**U2: Transplantation: immunosuppressive regimens**

**DATAILED ANALYSIS OF FIRST AND RECURRENT ACUTE REJECTIONS IN A LARGE, COMPARATIVE, MULTICENTRE, EUROPEAN TRIAL IN RENAL TRANSPLANTATION**

M. Salvadori for the European Tacrolimus vs. Cyclosporin-Microemulsion Renal Transplantation Study Group

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This large, prospective 6-month study was conducted at 50 European centres and involved 557 adult renal transplant recipients who were randomised to receive either tacrolimus (n=266) or cyclosporin-microemulsion (cs-me)(n=271) concomitant with corticosteroids and azathioprine after renal transplantation. The main endpoint was the incidence of acute rejections. Results: The treatment groups had comparable baseline characteristics. The incidence of first biopsy-proven acute rejection was 19.6% (56/286) with tacrolimus therapy and 37.3% (101/271) with cs-me therapy, p<0.001. Of these rejections, 9.1% (26/286) in the tacrolimus group and 17.3% (47/271) in the cs-me group were steroid resistant (p<0.05). Analysis of the Banff scores in the tacrolimus group showed: 22 grade I, 30 grade II, and 4 grade III rejections. In the cs-me group, 39 had grade I, 47 grade II, and 15 grade III rejection. Recurrent rejections occurred in 3 patients (1.0%) in the tacrolimus group and 15 patients (5.5%) in the cs-me group which switched the immunosuppressor (p=0.01). Of the recurrent rejections (2 tacrolimus and 14 cs-me) were resistant to steroid treatment (p=0.05). Histological grades of the subsequent rejections were: 2 Banff I and Banff II in the tacrolimus group compared to 9 Banff I, 7 Banff II, and 3 Banff III rejections in the cs-me group. During the recurrent rejection, 12 patients in the cs-me group were switched to tacrolimus therapy compared to no patient in the tacrolimus group. Conclusion: Therapeutic conversion group in second rejection was more effective compared to the cs-me group. MMF therapy has significant advantages over cs-me therapy with respect to the prevention of first and recurrent rejection after kidney transplantation.

**SOLUBLE CYTOKINE RECEPTORS CHANGE WITH RAPAMYCIN IN RENAL TRANSPLANTS**

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Previously, we have shown that RAPA induces significant changes on renal transplants (RXT) aspiration biopsy (AB) cultures synthesis of IL-1α, IL-2, IL-6, IL-10, MCP-1, TGF-β1 and soluble (s)TNFRI. Also, we observed that IL-2, IL-6, sTNFRI, sTNFRII sII-2-receptor-α, produced by AB cultures significantly correlated with acute rejection (rej) in RXT. Cytokines present in blood circulation are not helpful for the diagnosis of immunologic events post-RTX but their receptors, which are much more stable than cytokines might assist on immunologic surveillance post-RTX. We hypothesized that cytokine receptors present in circulation might be modulated by RAPA.

12 cadaver RXT treated with RAPA were compared to 18 cadaver RXT treated with MMF. Both groups also received CsA and Pred. All RXT remained rej-free for the first six months at least. Both were studied on day seven post-RTX. SII-2-receptor-α, sII-6R, sTNFRI and sTNFRII were measured by ELISA, R&D, USA. Furthermore, sTNFRII and sTNFRII were measured in 29 cadaver RXT with rej, treated with CsA-AZA-Pred. Every rej started within three weeks post-RTX and was confirmed by biopsy.

We did not find any significant differences comparing three groups for HLA matching, PRA before RTX, and blood CsA levels. The values are expressed in pg/ml, MMF/RAPA order, SII-2-receptor-α: 590±637/299±1170; sII-6R: 54233±13414/45591±10189; sTNFRI: 886±14583/4610±2508; sTNFRII: 938±3166/662±2214. All are significantly different, P=0.012, 0.011, 0.001, 0.0007 and 0.019 respectively (Kruskal-Wallis ANOVA). In rejection group, sTNFRI: 846±5239; sTNFRII: 932±3619; sTNFRII was not different comparing rej versus MMF and was significantly higher as compared with RAPA. DNFRII was significantly higher in rej than among either MMF or RAPA RXT. We conclude that RAPA downregulates serum cytokine receptors compared to MMF in the early days of. As STNFRII/II are upregulated during rej we speculate that RAPA induced changes may be associated with a stronger immunosuppressive effect.

**MICOFENOLAT MOFETIL IN TREATMENT OF ALLOGRAFT NEPHROPATHY IN THE MIDDLE AND LATE FOLLOW UP.**

M.M. Kaabak, V.A. Goriajnov, E.A. Molchanova

NEPHROPATHY IN THE MIDDLE AND LATE FOLLOW UP.

M.M. Kaabak, V.A. Goriajnov, E.A. Molchanova

This study was conducted in 50 European centres and involved 557 adult renal transplant recipients who were randomised to receive either tacrolimus (n=266) or cyclosporin-microemulsion (cs-me)(n=271) concomitant with corticosteroids and azathioprine after renal transplantation. The main endpoint was the incidence of acute rejections. Results: The treatment groups had comparable baseline characteristics. The incidence of first biopsy-proven acute rejection was 19.6% (56/286) with tacrolimus therapy and 37.3% (101/271) with cs-me therapy, p<0.001. Of these rejections, 9.1% (26/286) in the tacrolimus group and 17.3% (47/271) in the cs-me group were steroid resistant (p<0.05). Analysis of the Banff scores in the tacrolimus group showed: 22 grade I, 30 grade II, and 4 grade III rejections. In the cs-me group, 39 had grade I, 47 grade II, and 15 grade III rejection. Recurrent rejections occurred in 3 patients (1.0%) in the tacrolimus group and 15 patients (5.5%) in the cs-me group which switched the immunosuppressor (p=0.01). Of the recurrent rejections (2 tacrolimus and 14 cs-me) were resistant to steroid treatment (p=0.05). Histological grades of the subsequent rejections were: 2 Banff I and Banff II in the tacrolimus group compared to 9 Banff I, 7 Banff II, and 3 Banff III rejections in the cs-me group. During the recurrent rejection, 12 patients in the cs-me group were switched to tacrolimus therapy compared to no patient in the tacrolimus group. Lymphocyte counts in both treatment groups in the second rejection were compared. Conclusion: Therapeutic conversion group in second rejection was more effective compared to the cs-me group. MMF therapy has significant advantages over cs-me therapy with respect to the prevention of first and recurrent rejection after kidney transplantation.
The purpose of our study was to evaluate the regulation of the expression of heat shock protein 70 (HSP70), known as a cell protector against environmental stress, after cyclosporin A (CsA) and Mycophenolate Mofetil (MMF) administration in renal ischemia/reperfusion injured rats. Spraque-Dawley rats were classified five groups according to experimental methods. The left nephrectomy was performed then clamping the left renal vascular pedicle for 60 minutes of ischemia (ischemia group), control group underwent right nephrectomy then clamping the left renal pedicle for 60 minutes followed by 60 minutes reperfusion. CsA group was administrated cyclosporin A (25mg/kg/day, S.C.) after operation. CsA+MMF group was administrated cyclosporin A (25mg/kg/day, S.C.) and MMF (10mg/kg/day, P.O.). MMF group was administrated MMF (10mg/kg/day, P.O.). The left kidney was obtained 7 days after operation. The expression of HSP70 was examined by immunohistochemistry with Image Analyzer. By immunohistochemistry, the expressions of HSP70 were more increased in ischemia and agent-administered group than control group (p<0.05). Immunoreactivity in agent-administered group was higher than in ischemia group (p<0.05). There was a little difference between CsA, MMF and CsA + MMF group. These results suggest that CsA and MMF upregulate the expression of HSP70 in ischemia /reperfusion injury.

