American Journal of Transplantation

OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION
AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

TRANSPLANT 2001

CHICAGO
MAY 11-16
2001

SUPPLEMENT 1 • VOL 1 • 2001

MUNKSGAARD

PLENARY:
JOINT SESSION

Abstract# 428

SIROLIMUS PREVENTS TUMOR PROGRESSION: mTOR TARGETING FOR THE INHIBITION OF NEOPLASTIC PROGRESSION. Fulung Luan,[1] Mary Maluccio,[2] Vijay K. Sharma,[1] Minoru Hojo,[1] Milagros Lagman,[1] Manikkam Suthanthiran.[1]
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Post-transplant malignancy is a life-threatening complication. Immunosuppressive drug induced impairments in host-immune effector mechanisms are considered to be the prime mechanisms. This paradigm has been challenged by the report that cyclosporine (CSA) can promote tumor progression independent of its effect on the host immune cells and by a cell autonomous mechanism. The universality of this mechanism was investigated by exploring the effect of tacrolimus and sirolimus on tumor progression. SCID-beige mice that lack functional T-cells, B-cells and NK cells were used as the tumor bearing host, and a renal carcinoma was used as the tumor inoculum. The impact of these two immunosuppressants was diametrically opposite. Whereas tacrolimus (4 mg/kg, QOD, SQ) increased the number of pulmonary renal cancer metastases ($p<0.05$), Bonferroni p value), sirolimus (4 mg/kg, QOD,SQ) prevented pulmonary metastasis ($p<0.001$). Furthermore, the increase in metastases observed with CSA (20 mg/kg/QOD/SQ) was completely prevented by sirolimus ($p<0.001$). The dramatic effect of sirolimus was also evident in the immunocompetent BALB/c mice. Tacrolimus ($p<0.001$) as well as CSA ($p<0.001$) increased the number of pulmonary renal cancer cell metastases, and sirolimus ($p<0.001$) prevented metastases in the BALB/c mice as it did in the SCID-beige mice. Sirolimus ($p<0.01$) also prevented pulmonary metastasis in the CSA-treated BALB/c mice and in the highly malignant intrarenal cancer model. Survival experiments showed prolongation following sirolimus treatment of tumor-inoculated SCID-beige mice ($p<0.01$) or BALB/c mice ($p<0.01$). Studies to explore mechanisms for the salutory effects of sirolimus showed: 1) a reversal of the invasive phenotype of renal cancer cells (ascertained by scanning electron microscopy); 2) reduction in cell-division (determined by flow cytometric analysis of CFSE-loaded cancer cells); and 3) promotion of apoptosis (enumerated by flow cytometry). Our studies demonstrate that sirolimus has a diametrically opposite effect to that of calcineurin inhibitors on tumor progression. The unlinking of immunosuppression needed for allograft protection from mechanisms constraining neoplasia progression opens new avenues for the prevention and/or management of post-transplant neoplasia.

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FTY720 COMBINED WITH NEORAL® AND CORTICOSTEROIDS IS EFFECTIVE AND SAFE IN PREVENTION OF ACUTE REJECTION IN RENAL ALLOGRAFT RECIPIENTS (INTERIM DATA). Helio Tedesco,[1] Barry Kahan,[2] Georges Mourad,[3] Yves Vanrenterghem,[4] Josep Grinyo,[5] Willem Weimar,[6] Pascale Pellet,[7] Lawrence Chodoff,[8] Tomasz Sablinski.[8]
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FTY720 is a potent immunomodulator with unique effects on lymphocyte homing. Methods: Multicenter, randomized, open-label dose finding study to evaluate safety, tolerability and preliminary efficacy of FTY720 vs. mycophenolate mofetil (MMF) with Neoral® and corticosteroids (CS) in de novo renal transplantation. Adults aged 18-65 undergoing primary cadaver or living donor (non-HLA identical) renal transplantation, who exhibited good allograft function during the first 12 hours post-transplant, were randomized to one of four regimens of FTY720 (loading dose [LD] on Day 1, followed by a once daily maintenance dose), or to MMF 2 gm/day. All patients received concurrent Neoral + CS per center standard. Induction with antilymphocyte antibodies (Ab) or anti-IL-2Rα Ab was not allowed. Results. 209 patients were enrolled, and preliminary efficacy data are available for 159 patients who completed at least 30 days on study.

Treatment*	Number (%) Biopsy-confirmed Acute Rejection
FTY720 1mg LD + 0.25mg QD	8/39 (20.5%)
FTY720 2mg LD + 0.5mg QD	13/37 (35.1%)
FTY720 4mg LD + 1.0mg QD	4/20 (20.0%)
FTY720 4mg LD + 2.5mg QD	1/28 (3.6%)
MMF 2 gm/day	5/35 (14.3%)

Safety FTY720 was well tolerated. Episodes of transient bradycardia without symptoms or sequelae, most of which occurred within first 24h post-transplant, were reported in 11/124 (8.9%) of FTY720-treated patients vs. 2/35 (5.7%) of MMF-treated patients. Graft survival is 99% (one graft loss in the MMF group) and patient survival is 100%. Conclusions: Preliminary analysis indicates that FTY720 appears to be effective in the prevention of acute rejection in de novo renal transplant patients when used with Neoral and CS. Additional trials are underway to evaluate the role of FTY720 in the prevention of acute rejection and graft loss after renal transplantation.

