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Conversion Therapy to Everolimus in Renal Transplant Recipients: Results After One Year

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ABSTRACT

Background. Two new diagnoses have been causing graft loss during long-term follow-up, namely, chronic nephropathy and anticalcineurinic toxicity. The advent of the mammalian target of rapamycin (m-TOR) obviates anticalcineurine toxicity and reduces posttransplant malignancy incidence with good inmunosuppressive potential. We examinated the renal and metabolic behavior in renal transplant recipients who required conversion from an anticalcineurinic (cyclosporine or tacrolimus) to an m-TOR inhibitor (everolimus) as part of their immunosuppressive maintenance therapy.

Materials and Methods. Twenty-one first renal transplant recipients had everolimus added to their inmunosuppressive therapy combined with an antimetabolite (mycophenolate mofetil or sodium mycophenolate). The mean age of the patients was 35 ± 17 years (range, 6 to 65). The prevalence of male recipients was 57%; the overall mean weight, 64 kg (range, 48 to 95). All patients were hispanic with 15 transplants from cadaveric donors (71%). The mean follow-up posttransplant was 18 months (range, 3 to 40) and the mean follow-up on everolimus, 10 months (range, 2 to 22).

Results. There was no mortality or graft loss, but there were 3 (17%) biopsy-confirmed acute rejection episodes. There were no significant changes in metabolic function pre- or postconversion. Regarding renal function, the mean creatinine serum showed a trend to decline: preconversion 1.7 mg/dL; postconversion 1.5 mg/dL. In 10 patients, it was possible to discontinue at least one antihypertensive medication (48%).

Conclusions. Everolimus was an effective medication to manage renal transplant patients. It produced metabolic stability and low myelotoxicity, despite combination with an antimetabolite (mycophenolic acid). Also, reduction of antihypertensive medications was an additional benefits for many patients.

UNTIL RECENTLY, prevention of acute renal transplant rejection was the main purpose of inmunosuppressive maintenance therapy. However, efforts have been directed toward preventing and/or controlling the onset of chronic transplant nephropathy and anticalcineurin toxicity, two of the main causes of long-term graft loss.[1] The advent of a new type of agent—the proliferation signal inhibitors (PSI: sirolimus and everolimus)—offers an alternative to agents that block calcineurin.[1,2] Additionally, PSI are the only inmunosuppressive medications that seem to diminish the incidence of malignancy.

MATERIALS AND METHODS

We followed 21 de novo renal transplant patients who underwent conversion to everolimus combined with an antimetabolite (mycophenolate mofetil [MMF] or EC-MPS). All of the patients received a statin (lovastatin).

The mean age was 35 ± 17 years (range, 6 to 65), including five children (23.8%) of 6, 13, 14, 15, and 17 years of age. The prevalence of male recipients was (57%; the overall mean weight, 64 kg ± 13 (range, 48 to 95) with a mean body mass index (BMI) of 24 ± 4 kg/m^2 (range, 18 to 33), three of whom were obese with a BMI between 30 and 35. All patients were Hispanic. Cadaveric donors supplied 15 transplants (71%). The mean posttransplant time at entry was 18 ± 9 months (range, 3 to 40) and the mean

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follow-up time on everolimus was 10 ± 5 months (range, 2 to 22), including 6 (28.6%), for more than 12 months; 10 (47.6%), between 10 and 12 months; and 2 (9.5%), less than 3 months.

The cause of renal failure was unknown in seven (33%); glomerulonephritis in six (29%); an other disorder in four (19%); arterial hypertension in three (14%); and diabetes in one subject (5%). The type of calcineurin inhibitor (CNI) was cyclosporine (CsA) in 15 eases (71%); tacrolimus (TAC) in 1 (5%); and none in 5 (24%). The C2 levels of CsA before conversion were 732 ± 342 ng/mL (range, 194 to 1756), and the patient on tacrolimus showed a trough concentration of 4.5 ng/mL. Twelve patients (60%) were taking MMF, 8 (40%) were taking EC-MPS, and one not coadjuvant medication. Data are described as mean values (± standard deviations).

