Parallel Sessions 37–42

Session 37. Complications and outcome in liver transplantation

O-307 THE PREDICTIVE VALUE OF INITIAL GRAFT FUNCTION AFTER LIVER TRANSPLANTATION

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Background: Initial graft function plays a major role in the posttransplant recovery and prognosis after liver transplantation (LTX). No suitable diagnostic test has been available to quantify the individual graft function after surgery. Hence, initial graft function has been usually estimated by the serum level of liver enzymes during the first three days.
Methods: Ninety-nine patients receiving primary orthotopic LTX were enrolled into a prospective observational study. Graft function capacity was measured by the LiMAx test, a novel ^{13}C-methacetin breath test, at six hours, day 1, 3, 5, 10, 14, 28, and one year after LTX. Subjects were classified by LiMAx test as nonfunction (PNF, LiMAx <60 μg/kg/h), poor function (IPF, LiMAx 60-120 μg/kg/h), and immediate function (IF, LiMAx >120 μg/kg/h). Biochemical parameters and the indocyanine green test were used as comparators.
Results: Seventy-one percent of the grafts were classified as IF, 25% as IPF, and 4% as PNF, at first day. Patients classified PNF were actually retransplanted independently from the study results. Aspartat-aminotransferase (AST) was identified as the best biochemical parameter for PNF prediction and was applied as the comparator. The correct and false classification of LiMAx and AST were directly compared in a contingency table. A significantly better accuracy for the LiMAx test in comparison to AST was shown after 6h ($p<0.001$) and at first day (p=0.031). The classification IPF was associated with prolonged hospitalization (p=0.003), higher costs (p=0.008) and a decreased 1-year-survival (p=0.008).
Conclusion: The LiMAx test enables accurate evaluation of graft function earlier and with higher prognostic power compared to all current methods. Reliable information concerning the initial graft function is available not later than six hours after LTX. This might have a substantial effect on posttransplant management and survival.

O-308 EXTENDED RIGHT LIVER GRAFTS OBTAINED BY EX SITU SPLIT CAN BE USED SAFELY FOR PRIMARY AND SECONDARY TRANSPLANTATION IN ADULTS WITH ACCEPTABLE BILIARY MORBIDITY

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Background: Split-liver transplantation (SLT) is without doubt beneficial for pediatric recipients, while the increased risk of biliary complications in adult recipients of SLT in comparison to whole liver transplantation (WLT) is debated.
Objective: To investigate the incidence and clinical outcome of biliary complications in SLT using extended right split grafts (ERGs) after ex situ split in comparison to WLT in adults.
Patients and methods: The retrospectively collected data of 80 consecutive liver transplants using ERGs after ex situ split between 1998 and 2007 were compared with 80 liver transplants using whole liver grafts in matched-pair analysis paired by donor age, recipient age, indication, MELD-score, and high urgency status.
Results: Cold ischemic time was significantly longer in the SLT group (P=0.006). As expected, bile leakage from the transected surface occurred only in SLT (15%) without any mortality or graft loss. The incidence of all other early or late biliary complications (e.g. anastomotic leakage, stenosis) was not different between SLT and WLT. One- and 5-year patient and graft survival rates showed statistically no difference between SLT and WLT (83.2% and 82.0% vs. 88.5% and 79.8% (p=0.92); 70.8% and 67.5% vs. 83.6% and 70.0% (P=0.16), respectively).
Conclusion: ERGs can be used safely without increased mortality and with acceptable morbidity and should also be considered for re-transplantation while the use of ERGs contributes significantly to enable pediatric liver transplantation. The significantly longer CIT in the SLT group indicates potential for improved results and should be considered in the design of allocation policies.

O-309 LIVER STEATOSIS AND NAFLD AFTER LIVER TRANSPLANTATION: A STUDY ON PREVALENCE AND RISK-FACTORS

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Background/Aims: Fatty liver disease is a potential long-term complication of liver transplantation (LT). We therefore aimed to determine the prevalence and risk factors of liver steatosis in a large population of adult post-LT patients.
Methods: We evaluated the clinical, biological, histological and evolutive features of patients with a diagnosis of steatosis made at liver biopsy examination during post-LT follow-up. Risk factors were analyzed by univariate and multivariate analysis.
Results: 1,596 liver biopsies from 599 patients were available. Relapsing liver disease was present in 178 patients. A histological diagnosis of steatosis was made in 131 (31.1%) of the remaining 421 patients (51.1% had normal liver tests): 53% had grade 1, 31% grade 2 and 16% grade 3 steatosis. Perisinusoidal fibrosis was present in 38 patients (29.0%). Histological lesions were consistent with a diagnosis of NASH in 5 patients (3.8%). At the end of follow-up, cirrhosis or extensive fibrosis was observed in three patients (2.25%). Multivariate analysis showed that seven factors (post-LT obesity, tacrolimus-based regimen, diabetes mellitus, hyperlipidemia, arterial hypertension, alcoholic cirrhosis as primary indication for LT and pre-transplant liver graft steatosis) were risk factors for post-LT steatosis. If none, one, two, three, four, five or six factors were present, steatosis occurred in 6.0%, 12.0%, 22.1%, 29.9%, 65.5%, 81.5%, and 100.0% of the patients, respectively.
Conclusions: Liver steatosis is a frequent late complication of LT; its development depends on a combination of host and graft factors. LT is therefore an interesting model to study the natural history and the determinants of liver steatosis.