LIVING DONOR TRANSPLANT IN THE CYCLOSPORINE ERA. A SINGLE CENTER EXPERIENCE

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We report our experience with 190 living donor kidney transplants (txs) treated with calcineurin inhibitors (1984-1999). There were 121 males and 69 female. Patients (pts) age at tx was: 31.8±12.25 years with a mean dialysis time of 26.5±35 months; pre-emptive tx was performed in 14 pts; 168 tx had a living-related donor and 22 a living-unrelated one. The basic disease was glomerulonephritis (GN) in 87 pts, urinary tract congenital abnormalities in 30, inherited disease in 22, in 40 pts the disease was undetermined. Immunosuppressive regimens included mono or double therapy with cyclosporine (CyA) in 60 pts, triple therapy with CyA and tacrolimus in 116 and RAD or sirolimus was used in 11 pts. Survival probability was calculated with the Kaplan-Meier and compared by generalised Wilcoxon (Gehan) test. After a median follow-up of 69.5 months, 144 pts are still under clinical observation, their mean plasma creatinine is 2.0±1.1 mg/dl. 34 grafts were lost. Causes of graft failure were: 12 renal thromboses, 5 acute rejections, 13 chronic rejections, 4 recurrences of IgA GN. 6 patients died, 6 have been lost to follow-up. 100 pts had one or more rejection episodes, 91/100 pts still have a functioning graft after a mean time of 95.1±38.7 months. The 10 year graft survival and the 10 year pure graft survival were 76.47 and 80.21 % respectively. The graft half-life was 29.7 years. Less than one year pre-tx dialysis and absence of locus DR incompatibility, were significantly associated (P<0.01; P<0.05 respectively) with a better long-term graft survival while basic disease, rejection, source of living donor, were not. Living donor tx gives excellent results. Since long dialysis duration can adversely influence graft survival, pre-emptive or early tx is recommended.

ATG (FRESENIUS) AND T CELL ACTIVATION

Transplantation Institute, University Medical School; Department of Immunology, Warsaw University; Warsaw, Poland

Polyclonal antithymocyte globulins (ATGs) are currently used in severe aplastic anemia, for the treatment of organ allograft acute rejection or as prophylactic treatment of rejection and for the treatment of GVH disease. ATG treatment induces a major depletion of peripheral blood lymphocytes. The precise mechanism of action of ATGs remain largely unknown. ATGs are a mixture of multiple antibodies to various lymphocyte surface antigens. ATGs contain antibodies to CD2 and CD3, which account for their mitogenic properties.

We compared the sensitivity of naive versus OKT-3-activated PBL to ATG (Fresenius AG). T cells were cultured in plates coated with (or without) OKT3 and with (or without) ATG (100, 200, 400 mg/ml). Surface expression of CD69 and CD25 molecules was analysed by flow cytometry (FACS Calibur/ Becton Dickinson).

The data suggest that ATG concentrations used in vitro are mitogenic for peripheral T cells, MLR and decreased the proliferation of OKT-3-activated T cells. ATG induced CD69 and CD25 molecules expression on T cells (both CD4+ and CD8+ cells). The expression of CD69 was higher on CD8+ cells, although expression of CD25 was similar in both subpopulations. Our data suggest that ATG (Fresenius AG) induced activation of T cells (both CD4 and CD8 subpopulations), but decreased proliferation of OKT-3-activated T cells.

EXPRESSION OF THE LEUKOCYTE FAS MOLECULE DURING FIRST MONTHS AFTER RENAL TRANSPLANTATION

Transplantation Institute, University Medical School, Warsaw, Poland

Apoptosis may be induced in response to various cytotoxic stimuli, including activation of cell surface receptors such as Fas, TNFR1 or TCR. An area of particular interest has been the regulation of apoptosis by the receptor-ligand pair: Fas (CD95) and Fas, TNFR1 or TCR. An area of particular interest has been the regulation of apoptosis by the receptor-ligand pair: Fas (CD95) and Fas, TNFR1 or TCR. An area of particular interest has been the regulation of apoptosis by the receptor-ligand pair: Fas (CD95). 

The data suggest that ATG (Fresenius AG) induced activation of T cells (both CD4 and CD8 subpopulations), but decreased proliferation of OKT-3-activated T cells.

