# Open Prospective Study to Evaluate Cardiovascular Risk Factors and Renal Function in 2 Dosage Regimens of Tacrolimus Combined With Mycophenolate Mofetil and Steroids in Renal Transplant Patients: 5-Year Results

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ABSTRACT

Background. Cyclosporine and tacrolimus (TAC) are the most potent immunosuppressants. TAC is considered less nephrotoxic, but may be an important factor in chronic graft dysfunction. The aim of the study was to evaluate kidney function and cardiovascular risk profile in 2 groups of low immunological risk kidney allograft recipients receiving 2 TAC dosages.

Materials and methods. Patients were randomly assigned to 2 TAC-based treatments (group I [n = 14], standard dose; group II [n = 15], reduced dose). Patient and graft survival, graft function, occurrence of cardiovascular events (cardiac death, myocardial infarction, stroke), incidence of new-onset diabetes mellitus after transplantation, and cardiovascular risk factors were assessed over a 5-year period.

Results. Patient demographics and transplant characteristics were not statistically different between groups. TAC trough levels were significantly higher in group I for 24 months post transplant. Patient survival did not differ, but there were more acute rejection episodes and graft losses in group II. There were no significant differences in the rate of cardiac events. Graft function measured as serum creatinine levels and calculated glomerular filtration rate did not differ between groups. The same applies to new-onset diabetes mellitus after transplantation incidence. Office blood pressures were numerically higher in group I up to 24 months but this difference did not reach significance at any time. Similar results were obtained for serum lipids.

Conclusions. Immunosuppression based on low doses of tacrolimus seems to be safe in the group of low immunological risk patients but in the 60-month follow-up does not offer any clear benefits in terms of potential nephrotoxicity or cardiovascular risk.

RENAL transplantation is considered to be the best treatment option for patients with chronic renal disease. Available data show better survival of transplanted patients compared with those listed for transplantation but remaining on dialysis [1–3]. In addition, the quality of life is considerably better after renal transplantation [4]. Long-term survival of a kidney allograft is dependent on continuous use of immunosuppressive medications. Calcineurin inhibitors (cyclosporin A or tacrolimus) are considered the most important drugs in this respect. Despite the fact that use of both calcineurin inhibitors results in low acute rejection rates and similar long-term survival rates, they are not free from side effects and toxicities. Lower acute rejection rates have been reported in groups of patients treated with tacrolimus-based immunosuppression compared to cyclosporin [5,6]. Tacrolimus is also considered to be less nephrotoxic than cyclosporin; however, the incidence of glucose intolerance and new-onset diabetes mellitus after transplantation (NODAT) has been reported to be higher with its use.

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Chronic graft injury (interstitial fibrosis/tubular atrophy [IF/TA]) is 1 of the leading causes of late graft loss. Long-term calcineurin inhibitor use has been implicated as an important factor contributing to the development of IF/TA, although this view has been criticized [7,8]. Death with functioning graft becomes another important factor and cardiovascular events account for most deaths in this population. Both standard cardiovascular risk factors (hypertension, lipid abnormalities, obesity) and those specific for this population (eg, renal function, immunosuppressive regimen, and others) have a great impact on cardiovascular mortality and morbidity in kidney transplant recipients. Data from recently published studies suggest that the best short-term results have been achieved in patients treated with low-dose tacrolimus combined with mycophenolate mofetil [9,10].

The aim of the current study was to evaluate kidney function and cardiovascular risk profile in 2 groups of low immunological risk kidney allograft recipients receiving 2 dosage regimens of tacrolimus-based immunosuppression combined with mycophenolate mofetil and steroids.

## PATIENTS AND METHODS

This was a prospective, randomized, single-center, open-label study performed in accordance with the ethical principles described in the amended Declaration of Helsinki following approval from the institutional review committee at the Medical University of Gdańsk. Patients provided written informed consent prior to study randomization. The study was conducted between May 2007 and June 2013.

### Inclusion and Exclusion Criteria

Consecutive patients aged 18 to 65 undergoing primary renal transplantation from a deceased donor in our center were eligible for study enrollment. Only patients of low immunological risk (defined as panel reactive antibody <30% in the 6 months previous to transplantation) were considered for study participation. Excluded from the study were patients with severe gastrointestinal disease likely to influence tacrolimus or mycophenolate absorption, those with bone marrow depression (defined as continuously low leukocyte level $<2.5 \times 10^9$/L or platelets $<100 \times 10^9$/L), and patients with known prior adverse reactions to tacrolimus. Other exclusion criteria included continuously elevated levels of liver function tests (>3 times of upper laboratory limit), patient or donor HIV positive, previous recipients of an organ transplant other than kidney, organ cold ischemia time >24 hours, intolerance to any of the study drugs, or the requirement of additional immunosuppressive drugs or antibodies. The patient randomization ratio was 1:1.