O-310 SECOND LIVER RETRANSPLANTATION: INDICATIONS, PROGNOSTIC FACTORS AND OUTCOME

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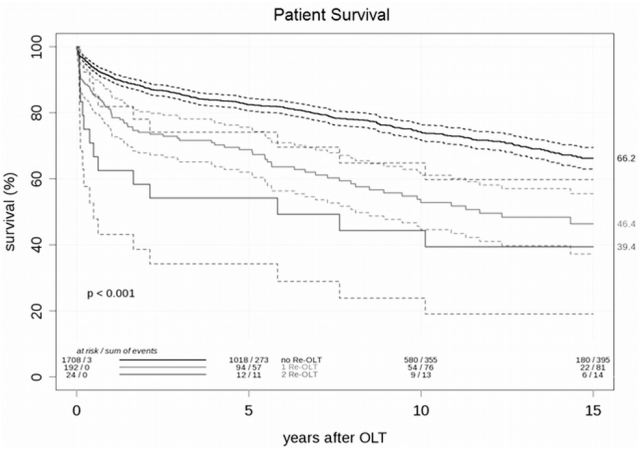
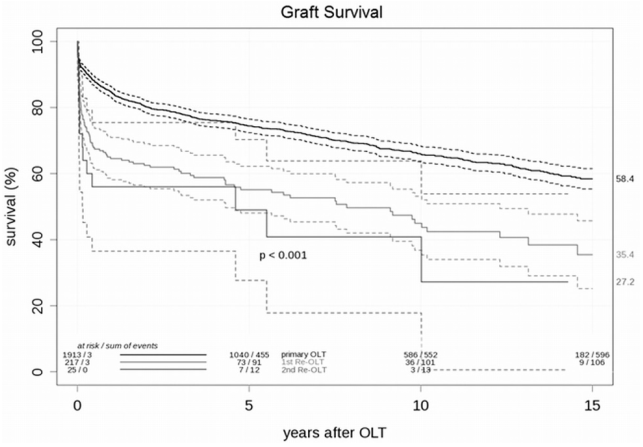
Purpose and methods: Although the outcome of liver retransplantation (re-LT) is still limited, it is the only available therapy option for irreversible liver graft dysfunction. Between 1988 and 2008, we performed 1912 (88,8%) LT, 217 (10%) re-LT and 25 second re-LT (1,2%) in 1924 patients. Patients were analyzed for demographic and clinical variables, indication for re-LT, postoperative complications, prognostic factors and treatment outcome.
Results: The main indications for a second re-LT were thrombosis of the hepatic artery (24%), initial nonfunction (20%) and acute or chronic rejec-





tion (20%). Second re-LT was performed after a median period of 70 (2-5320) days and the mean age of the recipients was 41,5±10,1 years. The course of AST and bilirubin was not significantly different at 6 and 12 months. The main causes of death were cardiopulmonary complications (26,7%), as well as multiorgan failure, sepsis and bleeding complications (13,3% each). Overall, 15 out of 25 patients (60%) died after second re-LT. Patient survival after second re-LT was 63% after 1 year, 54% after 5 years and 44% after 10 years. In comparison to the patient survival of primary LT (5-year-survival: 82%) or first re-LT (5-year survival: 69%), these inferior results differ significantly.
In the univariate Cox regression analysis of prognostic factors for patient survival after second re-LT, APACHE II or III before transplantation and time between first and second re-LT were significant. In the multivariate model only APACHE III could prove its prognostic value (p=0.02).

Univariate analysis of prognostic factors for patient survival after 2nd liver retransplantation

Parameter	P-Value
Recipient age	0.58
Recipient gender	0.91
Primary diagnosis	0.67
Diagnosis before 2nd re-LT	0.28
Time between 1st and 2nd re-LT	0.03
Cold ischemic time	0.26
Donor age	0.44
Packed cells intraoperatively	0.39
Fresh frozen plasma intraoperatively	0.35
Child-Pugh score	0.98
labMELD at listing	0.23
labMELD before transplantation	0.71
APACHE II at listing	0.34
APACHE II before transplantation	0.02
APACHE III at listing	0.20
APACHE III before transplantation	0.02
Dialysis before transplantation	0.16
Dialysis after transplantation	0.09

Conclusion: Second re-LT offers significantly reduced patient and graft survival rates. Although it is the only therapy option for this patient group, indication should be limited to carefully selected cases. APACHE III score might support a better evaluation in the future, but has to prove its prognostic value in further studies.