UP-REGULATION OF HSP70 OF CYCLOSPORIN A AND MYCOPHENOLATE MOFETIL IN ISCHEMIA AND REPERFUSION INJURED RAT KIDNEY

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Abstracts

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TREATMENT OF CHRONIC ALLOGRAFT NEFROPATHY WITH MYCOPHENOLATE MOFETIL AFTER KIDNEY TRANSPLANTATION: A SPANISH MULTICENTER STUDY

M. González Molina, D. Serrín, R. García del Moral, M. Carreras, E. Sola, P. Gómez Ulloa, C. Capelevich and M.A. Gentil as representatives of the Spanish Group for the Study of Mycophenolate Mofetil in Chronic Allograft Nephropathy. Hospital Carlos Haya, Avda de Carlos Haya s/n, Servicio de Nefrología Málaga, Spain

Mycophenolate Mofetil (MMF) has been shown to decrease the incidence of acute rejection but its role in Chronic Allograft Nephropathy (CAN) is still unclear. This is a prospective, multicenter, open-label study with the participation of 16 Spanish hospitals to analyze the effect of MMF on the renal function in patients with biopsy-proven CAN. A total of 122 (61 from cadaver donor) renal transplant recipients (age: 37±11.6 years) were included in the study: 61 treated with Cyclosporin (CsA) and Prednisone (P), to which MMF (2g/day) was added and 61 treated with CsA, P and Azathioprine (AZA), the latter being replaced by MMF (2g/day). Renal function was measured by serum creatinine and creatinine clearance (Ccr) calculated by the Cockcroft-Gault formula. Multiple regression was used to calculate the slopes of the inverted creatinine levels and the Ccr from 3 years before the addition of MMF to the treatment until the end of the study. The kidney biopsy (Banff ’97) were blindly assessed by 3 pathologists and the final results were calculated using concordance of two or more results as a criterion for semiquantitative variables: Fourteen (11.5%) patients showed CAN grade I, 65 (53.3%) grade II and 43 (35.2%) grade III. The median follow-up period after the addition of MMF was 18 months (13-36 months). Nineteen patients did not completely study the study; one died and the other 18 because of adverse effects related to MMF. The slopes of inverted creatinine levels and Ccr both before and after the administration of MMF were -0.0002±0.00007 (p<0.001) for all the patients, -0.0025±0.0004 (p<0.001) for the A2 group patients, and -0.0155±0.0032 (p<0.001) for the 65 patients who showed no changes in the blood levels of CsA throughout the study (142±543 vs 138±612, p=0.033). This study demonstrates that MMF has a protective effect against graft loss in patients with CAN and this effect is independent of the blood levels of CsA.

PHARMACOKINETIC INTERACTION BETWEEN TACROLIMUS AND LEVOFLOXACIN IN KIDNEY TRANSPLANT RECIPIENTS

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The aim of this study was to evaluate the influence of levofloxacin (LEVO), a new fluoroquinolone antimicrobial agent, on the tacrolimus (TACRO) pharmacokinetics. Five kidney transplant recipients treated orally with TACRO were evaluated: area under curve (AUC) and creatinine clearance (Ccr) obtained in the course of TACRO administration were significantly higher than those obtained with the administration of TACRO alone (p<0.005) while no significant difference was found for the other pharmacokinetic parameters investigated.

The results of the present study seem to suggest that tacrolimus disposition can be influenced by levofloxacin coadministration.

FIBROBLAST GROWTH IS INHIBITED BY MYCOPHENOLIC ACID

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There is some evidence from clinical and experimental in vivo studies that mycophenolic acid has a direct influence on fibroblasts. We reported that in patients treated with mycophenolic acid woundhealing disturbances are more frequent after solid organ transplantation. Furthermore recent experimental studies documented that mycophenolate suppresses interstitial fibrosis in the kidney of 5/6 nephrectomized rats. Former biochemical studies document that fibroblasts rely to a major extent on de novo purine synthesis. Therefore they are potential target cells for mycophenolic acid. To test the hypothesis that mycophenolic acid affects fibroblast growth we incubated fibroblast cultures with concentrations of mycophenolic acid to the subtherapeutic to supratherapeutic range (0.01, 0.1 and 1 mg/ml). Mycophenolic acid was incubated with fibroblasts isolated from 22 patients including 5 with L929 fibroblasts (PCS, minimum essential medium, Life Technology, Eckenstein, Germany). After 48 h inhibition of cell growth was measured by neutral-red assay (photometry). Cell growth was inhibited by 2.1%, 62.5% and 91.1% (p<0.01) respectively using the above concentrations.

The results document inhibition of fibroblast growth by mycophenolic acid at therapeutic concentrations. The results explain why mycophenolic acid causes i) woundhealing disturbances and ii) reduction of interstitial fibrosis in the kidney (e.g. after renal transplantation).
LIPID EFFECTS IN RENAL ALLOGRAFT RECIPIENTS RECEIVING SIROLIMUS-BASED THERAPIES

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Moderate elevations in total cholesterol (CHOL) and triglycerides (TG) have been reported in sirolimus (SRL)-treated renal transplant recipients. This report summarizes the lipid effects observed in 4 multicenter SRL studies in renal allograft recipients. There were 1792 renal transplant patients enrolled in 2 double-blind pivotal trials in which SRL 2 mg/day and 5 mg/day were compared with either azathioprine (AZA) or placebo (PLA), plus standard cyclosporine (CsA) and steroids. Additionally, 2 open-label CsA-sirolimus elimination studies enrolled 246 (phase II study) and 525 (phase III study) patients who were randomized to Group A (SRL 2 mg/day, CsA, steroids) or Group B, in which CsA was eliminated after 2 (phase II) or 3 (phase III) months of triple therapy. In Group B, SRL levels were concentration-controlled to about twice those in Group A. Lipid-lowering therapies were used more actively in the open-label studies than in the pivotal trials. The table below reports the lipid levels (mean ± SEM) at 12 months. CHOL and TG levels in the phase II combination trial were similar to those in the non-SRL groups in pivotal trials. In this trial, 98% of patients had normal or elevated HDL cholesterol (HDL-C), 41% had elevated (>1.6 mmol/L) LDL-C. While lipid levels in the phase II elimination trial were slightly higher than in the phase III trial, HDL-C remained elevated.

<table>
<thead>
<tr>
<th>Study/Phase</th>
<th>Treatments</th>
<th>CHOL (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 SRL 2 mg/d</td>
<td>6.2+/-0.2</td>
<td>2.8+/-0.3</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>#2 SRL+CsA</td>
<td>6.4+/-1.0</td>
<td>3.2+/-2.0*</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>#3 SRL 5 mg/d</td>
<td>6.7+/-1.0</td>
<td>3.7+/-2.0*</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>#4 CsA elim Phase II</td>
<td>6.1+/-2.0</td>
<td>2.6+/-0.3</td>
<td>1.4+/-0.1</td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>6.8+/-2.0</td>
<td>3.1+/-0.3</td>
<td>1.5+/-0.1</td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>6.0+/-1.2</td>
<td>2.2+/-0.1</td>
<td>1.5+/-0.04</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>6.3+/-1.2</td>
<td>2.5+/-0.1</td>
<td>1.6+/-0.05*</td>
<td></td>
</tr>
</tbody>
</table>