RESULTS

No significant changes were observed in hepatic functions: alanine aminotransferase (ALT; preconversion 29.3 IU; postconversion day 180, 30.5 IU), aspartate aminotransferase (AST; preconversion, 22.5 IU; postconversion day 180, 25.5 IU), leukocytes (preconversion 7335 ± 4364/mm^3, [range, 3000 to 23300]; postconversion after 1 year 7333 ± 2274/mm^3 [range, 5700 to 11700]), hemoglobin (preconversion, 11.9 ± 2 g/dL [range, 8.5 to 15.5]; postconversion after 1 year, 12.6 ± 1.9 g/dL [range, 9.9 to 15.6]), platelets (preconversion, 313,000 ± 112,000/mm^3 [range, 157,000 to 509,000]; postconversion after 1 year, 311,000 ± 116,000/mm^3 [range, 108,000 to 490,000]), total cholesterol (preconversion, 185 ± 48.8 mg/dL [range, 116 to 296]; postconversion after 1 year, 171 ± 46.2 mg/dL [range, 118 to 202.5]), high-density lipoprotein (HDL; preconversion, 42 mg/dL [range, 28.5 to 70]; postconversion after 1 year, 33 ± 3.8 mg/dL [range, 30.8 to 36.1]), or triglycerides (preconversion, 182 ± 86.6 mg/dL [range, 86.5 to 390.9]; postconversion after 1 year, 173 ± 113 mg/dL [range, 104 to 303.2]).

Dose adjustment of everolimus was required for one patient at day 14, three at day 30, three at day 60, five at day 90, three at day 180, and one at day 360.

Regarding renal function, a trend toward a creatinine decline was observed: preconversion, 1.7 ± 0.8 mg/dL (range, 0.5 to 3.3) and postconversion after 1 year, 1.5 mg/dL (range, 1.1 to 2.2). Regarding proteinuria, preconversion it was 241.5 ± 193.3 mg/24 h (range, 0 to 646); postconversion after 1 year, 295.1 ± 284 mg/24 h (range, 0 to 730).

Three cases (14%) of biopsy-confirmed acute rejection were reported; the first one at month 6, and the other two after 1 year, but there was no loss of the graft; In 10 patients (48%), it was possible to discontinue at least one antihypertensive medication: 8 patients (38%) were prescribed one hypotensor; 1 patient (5%), 2 agents, and 1 (5%), 3 agents. There was no loss of patient follow-up, discontinuation or mortality during follow-up.

DISCUSSION

Currently, the survival rate for renal grafts exceeds 90% per year.[4] However, diminishing graft loss in the long term is still a challenge. The advent of PSIs offers the possibility of decreasing renal toxicity with safety and efficacy.

In our experience, conversion to everolimus for immunosuppressive maintenance therapy in renal transplantation did not affect the number of leukocytes, hemoglobin, or platelets.[3,5] Unlike other publications where increased dyslipidemia was observed with everolimus in renal transplant recipients,[6,7] we noted stability of cholesterol and triglycerides at 1-year follow-up without statin dose adjustment, as reported by Pohanka.[3] None of our recipients showed increased proteinuria at 1 year compared with the initial value, unlike a study of sirolimus.[5] Conversion to everolimus led to renal functional stability or improvement, as shown by the creatinine values, similar to results observed by Morales et al[5] and Vitko et al.[6]

Regarding the incidence of acute rejection episodes, we observed 14%, which is within the expected range, without increased risk as confirmed by Webster et al.[17] We noted stability in C0 everolimus blood target levels, reflected in the small number of patients (average, 12%) who required dose adjustment.[8] Although there was no patient with neoplasia in our group, it has been shown that PSI diminishes the incidence of malignancy in renal transplant recipients.[5,9] Just as sudden discontinuation of CNI and start of sirolimus[10] is reflected in a significant reduction in hypertension, we observed a similar phenomenon in our study with everolimus.

It is interesting to note that we achieved adherence to treatment with everolimus in 100% of cases, unlike other publications that noted PSI discontinuations due to a low tolerance to the medication.

In conclusion, everolimus has become an excellent choice for conversion immunosuppression in maintenance therapy, offering safety and efficacy in outcomes that shape the survival rate, namely, acute rejection, chronic nephropathy, and recipient mortality. Also everolimus offered stability in metabolic functions. Long-term follow-up is required to confirm these results.

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