O-311 CARDIOVASCULAR RISK FACTOR PREVALENCE AMONG ACUTE LIVER FAILURE PATIENTS 5-YEARS AFTER LIVER TRANSPLANTATION

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Studies on the true increase in cardiovascular risk after solid organ transplantation are often hampered by the presence of pre-existing increased cardiovascular risk related to patient's primary disease. Acute liver failure (ALF) patients undergoing liver transplantation (LT) differ in the sense that their health status before disease onset is more comparable to that of the general population.
Aim: To compare the 5-year post-LT prevalence of cardiovascular risk factors among ALF patients with that of the general population.
Material and methods: The study included 77 consecutive ≥5-year-surviving adult ALF patients who underwent LT 1987-2004. The 5-year post-LT prevalence of hypertension, dyslipidemia, diabetes, impaired fasting glucose (IFG), obesity, and overweight were recorded and compared to the general population by dividing observed cases by age-, gender-, and residential area-standardized expected cases (standardized prevalence ratios, SPRs). Control data came from a large survey comprising 6483 individuals of the general population. Immunosuppression was mainly cyclosporine-based (85% of patients), otherwise tacrolimus-based.
Results: At 5 years after LT, 92% of patients presented with at least one cardiovascular risk factor. As shown in the table, the 5-year prevalence of treated hypertension was 2.73-fold that expected in the general population, whereas dyslipidemia was less frequent among patients than expected. Diabetes appeared somewhat more common among patients (N.S.), while IFG occurred significantly less frequent. When added together the observed and expected cases of diabetes+IFG were similar; 10 and 11. The 5-year incidence of new-onset diabetes after LT was 6.4% (5/77 patients). Overweight and obesity showed lower prevalence in patients than expected (N.S.).

Cardiovascular risk factors at 5-years after LT

Risk factor	Observed cases	Expected cases	SPR (95% confidence interval)
Overweight (BMI 25-30)	25	29.5	0.85 (0.55-1.25)
Obesity (BMI >30)	10	17.4	0.58 (0.28-1.06)
Antihypertensive drug therapy	55	20.2	**2.73 (2.06-3.55)**
Dyslipidemia	47	68.0	**0.69 (0.51-0.92)**
Cholesterol ≥5.0mmol/L	40	62.5	**0.64 (0.46-0.87)**
LDL ≥3.0mmol/L	31	56.2	**0.55 (0.37-0.78)**
HDL ≤1.0mmol/L	5	11.5	**0.44 (0.14-1.00)**
Triglyc. ≥2.0mmol/L	13	15.2	0.85 (0.45-1.46)
Antilipid medication	7	5.3	1.31 (0.53-2.71)
Diabetes (fP-glucose≥7.0mmol/L or medication)	8	4.2	1.9 (0.82-3.74)
IFG (fP-glucose 6.1-6.9mmol/L)	2	6.9	**0.29 (0.04-1.00)**

Bold figures highlight statistically significant levels

Conclusion: Liver transplantation and/or associated immunosuppressive treatment evidently causes hypertension, and possibly elicits diabetes in susceptible individuals. The often reported transplantation-associated increased burden of overweight/obesity and dyslipidemia, on the other hand, might be mostly related to other factors.

O-312 LIVER TRANSPLANT AND PREGNANCY

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Background: More than 50% of women with terminal liver disease presents with amenorrhea or infertility. Liver transplant is the treatment of choice in these patients. 90% of them recover their normal reproductive function with the consequently capacity of carry out a full term pregnancy.
Design: Retrospective with prospectively collected database.
Population: 29 pregnancies in 27 liver transplant women with different etiologies of liver disease during a period of 20 years (1988-2008).
Methods: Variables such etiology of liver transplant, age, time between transplant and conception, inmunosuppresor scheme, complications during pregnancy in the mother and the fetus, type of deliver, perinatal complications and evolution were evaluated.
Results: Median age at pregnancy was 23 years, median time between liver transplant and conception was 19 month (range 7-36). 50% present with preeclampsia and 80% have higher immunosuppressive requirements. 80% of new born have low weight but none have congenital malformations. There were one perinatal dead. Graft reject were similar with non pregnant women.
Conclusions: Pregnancy in liver transplanted women is possible and well tolerated with low rate of complications in the mother and baby. Close follow up must be done in order to detect maternal, fetal and graft complications.

Session 38. Clinical immunosuppression: the liver

O-313 TACROLIMUS (TAC) MONOTHERAPY IN LIVER TRANSPLANTATION (LT): ONE-YEAR RESULTS OF A PROSPECTIVE, RANDOMIZED, DOUBLE-BLINDED PLACEBO-CONTROLLED STUDY

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Background: Minimal immunosuppression is desirable in order to reduce side effects and promote tolerance.
Material and methods: Between Feb 2000 and Sept 2004, 156 adults (> 15 yrs old) receiving a primary liver graft were enrolled in a prospective, randomized, double-blind, placebo-controlled, investigator-driven study comparing TAC-placebo (PL) and TAC-low-dose, short-term (64 days) steroid (ST) IS. All patients had a 12 mo follow-up (range 12–84).
Results: By day 7, 3 and 12 mo, rejection treatment had been given in 3.8%, 17.9% and 21.8% (16 pts) of TAC-PL pts, and 1%, 10.5% and 17.9% (14 pts) of TAC-ST pts (ns). The number of pts treated at 3 (16pts-20.5% vs 10 pts -12.5%)and 12 (18 pts-23% vs 15pts-19.2%) mo was not different between TAC-PL and TAC-ST groups. Corticosteroid-resistant rejection at 3 and 12 mo was recorded in 12.8% (10pts) of TAC-PL pts and 3.8% (3pts) of TAC-ST pts (p 0.04). Three- and 12-mo patient survival rates were 93.6% and 85.9% in the TAC-PL group and 98.7% and 93.6% in TAC-ST group. Three and 12 mo graft survival rates were 92.3% and 83.3% vs. 97.4% and 92.3% (ns).
By 1 year, 78.2% of TAC-PL pts and 82% of TAC-ST pts were on TAC monotherapy. When considering the 67 TAC-PL and 74 TAC-ST survivors, these rates of monotherapy were 91% (61 pts) and 86.5% (64pts) (ns). At one year, 53.7% (36/67 pts) of TAC-PL survivors and 56.8% (42/74 pts) of TAC-ST survivors were on low-dosage (< 6ng/ml) TAC monotherapy (ns).
Conclusion: Although more corticosteroid-resistant rejections were noted in the Tac-Plac group, these events did not influence graft nor patient survival. Tac monotherapy can be achieved safely in primary adult LT. Such strategy should lay the basis for further large scale minimization studies.