In conclusion, hyperlipidemia in SRL-treated renal transplant recipients (1) can be effectively managed with standard lipid-lowering agents, (2) is similar to that in the general transplant population, and (3) is not exacerbated by CsA elimination. Elevated HDL-C levels may have a beneficial effect on cardiovascular risk in SRL-treated patients.
LONG TERM BENEFITS AND SIDE EFFECTS OF CYA TO MMF CONVERSION IN RENAL TRANSPLANT PATIENTS

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Background: To reduce renal toxicity of calcineurin inhibitors, the conversion from Cyclosporine (CyA) to mycophenolate mofetil (MMF) in immunosuppressive regimens has been proposed in several recent trials. Nevertheless, long-term side effects and renal outcome have not been reported yet. Aim: To evaluate the beneficial and adverse effects of CyA to MMF switch. Methods: A comparative and retrospective analysis of 40 renal transplant patients disclosing CyA renal toxicity (n=30), chronic rejection (n=4), severe symptomatic hyperuricemia requiring allopurinol treatment (n=5) or azathioprine indi-
dicated. During their treatment was switched step-wisely from CyA (25mg per month) to MMF (2g per day) (group 1). They were compared to 40 renal transplanted patients (group 2) matched for their date of birth (+/- 5 years), their transplant follow up before and after the switch, and their initial immunosuppressive treatment. Results: The mean follow up of both group was similar before the switch 72 +/- 41 months and after the switch 27 +/- 12. The mean serum creatinine concentration was similar in both groups. In group 1, the mean serum creatinine concentration decreased from 191±51mMol/l before the switch to 181±56mMol/l at 2 years (p<0.01), whereas it remained unchanged in group 2. The systolic blood pressure decreased from 155±23 to 143±17 mmHg at 6 months (p<0.05) and 21 months (p<0.005) respectively. It decreased discreetly but not significantly in group2 in the corresponding time and the lipid profile were not significantly improved after the switch. None of the patient developed acute rejection after the switch. SIX grafts were lost because of chronic rejection in the first group compared to NINE (NS) in the second group. Thirteen patients (32.5%) of the group 1 developed a severe disease (life-threatening infection n=5, 12.5%), malignancy (n=4, 10%) including lymphomas (n=2, 7.5%) or severe MMF side effects (n=4, 10%). In contrast patients in the second group had similar events (22.5%) (NS): Four (10%) had malignancies, four (10%) life-threatening infection and three (7.5%) severe cardio-
vacular events (myocardial infarction n=2, aortic dissection n=1). It is noteworthy that neoplasia and life-threatening infections seem as frequent in both groups whereas severe cardiovascular events were absent in group one. The decrease in blood pressure, in the mean serum creatinine concentration and the slight improvement in lipid profile can account for this result. In addition, 70% of the patients had mild side effects of MMF (diarrhea, myelotoxicity, non life-threatening infection or benign tumors) requiring a reduction of MMF for 47.5% of patients (15% had a reduction 25% of the MMF treatment and 32.5% a reduction of more than 50%). In contrast, only 7 patients (17.5%) had benign tumors or non life-threatening infection (NS). Conclusions: In renal transplant recipients, the CyA to MMF conversion seems to improve renal function and protect from cardio-
vacular morbidity. It is not associated with a higher rate of malignacies or life-threaten-
ing infections. However, mild MMF side effects were too frequent leading to evaluate other MMF dosage in the conversion strategy.

IMPROVED RENAL FUNCTION IN RENAL ALLOGRAFT RECIPIENTS WITH SIROLISOM (RAPAMUNE®) MAINTENANCE THERAPY AND EARLY CYCLOSPORINE WITHDRAWAL: 12-MONTH RESULTS

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The purpose of this study was to evaluate whether cyclosporine (CsA) could be withdrawn at 3 months from a sirolimus (SRL)-CsA-steroids regimen, thereby reducing CsA toxicities. This open-label study was conducted in 57 centers in Europe, Australia, and Canada. 525 patients were randomized, with 264 (50%) on CsA (50 mg/kg/d) and 261 (50%) on SRL (2 mg/kg/d) in combination with CsA and steroids when enrolled in the study. SRL blood levels were maintained above 5 ng/mL (immunoassay). At 3 months ± 2 weeks, eligible patients were randomized (1:1) to remain on triple-therapy (SRL-CsA-steroids), or to have CsA withdrawn over 6 weeks (SRL-steroids) and initiate concentration-controlled SRL therapy (blood trough levels 20-30 ng/mL, immunoassay). At 12 months, 430 patients (82%) had been randomized, many of whom experienced an acute rejection during the pre-randomization period. 92% of patients randomized to SRL-steroids had successful withdrawal of CsA. Graft survival (95.8% vs 97.7%), patient survival (97.2 vs 98.1%), acute rejection (13.5 vs 20.0%), and discontinuations (21 vs 28%) were not statistically different between patients randomized to SRL-CsA-steroids vs SRL-ster-
oids, respectively (intent-to-treat analysis). Blood pressures (systolic and diastolic) and calculated GFR (56 vs 62 mL/min, p<0.001) were improved when CsA was eliminated. Serum cholesterol levels did not differ between groups. Patients remaining on CsA had statistically higher incidences of hyper-
tension, increased creatinine, hyperuricemia, tachycardia, herpes zoster, and skin cancer. Thrombocytopenia, hyperkalemia, and abnormal liver function tests were reported more often in patients randomized to long-term SRL-ster-
oids maintenance therapy. In conclusion, this multicenter 525-patient study demonstrated that a combination of SRL, CsA, and steroids for 3 months post-
transplant followed by withdrawal of CsA offers an important alternative to long-term calcineurin inhibitor therapy, resulting in improved renal function in kidney transplantation.
ACUTE NEPHROTOXIC EFFECTS OF CYCLOSPORINE AND TACROLIMUS IN RATS WITH REDUCED RENAL MASS
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There has been an increase in the use of older donors to expand the organ pool available for renal transplantation, in recent years. Older donors, a significant component of the marginal donor pool, show considerable degree of reduced functional nephron mass. Thus, current approach to these suboptimal grafts is induction therapy with anti-lymphocyte globulins to avoid nephrotoxicity of calcineurin inhibitors in the early post-transplant period. The aim of this experimental study is to assess the acute nephrotoxic effects of cyclosporine A (CyA) and tacrolimus (FK-506) in reduced renal mass. Groups of control, FK-506 0.2 mg/kg/day, FK-506 0.4 mg/kg/day, FK-506 0.8 mg/kg/day, CyA 10 mg/kg/day, CyA 15 mg/kg/day and CyA 20 mg/kg/day, each containing 12 Wistar rats, undergone 5/6 nephrectomy. Renal function was assessed by blood urea nitrogen (BUN), creatinine levels and glomerular filtration rate (GFR). Followig sacrifice of the rats at day 10, remnant kidney was evaluated histopathologically. Only group CyA 20 mg/kg/day exhibited statistically inferior renal function in terms of BUN, creatinine level and GFR. No statistically significant differences in terms of histopathological scoring were found among groups. It is concluded that both CyA and FK-506 can be used in therapeutic doses in kidneys with reduced nephron mass. Increasing doses of CyA, not FK-506, exerts acute functional nephrotoxicity in this model of suboptimal graft with reduced nephron mass. Randomized studies of human subjects should therefore be conducted in suboptimal donors with reduced functional nephron mass to evaluate the need for induction therapies in the early transplantation period.

