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1648 EVEROLIMUS AS PRIMARY IMMUNOSUPPRESSANT IN STABLE KIDNEY TRANSPLANTS WITH CNI ELIMINATION: A SUCCESSFUL STRATEGY

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Introduction: Everolimus (EVL) was approved as immunosuppressive drug in 2005 but almost all clinical trials before approval were in combination with Cyclosporin A (CyA), for that reason experience in conversion with calcineurin inhibitor (CNI) elimination was very limited. We report the combined experience of two renal transplant centres in conversion of stable transplant patients from a CNI-based regimen to an EVE-based regimen for different indications.

Patients and methods: Between Mar/05 and Dec/07 155 patients were converted from a CNI to EVL with rapid and complete elimination of CNI (98 patients in HCM and 57 in HUMV). All patients were converted in the same way (Initial dose between 2 and 4 mg/day of EVL divided in two doses and half dose of CNI until EVL through level in the desired range and then suspension). EVL through levels were measured at 4 and 8 days after initiation and then monthly up to three months and every three months thereafter.

Results: Indications for conversion were: Chronic allograft nephropathy/CNI nephrotoxicity (36.8%), malignant neoplasm (29.0%), cardiovascular disease (16.8%), and other reasons in 13.5% of patients. In 6 patients (3.9%) conversion was performed as a preventive strategy in the first year postransplant in order to minimize the long-term CNI toxic effects. Two thirds of patients were males. Mean age at conversion was 55.8±12.6y and median time from transplant to conversion was 78 months (range 3-286m). Approximately the same proportion of patients were under CyA and Tacrolimus. Mean initial dose was 2.94±0.7 mg/day and mean through levels at four days were 9±5.4 ng/mL (range: 1.8-28.5). In 92.4% this first level was over 3 ng/mL and in 78.6 over 5 ng/mL. Mean time to CNI complete elimination was 5 days (p25-75 4-8 days).

EVL had to be prematurely eliminated in 33 patients (21.3%) due to drug intolerance/toxicity (8.9%), poor graft evolution (5.1%), severe infection (1.9%) or other reasons (5.2%). Among drug toxicity, dermal eruption (3.2%) and non-infectious pneumonitis (2.6%) were the most frequent reasons for EVL withdrawal. Median time for EVL suspension in this subgroup was 3.7 months (p25-75 1.4-11.1m). Among poor graft evolution the reasons were proteinuria (2.6%), deterioration of renal function (1.9%) and acute rejection (0.6%).

Renal function was analyzed in the 87 patients with a functioning graft and continuing on EVL at twelve months postconversion. Creatinine clearance (Cockcroft-Gault formula) significantly improved at six months (57.0±21.4 vs 59.9±23.4 mL/min; p=0.001) but that difference decreased at 12 months (58.3±22.9mL/min; p=0.15)

Conclusions: Conversion to EVL with complete suspension of CNI is a safe procedure in terms of risk of graft rejection. Approximately 10% of patients do not tolerate EVL due to drug toxicity and in an additional 10% of it must be eliminated for different reasons, specially poor graft evolution. This might be reduced with a more adequate selection of candidates. Progressive deterioration of renal function before conversion was apparently detained with this intervention.

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1649 EVEROLIMUS (EVE)IN MAINTENANCE TREATMENT IN RENAL TRANSPLANT RECIPIENTS SWITCHED FROM CALCINEURIN INHIBITORS (CNI)

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Everolimus is a proliferation signal inhibitor utilized in combination with CNI as immunosuppression therapy. This approach resulted in excellent efficacy when EVE is combined with reduced exposure to CNI. The present paper reports the results with patients who were switched from CNI to EVE, allowing cessation of CNI related toxicities and maintaining efficacy. From february 2005, 120 cadaver kidney grafted patients (82 men and 38 women), were switched from CNI to EVE. The age of patients was 55 15 years, with 8.5 6 (1-23) years follow-up period. The basal immunosuppressant was Prednisone, Mycophenolate Mofetil (MMF)/ Mycophenolic acid (MPA) and Neoral Cyclosporine/Tacrolimus. Everolimus blood levels were maintained between 3-5 ng/ml. CNI was stopped using an abrupt conversion protocol. CsA /Tac treatment was stopped after the morning dose and EVE was started at 1.0 mg/day. MMF/MPA-based therapy was continued as well as prednisone while target EVE trough blood levels (3-5 ng/ml) were achieved. At 1 year, graft and patient survival was 100% and there was no acute rejection. Blood pressure remained unchanged and there were not changes in glucose metabolism. Lipids increased silghtly during first 3 months after EVE treatment. Proteinuria appears in patients with previous glomerular lesion. GFR improved in 55% of patients.

Conclusion: Conversion of renal transplant recipients from CNI-based immunosuppressive regimen to EVE in renal transplant recipients is safe and affect slightly to lipid metabolism.

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1650 USE OF EVEROLIMUS IN DE NOVO RENAL RECIPIENTS: INITIAL EXPERIENCE IN THE GREEK POPULATION

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Although everolimus has proven to be as clinically efficacious as MMF, there are reports that proliferation signal inhibitors have resulted in poor tolerability. This study aims to report the experience of a Greek transplant center using either everolimus or MMF in de novo renal transplant recipients. In this retrospective study a cohort of 40 patients who received everolimus after renal transplant was matched for 10 descriptive parameters with a cohort of another 40 patients who received MMF. The primary endpoint was renal function measured by creatinine and its clearance as well as wound dehiscence and opportunistic infections. The mean creatinine clearance for month 3 was 61.03 ± 16.99 ml/min and 60.99 ± 8.03 for the living related recipients on everolimus and MMF respectively. The mean creatinine clearance for month 3 was 71.24 ± 12.61 ml/min and 62.61 ± 20.24 for the cadaveric recipients on everolimus and MMF respectively. In addition, the incidence of wound dehiscence was 33.34% and 3.92% and the incidence of CMV infection was 8.33% and 17.64% for the same two groups respectively.

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1651 PROLONGED EFFECTS OF EVEROLIMUS ON WOUND HEALING IN EXPERIMENTAL INTESTINAL ANASTOMOSES

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Introduction: Minimizing cyclosporine and steroid exposure has been the main reason to introduce mTOR inhibitors, such as Everolimus, in transplantation surgery, the ultimate goal being reduction of side effects of the post-transplant poly-drug regime. However, the use mTOR inhibitors in the solid organ recipient, has shown a worrying increase in surgical complications, which warranted further investigation. In an animal model of bowel anastomoses that is frequently validated for measurement of wound healing, Everolimus proved to have a negative, dose related effect on early wound healing. The duration of the effect is not known because previous experiments were limited to the first 7 days after operation. Here, we have investigated the effect of Everolimus over a longer postoperative period.

Materials and methods: Three groups of 48 Wistar rats received a daily oral dose of Everolimus of 1 mg/kg (E-1)or 2 mg/kg (E-2), or saline (controls) form the day of operation onwards. In each rat a resection of 1 cm ileum and 1 cm colon was performed, and end-to-end anastomoses were constructed using 8 interrupted sutures. On day 7, 14 and 28 the animals were killed and wounds, also those in the fascia, were analysed for mechanical (bursting pressure BP, breaking strength BS and histological (collagen) parameters.

Results: In both ileum and colon, a diminished ($p<0,05$ vs controls) BP was seen in the E-2 group after 7 days. The ileal BS at 14 days did not significantly differ between groups. However, after 28 days, ileal BS was significantly lower in both groups that received Everolimus ($p=0,0001$). In colon anastomoses a significantly reduced BS was seen in both experimental groups after 7 ($p<0,0001$