O-314 TACROLIMUS CONCENTRATIONS IN PERIPHERAL BLOOD MONONUCLEAR CELLS ARE ASSOCIATED WITH HISTOLOGICAL STAGING OF REJECTION IN THE EARLY PHASE AFTER LIVER TRANSPLANTATION

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Background: Therapeutic drug monitoring (TDM) of tacrolimus (TAC) is complicated by the weak and somewhat controversial relationship between trough blood TAC concentrations and clinical outcome. This prospective study evaluates the predictive value of tissue, peripheral blood mononuclear cells (PBMCs) and blood TAC concentrations for acute rejection in 24 patients under TAC-based immunosuppression after liver transplantation (LT).
Methods: Trough blood levels were monitored daily during the hospital stay. Liver biopsies were routinely performed at Day 7 post LT for both histological staging of rejection and analytical purpose. PBMCs TAC levels were measured at Day 1, 3, 5 and 7 post transplantation. PBMC's and tissue levels were measured by LC-MS/MS.
Results: Biopsy-proven rejection (BPR) at Day 7 (n:11) where characterized by significant lower mean TAC PBMCs levels at Day 3, 5 and 7 post LT ($P<0.05$) and by lower tissue concentrations ($P=0.0139$), whereas blood levels and Day 1 PBMCs levels were not significantly different. TAC tissue levels are significantly correlated with TAC PBMCs levels from Day 3 post transplantation.
Conclusions: These results suggest the interest of TAC PBMCs level as a marker of efficacy in the early phase after LT and shed new lights for development of more tailored approaches to immunosuppression in individual transplant.

Hepatic, whole blood and PBMCs mean tacrolimus concentrations according to the graft histological status

Mean (±SD) TAC levels	No BPR (n: 13)	BPR (n: 11)	P-value
Liver tissue D7 (pg/mg)	117.1 (±61.2)	38.1 (±20.4)	0.0139
Whole blood (ng/mL)	6.5 (±2.9)	6.9 (±2.0)	0.7259
PBMCs D1 (pg/10^6 cells)	19.6 (±11.7)	14.8 (±18.6)	0.1984
PBMCs D3 (pg/10^6 cells)	63.7 (±29.8)	32.3 (±17.3)	0.0069
PBMCs D5 (pg/10^6 cells)	75.3 (±32.9)	27.6 (±21.5)	0.0058
PBMCs D7 (pg/10^6 cells)	82.9 (±37.1)	40.8 (±22.2)	0.0039

O-315 THE SiLVER STUDY: AN INVESTIGATOR-INITIATED TRIAL TO DETERMINE IF SIROLIMUS USE IMPROVES HCC RECURRENCE-FREE SURVIVAL IN AFFECTED LIVER TRANSPLANT RECIPIENTS

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HCC recurrence after LT limits success as a treatment for this malignancy. Since the mTOR pathway is critical for angiogenesis and tumor development, it is an attractive target for cancer therapy. Considering mTORi activities, and potential to inhibit malignancy, we initiated a global, multi-center, RCT to evaluate sirolimus-based therapy in patients following LT for HCC, regarding HCC recurrence-free survival. The University of Regensburg is the study sponsor.
This is an open-labeled RCT comparing sirolimus-containing vs. mTORi-free IS in patients undergoing LT for HCC. A 2.5 year enrollment period with a 5-year follow-up is planned. Patients with histologically confirmed HCC are randomized into one of two groups after LT. The control group is kept on center-specific mTORi-free protocol. The treatment group is maintained on a center-specific mTORi-free regime for the first 4-6 weeks, at which time sirolimus is incorporated as monotherapy, or in combination with non-mTOR-based IS.
Currently, 500 patients (510 planned) are enrolled. Forty-five centers from 13 countries are presently recruiting. DSMB meetings in August 2007 and August 2008 recommended unaltered study continuation. Indeed, a novel interfacing (university and industry) model for handling the reporting of serious adverse events has been developed. Using an event-based statistical analysis plan, the first interim analysis of the primary endpoint is expected in mid-2009.
Development of this study was only possible with a scientifically motivated and energetic study group. Vital lessons can be learned from the setup of this IIT. Our study demonstrates that complex, investigator-driven, clinical trials can be successfully organized by an academic institution on a multi-continental basis. Scientifically, the trial is critical because it is the first RCT to determine if mTORi can improve HCC recurrence-free survival in affected LT patients.

O-316 ARE TACROLIMUS CONCENTRATION PATTERNS IN LIVER AND KIDNEY PARENCHYMA AND LYMPHOCYTES PARALLEL TO BLOOD CONCENTRATION PATTERNS?