CHRONIC CYCLOSPORINE NEPHROTOXICITY IS MEDIATED BY THE DOWN-REGULATION OF MATRIX METALLOPROTEASE-9 IN KIDNEY TRANSPLANTED RATS
C Esposito, T Mazzulii, M Maestri, M Polese*, R Rosso, N Bellotti, A Foschi, AR Plati, MM Comte, G Fasoli, A Dal Canton
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Chronic nephrotoxicity is the most important and limiting side effect of cyclosporine treatment in transplanted patients. Although extensively studied the mechanism(s) leading to tubular atrophy and interstitial fibrosis are not yet clear. Pentosan polysulfate (PPS) has been shown to reduce the effects of cyclosporine in in vitro studies. Our study was carried out to investigate the molecular mechanisms leading to chronic cyclosporine nephrotoxicity in rats undergone kidney transplantation, and to study whether PPS could ameliorate cyclosporine-induced kidney changes. Sprague-Dawley rats underwent kidney transplantation after a week of low-salt diet. They were assigned to three groups: untreated rats (U), cyclosporine treated rats (C) and PPS and cyclosporine treated rats (PPS). The treated rats received either cyclosporine (10 mg/kg/day) or cyclosporine (10 mg/kg/day) + PPS (10 mg/kg/day) for 30 days starting from the day after surgery. Serum creatinine, blood cyclosporine level and proteinuria were evaluated every 10 days. At sacrifice GFR was measured by inulin clearance, renal changes were evaluated by histology and ICAM-1, MMP-9, (2)IV collagen and TGF-β mRNA levels were measured by PCR. Blood cyclosporine level was not significantly different in the treated groups. GFR was higher in PPS than C group (140 ± 43 vs 85 ± 32 U/min/100 g bw). Proteinuria was non different among the groups. C showed marked tubular atrophy and interstitial fibrosis that were only slightly reduced by PPS treatment. While (2)IV collagen and TGF-β mRNA levels were not changed by treatments, MMP-9 was strongly downregulated in C but not in PPS. Chronic cyclosporine nephrotoxicity results from a downregulation of the extracellular matrix degradative pathway. PPS treatment may blunt cyclosporine induced renal changes.

PROTEINURIA AS A USEFUL CLINICAL MARKER OF CYCLOSPORINE NEPHROTOXICITY IN RENAL TRANSPLANT PATIENTS.
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Cyclosporin (CyA) trough blood levels must be monitored, but this may not always detect nephrotoxicity (NT) that is difficult to distinguish from chronic rejection (CR). Morphological criteria have been proposed but the risk of biopsy is limiting. CR is frequently associated with proteinuria (P), but since tubulointerstitial damage is an important effect of CyA, P should not be present. We analyzed if the presence of P could be a useful clinical hallmark to distinguish CR from NT. We measured CyA trough blood levels of 270 renal transplant patients since 1990 with functioning graft for more than 1 year. Mean CyA levels at 1-y after transplant were 141.6 ± 32 ng/ml, with a normal distribution, and we considered two groups: group A (patients with levels < mean – 1 SD, <112, n = 56) and group B (patients with levels > mean + 1 SD, >176, n = 35). We studied the development of persistent P and renal function and histological findings in those biopsies made 6 months after transplantation. Evolution of P (g/24 h) at 1, 2, 3, 4 and 5-y was: group A [0.5, 0.9, 1.17, 1.08, 1.42] and group B [0.2, 0.34, 0.13, 0.3, 0.11] (p<0.01) and serum creatinine (mg/dl) was: group A [1.6, 2.1, 2.5, 2.09, 2.41] and group B [1.5, 1.65, 1.56, 1.84, 1.82] (p<0.05). In biopsies: 50% of patients in group B had NT vs 40% in group A (pNS). 93% in group A had chronic changes vs 50% in group B (p<0.05). Patients with higher CyA blood levels developed less P. However, some patients with low CyA blood levels had histological findings of NT, which suggests that trough blood levels did not reflect properly systemic exposure to CyA. Persistent P could be a useful clinical tool in patients with slow impairment of renal function due to chronic allograft nephropathy.
The cytomegalovirus (CMV) status of donor (D) and recipient (R) at time of transplantation (tx) is considered a risk factor in the development of CMV infections. The influence of CMV on graft survival, rejection episodes (RE) and longterm renal function (RF) concerning kidneytransplanted children and adolescents under various regimens of immunosuppressive therapy is unclear. The data of 64 pediatric patients (P) treated with mycophenolate mofetil (MMF), cyclosporin and steroids following renal transplantation (RTx) were compared after 1, 2 and 3 years with 54 P, who had received azathioprin (AZA) instead of MMF. In the MMF group there were 19 P (30%) at high risk for CMV (D+/R-), 14 (22%) at lower risk (D+/R+; D-/R+) and 28 (45%) at no increased risk (D-/R-). In the AZA group 19 P (35%) were at high risk, 8 (15%) at lower risk and 22 (41%) at no risk. For 3 and 5 P were no data available retrospectively.

Creatinine clearance, as a measure of RF, was significantly lower in high risk P of the AZA group after 1, 2 and 3 years (median: 52 ml/min/1,73 sqm) compared with the respective MMF group (median: 90, 80, 75 ml/min/1,73 sqm). 42% of the MMF group showed clinical signs of a RE (19% D-/R-; 13% D+/R-), in the AZA group there were 66% with a treated RE (35% D-/R-; 17% D+/R-) after 3 years. Graft loss occurred in 20% of the AZA group (3x D-/R-; 2x D+/R-; 1x missing status) and in none of the MMF group. These results indicate that CMV has a worsening effect on RF, but only in the AZA group. However, there is no overall increased percentage of RE or graft loss due to a high risk constellation for CMV per se.