### Treatments

Patients were randomly assigned to 1 of 2 treatment groups. Group I (n = 14) received tacrolimus initial dose of 0.2 mg/kg b.w. in 2 doses. The dose of tacrolimus was then adjusted to obtain blood levels of 10 to 20 ng/dL in the first month and then reduced to maintain whole blood levels of 8 to 12 ng/dL.

Group II (n = 15) received tacrolimus initial dose of 0.2 mg/kg b.w. in 2 doses. The dose of tacrolimus was then adjusted to obtain blood levels of 8 to 12 ng/dL in the first month and then reduced to target whole blood levels of 4 to 6 ng/dL.

Patients in both groups received mycophenolate mofetil 2.0 g/day in the first month and 1.0 g/day thereafter to the end of the study. Steroids were given as an initial perioperative bolus of methylprednisolone (500 mg i.v.) followed by 250 mg i.v. on the first day and 125 mg i.v. on the second day post transplantation, then replaced by oral prednisone 0.5 mg/kg b.w. in the first 2 weeks. The dose of steroids was later tapered to achieve 10 mg daily at the end of month 3. The dose of prednisone could be further reduced at the investigator's discretion.

First-line treatment of acute rejection was corticosteroids administered as methylprednisolone i.v. bolus doses (500 mg; 3–6 doses); antibody administration was permitted if a biopsy revealed a severe vascular rejection (Banff '07 IIb or III) or if steroid-resistant rejection was diagnosed. Other systemic immunosuppressive medications were prohibited. Prophylactic treatment for *Pneumocystis carinii* pneumonia consisting of cotrimoxazole was required until month 6. Prophylactic antiviral treatment for cytomegalovirus (CMV) consisting of gancyclovir followed by valgancyclovir was required in cases in which a CMV-positive donor graft was transplanted to a CMV-negative recipient.

Patient and graft survival, graft function (measured as serum creatinine levels and calculated eGFR by 4-point MDRD formula), occurrence of cardiovascular events (cardiac death, myocardial infarction, stroke), incidence of new-onset diabetes after transplantation (NODAT, diagnosed according to WHO guidelines), and cardiovascular risk factors were assessed over a 60-month period in a prospective manner.

All laboratory assessments were performed by routine methods at a local university hospital diagnostic unit. Blood pressures were measured in sitting position, following 15 minutes of rest, by using a semiautomated cuff manometer (Omron Intelli sense M3, Omron Healthcare Co, Ltd, Kyoto, Japan).

Data are expressed as means and standard deviation or range as appropriate. Statistical analysis was performed with the use of the Student *t* test, Mann-Whitney *U* (Wilcoxon) statistic, or repeated-

**Table 1. Patient Demographics and Transplant Characteristics**

| | Group I (n = 14) | Group II (n = 15) | *P* |
|---|---|---|---|
| Age, y (mean ± SD) | 41.15 ± 13.7 | 46.13 ± 17.25 | NS |
| Sex ratio: male/female (%) | 62/38 | 50/50 | NS |
| Primary kidney disease, n (%) | | | |
| Diabetes | 2 (14.3) | 3 (20.0) | NS |
| GN | 4 (28.5) | 5 (33.3) | NS |
| Hypertension | 2 (14.3) | 2 (13.3) | NS |
| Interstitial | 2 (14.3) | 1 (6.7) | NS |
| ADPKD | 2 (14.3) | 1 (6.7) | NS |
| Unknown/other | 2 (14.3) | 2 (13.3) | NS |
| Time of dialysis before transplantation, mo (mean ± SD) | 13.5 ± 11.75 | 28.8 ± 28.12 | NS |
| Donor age, y ± SD | 42.69 ± 13.14 | 41.63 ± 12 | NS |
| Mismatch, mean ± SD | | | |
| AB | 2.21 ± 0.89 | 2.53 ± 0.64 | NS |
| DR | 0.57 ± 0.51 | 0.87 ± 0.35 | NS |
| TIT, h | 9.1 ± 3.1 | 7.34 ± 2.38 | NS |
| WIT, min | 24.23 ± 5.13 | 27.4 ± 7.4 | NS |
| DGF, No. (%) of pts | 3 (21%) | 4 (26%) | NS |
| DGF, days (mean ± SD) | 7.33 ± 3.79 | 5.75 ± 2.99 | NS |

Abbreviations: TIT, total ischemia time; WIT, warm ischemia time; DGF, delayed graft function; GN, glomerulonephritis; ADPKD, adult dominant polycystic kidney disease; AB, HLA class I; DR, HLA class II.