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Introduction: The metabolism of tacrolimus (Tac) is achieved both in the liver parenchyma and in renal tubular epithelial cells, resulting in intracellular drug/metabolite exposure variability. The aim of the study is to investigate if Tac concentration patterns in liver, kidney and lymphocytes are parallel to blood concentration patterns.
Material and methods: Male adult pigs were given 5mg (n=3) or 10mg (n=3) of Tac orally every morning for 4 days. On day zero, 30 minutes after oral Tac administration, the pigs were anesthetized and kept under general anesthesia with hemodynamic monitoring for 9 hours. Blood samples and serial biopsies were taken every hour. Biopsies were obtained from the liver, kidney, pancreas, lymph nodes, lymphocytes, fat tissue and muscle. The pigs were euthanized on day 1 after blood sampling and different tissue biopsies. Tac concentrations in blood and in tissues were determined by LC/MS.
Results: In the blood, Cmax was reached after one to 2 hours. In liver, kidney and lymphocytes, intracellular Cmax was observed 4 to 5 hours later. The difference between blood profiles and tissue profiles was even better defined when results are expressed as tissue/blood concentration ratios. The greatest difference was found around 7 hours after drug administration.
Conclusions: There is no parallel between Tac concentration profiles in blood and hepatic, renal tissue and lymphocytes. The differences between blood and intracellular patterns might be related to drug transport. This delay should be taken into account in routine biopsy protocols when intracellular Tac concentrations are considered.

O-317 A NOVEL CONCEPT FOR IMMUNOSUPPRESSIVE THERAPY IN ABO-INCOMPATIBLE LIVER TRANSPLANTATION: TEMPORAL DEPLETION OF B CELLS COMBINED WITH B-1 CELL DIFFERENTIATION BLOCKADE

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We have recently demonstrated that B cells with receptors for group A carbohydrates belonging to the B-1 subset, and calcineurin inhibitors (CNIs) specifically block T cell-independent B-1 cell differentiation (*Blood* 2007 T.Irei, H.Ohdan, et al). On the basis of these results, we established a novel immunosuppressive regimen for persistently eliminating B cell response to blood group carbohydrates. In this regimen, anti-CD20 mAbs are administered 2 weeks before the transplantation for temporarily eliminating differentiated B-1 cells. Further, CNI and mycophenolate mofetil are simultaneously administered for blocking B-1 cell differentiation and inhibiting the preexisting plasma cells, respectively. We performed 10 adult ABO-incompatible living donor liver transplantations by using this regimen. After pretransplant plasma exchange, the anti-donor blood group IgM and IgG titers were persistently maintained at less than 16. Ab-mediated rejection did not occur in any of the patients, and they were healthy at the time of discharge. Biliary stenosis subsequently occurred in 4 cases, and severe infections such as sepsis, hepatic abscess, and suppurative discitis were observed in 4 cases, though all the patients eventually recovered from these complications. All the 5 recipients infected with HCV showed a rapid increase in HCV-RNA, and anti-HCV Abs were reduced after the operation; these observations probably reflect desensitization against HCV. During the follow-up period of 6–22 months, 8 patients remained healthy, but 2 died due to recurrence of HCV infection at 1 year after LT. Thus, the immunosuppressive regimen aimed at temporally depleting B cells and blocking B-1 cell differentiation was used successfully in ABO-incompatible liver transplantation. Further studies may be required to modify this immunosuppressive regimen for HCV-infected LT recipients in order to preserve the host immune responses controlling HCV replication.

O-318 EXCELLENT EFFICACY AND RENAL FUNCTION IN LIVER RECIPIENTS WITH ONCE-DAILY PROLONGED-RELEASE TACROLIMUS (ADVAGRAF®)

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Purpose: To assess efficacy and safety of Advagraf® long-term treatment in liver transplant recipients.
Methods: A multicentre, open, prospective, single-arm 1-year follow-up study of Advagraf in adult transplant recipients who had participated in the European Phase III *de novo* liver study for a duration of 12–23 months (mean time post-transplant approximately 17 months). Patients' original immunosuppressive regimen was maintained unless medical needs necessitated otherwise. Biopsy was performed for suspected rejection. Primary endpoints were patient and graft survival. Secondary endpoints included adverse events (AEs), BPAR incidence and renal function (Cockcroft–Gault).
Results: 119/130 (91.5%) patients completed this additional 1-year follow-up. There was 1 death (cardiac disorder) and 10 patients were withdrawn due to: AE (3), withdrawal of consent (1), pregnancy (1), loss to follow-up (1) and switch to other immunosuppression (4). Mean total tacrolimus daily dose, without body weight correction (months 10–12), was 4.4 mg/day and mean whole blood trough level was 6.9 ng/mL. At 1-year follow-up, 64% of completers were on Advagraf monotherapy and 14% on Advagraf plus corticosteroids.
Kaplan-Meier patient and graft survival at 1-year follow-up were both 99.2%. There were 5 BPAR episodes in 5 patients (3.8%), of which 4 were mild/moderate and 1 was corticosteroid resistant. Most commonly reported causally related AEs: hypertension (23.8%), renal insufficiency (18.5%), non-insulin-dependent diabetes mellitus (10.0%) and hepatitis C (10.0%). AE profile was consistent with the known safety profile of tacrolimus. Renal function (serum creatinine and creatinine clearance) remained stable throughout the 1-year follow-up (Table 2).
Conclusions: A majority of *de novo* liver transplant patients can be maintained on a simplified tacrolimus once-daily monotherapy regimen (Advagraf). Adverse events and rejection episodes in the 1-year follow-up were infrequent, and renal function was excellent.