**AVOIDANCE OF CYCLOSPORINE IN THE IMMEDIATE POST-TRANSPLANT PERIOD IN LIVING-RELATED DONOR KIDNEY TRANSPLANTS**

**Abstract**

A number of trials have been conducted to examine whether cyclosporine (CsA) can be safely withdrawn after kidney transplantation. Nevertheless, there are no data about the effects of avoidance of CsA in the immediate post-transplant period in living-related donor kidney transplants. In a single centre retrospective study, living-related kidney transplantation in 46 patients (31.9%) (Group 1), whilst the other 98 (68.1%) were allocated CsA. Prednisone- and azathioprin-based immunosuppression (MMF-CS: p<0.025) and irreversible AR was BXM: 0%, MMF: 0%, CsA: 13.5%, respectively (MMF-CS: p<0.05).

The six months graft survival was: BXM:92.2%, MMF:99% (p=0.05) and the patient survival was 100% in both groups. Delayed graft function was in group BXM: 35.3%, MMF:15.2% (p=0.01) and there was a higher incidence of upper respiratory tract infection (BXM:21.6%, MMF:34%, p<0.001), and anemia in the MMF group (BXM:5.9%, MMF:18.2%, p=0.05). There were no differences regarding the occurrence of other infections. The efficacy of BXM or MMF therapy for the prevention of AR proved to be identical. BXM therapy as well as MMF therapy was safe with good tolerability.

**COMPARATIVE ANALYSIS OF BASILIXIMAB VERSUS MYCOPHENOLATE-MOFETIL ADDITION TO CYCLOSPORIN BASED IMMUNOSUPPRESSION FOR THE PREVENTION OF ACUTE REJECTION IN PRIMARY KIDNEY TRANSPLANTED RECIPIENTS**

**Abstract**

Basiliximab (BXM), recently involved into the Cyclosporin microemulsion formulation (CSA-MOF) based immunosuppressive protocols significantly reduced the occurrence and severity of acute rejections (AR) in kidney transplant patients. A comparison of BXM versus Mycophenolate-mofetil (MMF) addition to CSA-MOF based immunosuppression has not been investigated extensively in a single centre experience.

In a single centre prospective, open label parallel group comparative six months study occurrence of AR (diagnosis of steroid sensitive AR. Based on clinical evidence, steroid resistant AR was biopsy proved), were analysed in primary kidney transplanted patients receiving BXM or MMF therapy. Graft/ patient survival, safety and tolerability were secondary endpoints. In the BXM group 51 patients received BXM 20 mg on the day 0 and day 4. Followed by CSA-MOF and mycophenolate nico-lone (MMF) therapy. In the MMF group 99 patients, they received the same CSA-MOF-MMF therapy and 2.0 g MMF a day was added within 48 hours postoperatively. CSA target trough level (TDX monoclonal) was 250-450 mg/ml at the start and 150-250 mg/ml at the end of the study. 163 patients were treated with CSA-MOF-MMF therapy in 1995 served as retrospective control group (CS).

Occurrence of AR was in group BXM:39.2%, MMF:37.4%, CS:35.6% (all n.s.). The proportion of steroid resistant AR was BXM: 4.8%, MMF: 5.4%, CS:25.0%, (MMF-CS: p<0.025) and irreversible AR was BXM: 0%, MMF:0%, CsA:13.5%, respectively (MMF-CS: p<0.05).

The proportion of steroid resistant AR was BXM: 4.8%, MMF: 5.4%, CS:25.0% (MMF-CS: p<0.025) and irreversible AR was BXM: 0%, MMF:0%, CsA:13.5%, respectively (MMF-CS: p<0.05).
INSULIN-LIKE GROWTH FACTOR POLYMORPHISMS ARE ASSOCIATED WITH ACUTE REJECTION RISK
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Acute rejection remains a major cause of reduced survival of renal allografts. Insulin-like growth factor (IGF-1) plays a prominent role in T-cell mediated immune responses including proliferation, differentiation and function. Genetic variation in IGF-1 expression may result in variable renal allograft rejection risk. We have analysed the association between two polymorphisms in the promotor region of the IGF-1 gene (positions -382 and -1088) and rejection risk in 179 renal transplant recipients (67% male; mean (range) age 37(17) years). PCR-RFLP genotyping was performed using DNA extracted from peripheral blood. Details of rejection episodes were extracted from case notes. Acute rejection episodes occurred in 37.6% (n=67); median (interquartile range) time to first rejection episode was 191.5 weeks. IGF-1 -1088 T/T genotype was significantly associated with acute rejection risk at 3 months (p=0.01; Odds ratio(OR) 3.1; 95% CI 1.3-7.2). The -382 C/C genotype was increased in those with acute rejection though this failed to achieve statistical significance (p=0.067). OR 7; 95% CI 0.9-56.1).

This data shows that the IGF-1 -1088 T/T and -382 C/C genotypes are associated with acute renal allograft rejection risk. Further investigation is required to assess the functional significance of this finding, as these polymorphisms may be potentially important markers of rejection risk for the targeting of patient-specific immunosuppression.

OUTCOME OF ANTICALCINEURIN-FREE RENAL TRANSPLANTATION IN RECIPIENTS WITH MARGINAL DONORS
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Due to the shortage of organs, more and more renal transplant (RT) patients receive graft from marginal donors. In this setting, the (early) use of anticalcineurin agents might be detrimental, at least in terms as renal function is concerned. We designed a prospective open study, in which RT patients grafted with marginal donors, were offered anticalcineurin-free immunosuppression. The latter was based on steroids (+Pred- : 1 mg/kg/j for 2 weeks then tapered to 0.3 mg/kg/j at day 90), mycophenolate mofetil (Cellcept®) 2 grammes/dl, in association with induction therapy (Thymoglobulins® 1 mg/kg/j for 3 consecutive days, then adapted to the CD2 count to be less than 50/mm³). We included 12 patients aged 68 ± 3 (SE) years; HLA ABDR matching was 3 ± 0.44; cold ischemia time was 25 ± 2 hours. The overall mean dose of Thymoglobulins® was 450 ± 55 mg and its duration was 9.6 ± 0.7 days. Acute tubular necrosis occurred in 5 cases (45 %). Mean daily doses of Cellcept were 2 ± 0.05; 1.96 ± 0.07, and 1.68 ± 0.1 g/day respectively at day 15, day 30 and day 90; doses of –Pred- were 0.76 ± 0.06; 0.62 ± 0.06, and 0.3 ± 0.02 mg/kg/day at the same dates (days 15, 30 and 90). At last follow-up patient and graft survivals were 100 %. We observed 4 cases of acute rejection in 4 patients (days 25, 90, 107 and 135) treated with methylprednisolone pulses; 2 required in addition either OKT3® or Thymoglobulins®. In addition to these therapies, anticalcineurins were added (cyclosporine A: 2 cases; tacrolimus: 2 cases). Six patients (50 %) experienced CMV disease. Serum creatinine levels were 147 ± 22 µmol/l at months 1, 3 and 6 respectively. Finally at last follow-up 8 patients had dyslipidemia requiring treatment and 6 had hypotensive therapies. Conclusion: Avoidance of anticalcineurin agents in RT patients grafted with marginal donors is associated with good results when using Thymoglobulins® therapy induction, in addition to MMF and steroids but at the high rate of CMV diseases.

