group. To our knowledge, there are no other studies reporting such results, suggesting a better wound healing and tissue scarring profile for tacrolimus.

In the case of MMF and azathioprine, our results confirm that MMF exhibits superior immunosuppressive potential, reducing the incidence of acute rejection and providing a better safety profile.[21–23] On the other hand, despite these advances, we have observed an increase in wound eventrations rates compared with those treated with azathioprine. Moreover, MMF has been described as an independent risk factor for hernia or suture dehiscence development.[24]

Finally, no improvements were found in the graft survival analysis with modern immunosuppressive drugs. This finding is supported by some authors that sustain that new immunosuppressive drugs only provide an improvement for short-term graft survival while long-term survival remain unchanged.[25]

Limitations of the present study include the retrospective design and long study period, which spanned 15 years. However, a sample size of 415 transplantations helped to address limitations of previous studies enabling the characterization of the different subtypes of surgical complications (Table 1). Furthermore, most previous studies included shorter follow-up periods than the present study, and longer follow-up is crucial because some surgical complications,

such as ureterovesical stenosis, hydronephrosis, and wound complications, may develop more than a year after surgery.

In conclusion, the immunologic profile of immunosuppressive agents has improved substantially, reducing the incidence of acute rejection. However, their side effects have also changed. As specialists involved in the transplantation process, we must become familiar with the range of medical and surgical complications related with modern immunosuppression, in order to be able to individualize treatments. More prospective clinical studies with greater statistical power and longer follow-up periods are necessary to assess the impact of new immunosuppressive therapies on the development of medical and surgical complications.

Table 3. Clinical Characteristics and Postoperative Complications in CSP + AZTP and CSP + MMF Groups

	CSP+AZTP (Mean ± SD)	CSP+MMF (Mean ± SD)	*P*
Recipient age (ys)	47.1 ± 14.2	51.7 ± 13.03	.024
Donor age (ys)	43 ± 17.8	47.9 ± 18.1	>.05
Recipient BMI (kg/m^2)	23.9 ± 3.9	25.3 ± 3.7	>.05
Residual diuresis (mL)	824.6 ± 602.7	986.6 ± 710.6	>.05
Pretransplant dialysis duration (mos)	30.6 ± 39.2	30.6 ± 56.5	>.05
HLA matches	2.2 ± 0.9	2.2 ± 0.9	>.05
	N/%	N/%	
Overall surgical complications	21/29.6	45/37.2	>.05
Wound infections	3/4.2	5/4.1	>.05
Wound eventration	2/2.8	16/13.2	.018
Lymphocele	6/8.5	9/7.4	>.05
Hematoma	1/1.4	5/4.1	>.05
Hydronephrosis	10/14.1	13/10.7	>.05
Urinary fistula	3/4.2	7/5.8	>.05
Ureterovesical junction stenosis	2/2.8	4/3.3	>.05
Graft lithiasis	0/0	2/1.7	>.05
Postoperative hemorrhage	1/1.4	6/5	>.05
Renal vein thrombosis	1/1.4	2/1.7	>.05
Renal artery stenosis	0/0	1/0.8	>.05
Renal artery thrombosis	0/0	1/0.8	>.05
Arteriolyenous re-anastomosis	1/1.4	2/1.7	>.05
Early surgical re-intervention	4/5.6	12/9.9	>.05
Type of complication			>.05
Early complications	4/5.6	15/12.4	>.05
Late complications	15/21.1	33/27.3	>.05
Wound complications	5/7	19/15.7	>.05
Urological complications	12/16.9	22/18.2	>.05
Vascular complications	1/1.4	10/8.3	>.05
Collection	7/9.9	16/13.2	>.05
Severity of complications			
Clavien grade 1	3/4.2	5/4.1	>.05
Clavien grade 2	1/1.4	5/4.1	>.05
Clavien grade 3	17/23.9	39/32.2	>.05
Clavien grade 4	1/1.4	9/7.4	>.05
Medical complications			
Hospitalization related with digestive disease	8/11.3	30/24.8	.023
Chronic rejection	20/28.6	13/10.7	.002
Acute rejection	51/71.8	54/44.6	<.001
Acute rejection episode in the first year	41/57.7	45/37.2	.006

Abbreviations: AZTP, azathioprine; CSP, cyclosporine; MMF, mycophenolate mofetil.

Table 4. Clinical Characteristics and Postoperative Complications in CSP + MMF and TCR + MMF Groups

	CSP + MMF (Mean ± SD)	TCR + MMF (Mean ± SD)	*P*
Recipient age (ys)	51.7 ± 13	50 ± 14.6	>.05
Donor age (ys)	47.9 ± 18.1	51.9 ± 17.6	>.05
Recipient BMI (kg/m^2)	25.3 ± 3.7	25 ± 4	>.05
Residual diuresis (mL)	986.6 ± 710.6	749.6 ± 724.8	>.05
Pretransplant dialysis duration (mos)	34.1 ± 56.5	32.7 ± 39.3	>.05
HLA matches	2.2 ± 0.9	2.3 ± 1	>.05
	N/%	N/%	
Overall surgical complications	45/37.2	56/30.9	>.05
Wound infections	5/4.1	9/5	>.05
Wound eventration	16/13.2	7/3.9	.003
Lymphocele	9/7.4	9/5	>.05
Hematoma	5/4.1	14/7.7	>.05
Hydronephrosis	13/10.7	12/6.6	>.05
Urinary fistula	7/5.8	8/4.4	>.05
Ureterovesical junction stenosis	4/3.3	8/4.4	>.05
Graft lithiasis	2/1.7	2/1.1	>.05
Postoperative hemorrhage	6/5	13/7.2	>.05
Renal vein thrombosis	2/1.7	8/4.4	>.05
Renal artery stenosis	1/0.8	2/1.1	>.05
Renal artery thrombosis	1/0.8	0/0	>.05
Arteriovenous re-anastomosis	2/1.7	4/2.2	>.05
Early surgical re-intervention	12/9.9	21/11.6	>.05
Type of complication			
Early complications	15/12.4	27/14.9	>.05
Late complications	33/27.3	32/17.7	.047
Wound complications	19/15.7	14/7.7	.03
Urological complications	22/18.2	18/9.9	.039
Vascular complications	10/8.3	22/12.2	>.05
Collections	16/13.2	21/11.6	>.05
Severity of complications			
Clavien grade 1	5/4.1	9/5	>.05
Clavien grade 2	5/4.1	14/7.7	>.05
Clavien grade 3	39/32.2	35/19.3	.011
Clavien grade 4	9/7.4	20/11	>.05
Medical complications			
Posttransplant diabetes mellitus	8/6.6	32/17.7	.005
Acute rejection	54/44.6	49/27.1	.002
Acute rejection episode in the first year	45/37.2	40/22.1	.004

Abbreviations: CSP, cyclosporine; MMF, mycophenolate mofetil, TCR, tacrolimus.

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