Table 1. Tacrolimus mean daily dose and trough levels over time

Follow-up (months)	1–3 (n=130)	4–6 (n=129)	7–9 (n=126)	10–12 (n=122)
Mean (SD) daily dose (mg/kg)	0.066 (0.050)	0.064 (0.048)	0.061 (0.046)	0.059 (0.043)
Mean (SD) trough level (ng/mL)	7.1 (2.6)	7.1 (2.6)	7.1 (2.6)	6.9 (2.7)

Table 2. Renal function over time

Follow-up	Day 1 (n=128)	Month 3 (n=76)	Month 6 (n=126)	Month 9 (n=82)	Month 12 (n=120)
Mean serum creatinine (SD) μmol/L	109.3 (33.4)	103.7 (32.1)	107.5 (31.1)	111.0 (40.6)	108.4 (33.2)
Mean creatinine clearance (SD) mL/min	76.0 (23.8)	83.5 (24.3)	77.3 (22.9)	78.7 (25.3)	77.9 (24.0)

Session 39. Clinical immunosuppression: side effects & prevention

O-319 INFLUENCE OF IMMUNOSUPPRESSION IN TRADITIONAL CARDIOVASCULAR RISK FACTORS. A SPANISH, MULTICENTER, CROSS-SECTIONAL STUDY

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Background: Immunosuppression plays an important role in the prevalence and severity of traditional cardiovascular risk factors. The National Kidney Foundation has recommended target for traditional cardiovascular risk factors in patients with chronic kidney disease. The purpose of the present work was to investigate the degree of achievement of these targets in a population of kidney transplant patients according to immunosuppressive therapy.
Patients and methods: 2156 renal transplant recipients followed at the outpatient clinics in 4 Spanish hospitals were included in the study. There were 1374 males and 782 females, the mean age was 53.5±13.2 years and the follow-up 104±76 months. Immunosuppression was cyclosporine-based (CsA) in 814 patients, tacrolimus-based (TAC) in 1081 patients and no anticalcineurinic agents (noCNI) in 261 patients.
Results: eGFR was lower in CsA than in the other two groups (47.3±19.2 in CsA; 52.4±20.5 in TAC and 52.9±22.9 ml/min/1.73m^2 in noCNI; $p<0.001$). The prevalence of K/DOQI standards is expressed in the table (%).

Prevalence of K/DOQI standards (%)

	CsA	TAC	noCNI	p
SBP >130 mmHg	73.4	70.0	63.1	0.016
DBP >80 mmHg	64.4	59.5	59.0	0.131
Total cholesterol > 200 mg/dl	39.7	35.0	53.3	<0.001
LDL-cholesterol > 100 mg/dl	61.9	61.4	77.5	<0.001
Glucose > 125 mg/dl	9.3	11.9	8.6	0.138
Albumin < 4 g/dl	17.0	11.6	24.1	<0.001
Statin therapy	59.1	39.4	59.3	<0.001

SBP = systolic blood pressure; DBP = diastolic blood pressure

There were no differences in the percentages of patients on treatment with ACEI/ARB nor in those on treatment with insulin or oral antidiabetic agents
Conclusions: The control of cardiovascular risk factors is below targets established for nontransplant CKD patients. Patients on treatment with TAC and with noCNI have a better cardiovascular risk profile than those on CsA.

O-320 POLYOMAVIRUS BK VIRURIA AND VIREMIA IN *DE NOVO* RENAL TRANSPLANTATION COMPARING CYCLOSPORINE AND TACROLIMUS: A MULTIVARIATE ANALYSIS FROM THE DIRECT STUDY

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Emergence of polyomavirus BK-associated nephropathy (PVAN) since the mid-1990s coincided with increasing use of tacrolimus (Tac) vs cyclosporine (CsA), but prospective multicenter studies are lacking.
Methods: BKV DNA load was analyzed at month (M) M1, M2, M3, M6 and M12 in urine and plasma of 682 *de novo* renal transplant pts randomized in a 6-month prospective, open-label study with a 12-month follow-up visit to CsA (C_2 monitored; N=336) or Tac (C_0; N=346) with basiliximab, MPA and steroids. Key parameters (including age, sex, race, DGF, HLA, diabetes mellitus) were analyzed in univariate and multivariate logistic regression models.
Results: Overall rate of BKV viruria reached 25.4% at M6 (median 2.4×10^6 copies/mL), and 20.3% (median 1.0×10^6 copies/mL) at M12. Rates of BKV viremia were 13.7% (median 2.3×10^4 copies/mL) at M6 and 8.6% (median

4.5×10^4) at M12. At M6, biopsy-proven rejection had occurred in 13% of viremic pts vs 6.2% non-viremic pts (p=0.03). The rates and levels of BK viremia and viruria were consistently lower with CsA than Tac at months 6 and 12 (Table). In multivariate models, Tac was significantly associated with BK viremia, high-level viremia and high-level viruria at M6 and M12 and with viruria at M6 (see Table). MPA dose was not a significant risk factor at M12.