JAK-3 INHIBITION IN HUMAN T CELLS ABROGATES IL-2 PRODUCTION AND EARLY T CELL CLUSTERING: EVIDENCE FOR AN IMPAIRED EARLY TCR-SIGNALLING
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Considerable interest exists in the development of new immunosuppressive drugs that target the IL-2-receptor coupled signalling pathway. Recent evidence from our group as well as from SClD-animals suggests an interference of the IL-2-receptor associated tyrosine kinase JAK-3 with early IL-2 production in T-cells. The following study was designed to evaluate the impact of a new selective JAK3-inhibitor AG490 on several aspects of early T-cell activation with special emphasis on IL-2 production. Isolated human T-cells or unfractioned PBMC were challenged either allogeneically or with distinct monoclonal (mAbs) in the presence/absence AG490 The addition of AG490 to human T-cells stimulated with allogeneic cells, OKT-3 or OKT-3 plus CD28 mAb led to a profound inhibition of IL-2 production. This was confirmed at the transcriptional level by means of luciferase mobility shift assays revealed profoundly reduced nuclear NF-AT binding, which is essential for IL-2 transcription. Interestingly, AG490 supplemented cultures contained no or only a few T-cells with a T-cell-like for early T-cell activation. In contrast, calcineurin inhibition not or only marginally interfered with T-cell clustering suggestive of an alternative mode of T-cell activation interference. We conclude that AG490 not only interferes with IL-2-receptor signalling, but instead profoundly downregulates IL-2 production in human T-cells presumably by interfering with TCR-triggered signals. Due to this peculiar characteristic, which is not shared by classical immunosuppressants we anticipate a strong immunosuppressive activity of such drugs in vivo.

TACROLIMUS AND DACLIZUMAB AFTER RENAL TRANSPANTATION; A FEASIBLE REGIMEN?
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With the increasing number of different immunosuppressive agents, more and more combinations are possible. Daclizumab is a new interleukin-2-receptor (CD25)-antibody with persuasive effects in the recently published clinical multicenter trials. We investigated the feasibility of a combination of Tacrolimus and Daclizumab in renal transplantation with or without Mycophenolate Mofetil. Up to now we treated 25 patients with Tacrolimus, Daclizumab (50-85 mg for up to 5 times) and steroids. 15 of these patients received additionally Mycophenolate Mofetil due to increased risk for rejection or delayed/reduced graft function. Follow-up was up to January this year 12.6 ± 3.2 months (range 3 -19 months). 14 patients received their first, 9 their second, 1 his third and 1 his fourth graft. Mean age at inclusion was 48.6 ± 12.4 years (range 29 - 67). Up to now 23 out of the 25 patients have a functioning graft. 15 out of 25 patients had primary graft function. Medium creatinine level was 1.2 ± 0.5 mg/dl at month six, 1.1 ± 0.5 mg/dl at month 9 and 1.1 ± 0.3 mg/dl at month 12. Tacrolimus trough level after 6 months was 8.5 ± 2.6 and after 12 months 6.7 ± 1.0 ng/ml. One patient died with functioning graft due to abdominal bleeding two months after transplantation. Another patient lost his graft two weeks after transplantation due to hemolytic uramic syndrome. Three acute rejection episodes occurred in patients immunosuppressed without MMF. One was steroid-sensitive and two were treatable by steroids and addition of MMF. We had one CMV-infection. We observed two pneumonia and one herpes zoster infection. In one patient we observed a new onset of diabetes. After conversion of cyclosporine blood glucose levels returned to normal range. The combination of Daclizumab and Tacrolimus seems to be a feasible, safe and effective immunosuppressive regimen. Especially for patients at an increased risk, this regimen in combination with MMF may be a reasonable alternative.

Transplantation: immunosuppressive regimens
Two year follow-up of a large, multicentre study comparing dual with triple tacrolimus-based therapy in renal transplantation: sustained low rejection rates and excellent graft survival.

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In this study the efficacy and safety of tacrolimus-based dual therapy (tacrolimus/steroids) and triple therapy (tacrolimus/steroids/azathioprine) in adult renal transplantation was compared. Methods: In this 3-month (with a 21 month follow-up), prospective, open, parallel-group study, 25 centres in 21 countries in 11 countries in Italy randomized 475 adult patients to either dual (n=236) or triple (n=239) therapy. The baseline characteristics of the two treatment groups were similar, with the first 3 months, the incidence of acute rejection was 18.0% (dual) and 15.5% (triple) of patients, steroid-resistant rejections were experienced by 5.1% (dual) and 3.8% (triple) of patients. Between Months 4-24, new acute rejections were experienced by 5 (dual) and 8 (triple) patients; new steroid-resistant rejections were reported in 2 (dual) and 1 (triple) patients. Two years post-transplant, patient survival was 97.8% (dual) and 96.0% (triple); graft survival was 91.9% and 96.1% respectively (Kaplan-Meier method). Serum creatinine at Month 24 was 150.1 µMol/L (dual) and 154.1 µMol/L (triple). The incidence of leukopenia in Months 4-24 was 2.1% (dual) and 10.5% (triple). Acute rejection, the mean incidence of de novo IDDM was 5.5% (dual) and 4.4% (triple). During the follow-up, de novo IDDM occurred in 1 patient in the triple therapy group. At 24 months, 3 (dual) and 7 (triple) patients had developed malignancy. The mean oral daily tacrolimus dose at Month 24 was 0.1 mg/kg in both groups, the corresponding mean whole blood trough levels were 10.04 ng/mL (dual) and 10.23 ng/mL (triple). Conclusions: Both dual and triple therapy regimens were efficacious and safe over a 2-year period. The addition of azathioprine to dual therapy of tacrolimus and steroids does not convey an increase in efficacy.