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ICOS/B7RP-1 COSTIMULATION IN ACUTE AND CHRONIC ALLOGRAFT REJECTION. Engin Ozkaynak,[1] Wei Gao,[1] Nida Shemmeri,[1] Chi Wang,[1] Anthony J. Coyle,[1] Wayne W. Hancock.[1]
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In vitro data show activation of primary T cells requires CD28/B7 costimulation but effector T cell functions are CD28/B7-independent. In addition, costimulation blockade with CTLA4-Ig or CD154 mAb causes prolonged graft survival but chronic rejection intervenes, indicating additional costimulatory pathways are active in vivo. We present data on the role of inducible costimulatory molecule (ICOS) and its ligand, B7RP-1, in transplantation (Tx). Serial Northerns showed that whereas normal heart lacked ICOS mRNA, intragraft expression was detected by 5d and peaked at rejection at 7d in unmodified BALB/c->BL/6 mouse cardiac allograft recipients; immunohistology with a blocking rat anti-mICOS mAb (12A8) localized ICOS to infiltrating T cells. Therapy with 12A8, but not an isotype-matched, non-blocking rat anti-mICOS mAb (15F9), prolonged graft survival (20±1d vs. 7-8d, respectively, $p<0.001$), and in ongoing studies, a mICOS-Ig fusion protein prolonged survival to >18d ($p<0.01$). Molecular assays of 7d grafts showed that compared to controls, anti-ICOS mAb suppressed intragraft expression of IFN-γ, IL-10 and multiple chemokines and their receptors. Mice treated with a subtherapeutic course of CsA rejected their allografts by 10d, as did mice treated with IgG/low CsA, whereas allografts in recipients treated with anti-ICOS mAb/low CsA are currently >60d post-Tx ($p<0.001$). A role for ICOS in chronic rejection was also assessed; allografts were performed in conjunction with CD154 mAb (250 µg, i.p. at Tx) plus anti-ICOS or control IgG therapy (500 µg/d, bid, i.p., for 14 d), and were harvested at 30d post-Tx. Scoring of elastin-stained allografts (>6/group) showed IgG-treated controls had severe Tx arteriosclerosis (4.4 ± 0.6, mean ± SD) whereas vessels were largely normal post-ICOS mAb (0.2 ± 0.1, $p<0.001$), and the myocardium was well preserved. In summary, we show that (i) ICOS is involved in acute rejection; (ii) targeting ICOS/B7RP-1 interactions prolongs allograft survival and suppresses intragraft cytokine expression and T cell activation; (iii) the beneficial effects of blocking ICOS/B7RP-1 costimulation are not impaired by concomitant CsA therapy; and (iv) ICOS-dependent costimulation plays a key role in the development of Tx arteriosclerosis, including after interruption of CD40/CD154 signaling. Hence, our data demonstrate for the first time a key role of the ICOS/B7RP-1 pathway in acute and chronic alloresponses.

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TWO-YEAR INSULIN INDEPENDENCE AND METABOLIC FOLLOW-UP AFTER ISLET-ALONE TRANSPLANTATION IN AUTOIMMUNE DIABETES. A. M.J. Shapiro,[1] E. A. Ryan,[1] R. V. Rajotte,[1] G. S. Korbutt,[1] T. Kin,[1] K. O'Kelly,[1] G. L. Warnock,[1] D. L. Bigam,[1] N. M. Kneteman,[1] J. R.T. Lakey.[1] *[1]Surgery, University of Alberta, Edmonton, AB, Canada.*

Purpose: To evaluate longer-term outcomes of islet-alone transplantation in autoimmune diabetes.

Methods: 15 consecutive patients with longstanding Type 1 diabetes underwent islet-alone transplantation with ABO-compatible cadaveric islets infused intraportally by percutaneous access. Steroid-free immunosuppression consisted of daclizumab induction with maintenance sirolimus and low-dose tacrolimus.

Results: Median follow-up is 17.6 months (first 7 patients) and 8.5 months overall, with the longest patient remaining off insulin for 21 months currently. All patients have sustained insulin production (C-peptide meal: mean 1.99 ± 0.2 pre, rising to 3.90 ± 0.7 ng/ml at 90 min). 12/15 patients are free of insulin currently (4 have normal glucose tolerance). 2/15 have a stable form of type II diabetes controlled with oral hypoglycemic agents and occasional low doses of insulin (<10 units/day), and 1/15 awaits a second islet infusion. All patients have required more than one pancreas donor (mean islet mass 11,437 IE/kg). There have been no episodes of CMV infection (mismatches in 8/15 cases). There have been no cases of PTLD, malignancy or serious infection to date. Mean serum creatinine was unchanged pre-transplant vs current (1.1 pre vs 1.1 mg/dl), although 2 patients with inadequate pre-transplant clearance had post-transplant elevation which has improved by withdrawal of tacrolimus and replacement with mycophenolate.

Mean HbA1C was completely corrected by islet transplant (mean 8.9% pre vs 5.6% (3 mo), 5.7% (6 mo) and 5.6% (12 mo)). IVGTT data indicate that acute insulin response (AIRg) was consistently maintained for up to 12 months of available follow-up, with no evidence of deterioration in function over time (no acute rejection and no autoimmune recurrence). The increment in AIRg was more marked after the subsequent transplant than after the first (0.12 ±0.1 initial vs 2.42±0.6 mU/ml subsequent, $p<0.01$), suggesting that the initial transplant may have facilitated engraftment of the subsequent graft.

Conclusions: Sustained long-term independence from insulin can be achieved with low risk in patients undergoing islet-alone transplantation using a steroid-free immunosuppressive protocol.