		CsA n/N (%)	Tac n/N (%)	Univariate p-value	Multivariate p-value
Viremia	Month 6	28/264 (11%)	49/300 (16%)	0.0496	0.0014
(>1000 copies/mL)	Month 12	11/231 (5%)	31/256 (12%)	0.0053	0.0124
High-level Viremia	Month 6	17/264 (6%)	30/300 (10%)	0.1297	0.0045
(>104 copies/mL)	Month 12	5/231 (2%)	24/256 (9%)	0.0021	0.0343
Viuria	Month 6	61/258 (24%)	81/300 (27%)	0.3644	0.0484
(>2500 copies/mL)	Month 12	36/215 (17%)	58/247 (23%)	0.0739	0.9893
High Level Viuria	Month 6	20/258 (8%)	38/300 (13%)	0.0602	0.0008
(>107 cfopies/mL)	Month 12	5/215 (2%)	24/247 (10%)	0.0026	0.0026

Conclusion: Tac significantly increases the risk of high-level BKV viruria, viremia and high-level viremia at M6 and M12 as compared to CsA. Further investigations into factors contributing to risk for viuria and viremia are ongoing.

O-321 RISK OF KAPOSI'S SARCOMA FOLLOWING SOLID ORGAN TRANSPLANTATION. A MULTICENTER STUDY IN 4767 RECIPIENTS: ITALY 1970-2006

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Background: Given the high prevalence of infection with the human herpesvirus type 8 (HHV-8), Italy is an area of utmost interest for studying Kaposi's Sarcoma (KS). This investigation estimated, in Italy, the risk of KS in transplant recipients as compared to the general population of the same sex and age.
Methods: A longitudinal study was conducted on 4767 (72.3% male, median age 48-yrs) renal- (KTx), heart- (HTx), liver- (LTx) and lung-transplant-recipients (LuTx) from 7 distinct Italian transplantation-centers (1970-2006). Person-years (PY) at risk for KS were computed from 30-days after transplantation to date of KS, death, last follow-up or study closure (31/12/2007). Standardized Incidence Ratios (SIR) and 95% confidence intervals (CI) were computed to quantify the risk of KS in transplants, as compared to the Italian general populations. Incidence rate ratio (IRR) were computed to identify risk factors (adjusted Poisson regression).
Results: Based on 33621 PY, 73 KS (62 in males) were diagnosed: 31 in KTx-, 27 in HTx-, 8 in LTx- and 7 in LuTx-recipients. Overall incidence was 217 cases/105PY, with a significantly increased SIR=125. SIR was particularly high among women (304) and in LuTx-recipients (428). Main predictors for increased KS-risk were male gender, older age, LuTx, while a 5-fold reduction was observed >18months post-transplant. Patients born in Southern Italy shown, after adjustment, a significative 2.2-fold increased risk (vs. Northern Italy counterparts).
Conclusions: Our findings confirm that Italian transplanted patients are at higher risk of KS compared to the general population, particularly high in LuTx-recipients, in the early post-transplant period and in patients from Southern Italy, urging the need of appropriate models for careful monitoring transplanted-subjects for KS, especially those at higher risk and in the early post-transplantation period.

O-322 CONVERSION TO SIROLIMUS FROM CALCINEURIN INHIBITORS TO PREVENT NON-MELANOMA SKIN CANCER (NMSC) IN RENAL TRANSPLANT RECIPIENTS AT HIGH RISK FOR NMSC

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Purpose: Skin cancer is a significant cause of morbidity and mortality after renal transplantation. We evaluated the rate of NMSC after conversion to sirolimus (SRL) immunotherapy from calcineurin inhibitors (CNIs) versus continued CNI therapy.
Methods: This randomized, controlled, multicenter trial was conducted in Australia, New Zealand, and the US. 86 renal transplant recipients with a history of NMSC (defined as basal cell carcinoma [BCC] or squamous cell carcinoma [SCC]) were randomly assigned (1:1) to either convert from CNI to SRL or continue CNI. Patients were stratified based on the number of lesions (0-5 vs. 6-20) in the previous 12 months. Eligible patients were ≥1 year posttransplant and diagnosed with NMSC during the past 3 years, excluding those with metastatic disease or excessive number of lesions (>20 in previous 12 months). Patients were followed for up to 2 years. The primary endpoint was the number of new biopsy-confirmed NMSC lesions per patient-year.
Results: Baseline demographic characteristics were similar between groups (see Table). Most patients had 0-5 NMSC lesions within 12 months before enrollment. Preliminary data (ITT) showed a significantly lower yearly rate of NMSC in patients converted to SRL (Table). Similarly, the percentage of patients with ≥1 SCC was significantly lower in patients receiving SRL-based therapy (Table). The incidence of treatment-emergent adverse events was not significantly different between SRL and CNI groups (97.4% and 85.1%, respectively, p=0.067). However, discontinuation rates due to adverse events was higher in the SRL arm (46.2% vs. 0%, p<0.001).