Correlation of early acute rejection and infection rates with cyclosporine levels and effects on long-term graft survival.

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High doses of immunosuppression is known to result in high rates of infection; however, inadequate immunosuppression leads to higher acute rejection rates. It is still controversial whether acute rejection leads to long-term graft failure. The aim of this study was to demonstrate the effects of Cyclosporine (CSA) levels on acute rejection and infection rates early after transplant (≤ 1 year) and effects of acute rejection and infection rates on late (>1 year) graft survival. 105 patients with functioning grafts, at least 1 year out of transplantation were retrospectively reviewed. CSA levels, infection and biopsy-proven acute rejection rates in the first year were analysed in 4 time period of three months each. The correlation between 1. CSA levels and acute rejection rate, 2. CSA levels and infection rate, and 3. anti-rejection treatment and infection rates, in the early post-transplant period (<6 months), the effect of age, sex, donor origin, early acute rejection and infection rates on late graft survival were analysed. Immunosuppression therapy consisted of steroids, immunuran and CSA in living-related transplants, ATG was added for induction in the cadaver group. The CSA levels were measured twice weekly in the first three months and once monthly in the second three months, and then every 3 months. Mean age was 31 yr. M/F ratio was 2.1. Living-related/cadaver transplant rate was 2.1/1. Mean follow-up period was 47.3 months. 43 patients (41%) had 50 acute rejections, the rate being highest in the first three months (30.5%). In the cadaver transplant group, acute rejection rate was significantly higher in the second three months' period (p<0.04); there was no difference between living-related and cadaver transplants in other time periods. Therapy for acute rejection consisted of prednisolone 500 mg/day for 3 days, steroid resistant cases received ATG or OKT, for a mean of 7 and 13 days, respectively: 82 patients (78%) had 174 infection episodes (1.5 episode per patient in the total series), most frequently seen in the first three months (61%). The most common type was lower airway tract infection (40%). There was a peak infection rate early after transplant (1.6 episode per patient in the total series), most frequently seen in the first three months. Effects of age, sex, donor origin, acute rejection and infection rates on late (>1 year) graft survival was demonstrated by Cox-regression test. Although the mean levels of CSA resulted in higher rates of infection in the second 6 months’ period after transplantation, this did not lead to late graft loss in our series. Similarly, we could not demonstrate an effect of early acute rejection rates on long-term graft survival.

IgG IMMUNOADSORPTION WITH IgG-THERSORB IN HIGHLY SENSITIZED RENAL TRANSPLANT RECIPIENTS: LONG-TERM RESULTS


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Due to preformed HLA-antibodies sensitized individuals frequently display a positive crossmatch with most of the potential donors, therefore the waiting period for a potential donor kidney graft is remarkably increased compared to non-sensitized patients. Moreover, graft loss due to early rejection and reduced transplant (TP) survival have been reported. We evaluated the safety and efficacy of immunoadsorption (IA), designed to remove IgG antibodies (AB) in 15 highly sensitized dialysis patients (11 female, 4 male, mean age 38±12 years). Removal of IgG was performed prior and after renal transplantation (RT). Initially the first 3 months, therapy consisted of ATG, ciclosporine A, azathioprine (or mycophenolate mofetil), and prednisolone. For statistical evaluation medians and interquartile range (IQR), or mean ± standard deviation (SD) were used. The years on hemodialysis before RT were T0=5(IQR 4.3 to 8.3). TP loss occurred in 3 patients, 12 patients achieved sufficient TP function (80%) for a median of 20.3 months (IQR 10.5 to 57.6). The lowest serum creatinine in these 12 patients was 1.2±0.3 mg/dL. Four patients were on hemo-dialysis after 44 months (IQR 11 to 74), while the latest serum creatinine in 8 patients with still functioning TP was 1.6±0.7 mg/dL (20.3 months (IQR 10.5 to 52.8) after RT). 5 years TP survival was 64%. Prior to RT 13.6±10.5 IA had been performed. Addition month incidence of intravenous immunoglobulins were substituted at a dosage of 0.3 g/kg BW. Following RT 22.3±13.2 IA were done. 3 patients had no functioning TP at any time due to BANFF II rejection. The frequency of infection complications was not higher compared to patients treated without additional IA. We conclude that IA effectively reduces HLA-AB and enables successful RT even in high risk patients.

ACUTE HUMORAL RENAL ALLOGRAFT REJECTION: EFFECTIVE TREATMENT BY IMMUNOADSORPTION

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There is increasing evidence for an important pathogenetic role of alloantibodies in acute renal allograft rejection. Acute humoral rejection (AHR) has been reported to be associated with a poor transplant survival. While treatment modalities for cellular rejection are fairly well established, the optimal treatment for AHR remains undefined. Ten out of 352 kidney allograft recipients transplanted at our institution between November 1998 and September 2000 were diagnosed as having AHR, characterized by severe graft dysfunction, C4d deposits in peritubular capillaries (PTC), and accumulation of granulocytes in PTC. AHR was diagnosed 18.9 ± 17.5 days posttransplantation. All patients were subjected to immunoadsorption (IA) with protein A (median number of treatment sessions: 9, range: 3-17) Seven recipients with additional signs of cellular rejection (according to the Banff classification) received also antilymphocyte globulin (ALG). In 9 of 10 patients AHR was associated with an increase in panel reactive antibody (PRA) reactivity. A pathogenetic role of alloantibodies was further supported by a positive posttransplant cytotoxic crossmatch in all tested recipients (n = 4). In 9 of 10 recipients, renal function recovered after initiation of antihumoral therapy. One patient lost his graft shortly after initiation of specific therapy. Another recipient with partial AHR returned to dialysis 8 months after transplantation. Mean serum creatinine in functioning grafts was 2.2 ± 1.2 mg/dL after the last IA session (n = 9), and 1.5 ± 0.5 mg/dL after a follow-up of 14.2 ± 7.1 months (n = 8). In conclusion, our study suggests that AHR, characterized by severe graft dysfunction, C4d staining, and peritubular granulocytes, can be effectively treated by timely IA. In the majority of patients, IA treatment can restore excellent graft function over a prolonged time period.

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