	SRL Regimen (n=39)	CNI Regimen (n=47)	p-Value
DEMOGRAPHIC CHARACTERISTICS			
Mean age, years	59.1	59.0	0.958
Sex – Male, %	79.5	72.3	0.466
Race – White, %	97.4	100	0.453
Mean time after transplant, years	9.6	9.1	0.658
Primary transplant, %	89.7	83.0	0.534
Stratification, % with lesions in previous 12 mo			
0-5 lesions	87.2	78.7	0.306
6-20 lesions	12.8	21.3	
NMSC lesions within previous 12 months			
BCC, mean (SD, min-max)	0.56 (0.72, 0-2)	0.79 (1.16, 0-4)	0.299
SCC, mean (SD, min-max)	2.00 (2.33, 0-9)	1.68 (1.72, 0-10)	0.477
PRELIMINARY RESULTS (ITT)			
Rate of NMSC per patient-year	1.18	2.41	0.017
% patients with ≥1 SCC	28.5	70.2	0.006
% patients with ≥1 BCC	35.9	51.1	0.168

Conclusion: Preliminary data suggest SRL-based therapy may be associated with a lower rate of NMSC in renal transplant recipients at high risk for NMSC when compared with patients who remained on CNIs.

O-323 STEROID AVOIDANCE IMMUNOSUPPRESSIVE PROTOCOL: LONG TERM EVALUATION OF PROSPECTIVE RANDOMIZED STUDY AFTER LIVE DONOR RENAL ALLOTRANSPLANT

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Introduction: Steroids had the main role in renal transplantation for nearly five decades. However; chronic use of steroids was associated with a lot of comorbidities. So we aimed to assess the long term safety and efficacy of steroid free immunosuppressive regimen in live donor renal transplant recipients in prospective randomized manner.
Patient and methods: A total of 100 patients with end stage renal disease, received their first live donor renal allotransplantation from June 2004 to July 2005, were recruited into the study. All patients were treated with basilixmab, tacrolimus, MMF and then randomized to receive steroids for three days (study group) or for maintenance (control group). Median follow up was 32.2 months.
Results: By the end of the third year, patient and graft survivals were 100% in both groups. Biopsy proven acute rejection episodes were 16% in both groups at one year and 34% vs. 36% at three years respectively. Mean serum creatinine was 1.34 mg/dl in steroid free group vs. 1.33 mg/dl in the

control group. Post-transplant hypertension was 4.1% vs. 14.3% respectively (p=0.08). Post-transplant D.M. was 0% vs. 26.5% respectively (p=0.0001), while post-transplant weight gain was comparable in both groups (p=0.951). The two groups were comparable regarding cases with hepatic impairment, serious bacterial infections or malignancies (p=>0.05).
Conclusion: In cases with low immunological risk, steroid free regimen was safe and tolerable in live donor kidney transplants, however long term use of steroids was associated with post-transplant diabetes. Steroid avoidance was associated with lower total cost in spite of comparable immunosuppression cost, which was attributed to low cost management of lower associated morbidities.

O-324 GASTROINTESTINAL DISORDERS IN PATIENTS WHO UNDERGONE TRASNPLANTATION: DO IMMUNOSUPPRESSIVE DRUGS REALLY INFLUENCE THE SMALL OR LARGE BOWEL TRANSPORT AND BARRIER FUNCTION?

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Introduction: Gastrointestinal side effects of the immunosuppressive drugs (ISD) can even double the risk of graft loss or patient death. The aim of this experimental study was to characterize the impact of commonly used ISD on the small and large bowel transport and barrier functions. Therefore, the influence of 14 days treatment with a low and high therapeutic dose of: ciclosporin A, tacrolimus, mycophenolate mofetil (MMF), enteric coated MPA (EC-MPA), sirolimus, everolimus and FTY720 on the glucose and sodium absorption, the chloride secretion, and the barrier function in jejunum and colon was investigated.
Methods: Jejunum or terminal colon of Wistar rats treated over 14 days with one of the mentioned ISD was mounted into modified Ussing-chamber. Glucose absorption was measured by 3-O-methyl-D-glucopyranose absorption kinetics in jejunum, sodium re-absorption in the colon by amiloride, and chloride secretion through bumetanide and theophylline + PgE2 induced short circuit current difference. The barrier function was assessed by transepithelial resistance and 3H-Lactulose-flux in colon and jejunum.
Results: All rats survived well the treatment period and had similar weight gain. Tacrolimus cause glucose malabsorption, everolimus: glucose malabsorption, small bowel barrier function alteration and chloride secretion depletion, MMF small bowel barrier function alteration and EC-MPA glucose malabsorption and small bowel barrier function decrease. Above changes were dose dependent.
Conclusions: Tacrolimus, everolimus, MMF and EC-MPA therapy can lead to the pathological changes of the small and large bowel barrier or transport function. Such influence might be responsible for gastrointestinal disorders in the transplanted patients even without bacterial translocation or any other complication of the immunosuppressive therapy.

Session 40. Pediatric transplantation

O-325 IS THERE A NEED FOR LONG TERM PROTOCOL LIVER BIOPSIES IN PEDIATRIC LIVER TRANSPLANTATION RECIPIENTS?

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Chronic rejection is the main cause of late liver graft loss, mainly in adolescents, that are poor compliant to immunosuppressants. However, early chronic rejection (CR) is treatable and potentially reversible.We have therefore undertaken a prospective study assessing liver graft function and histology at 10 years post liver transplantation (LT) whether there was or not clinical or biochemical evidence of graft dysfunction.
Patients and methods: 215 patients (mean age 15 years $\pm$ 4) were included in the study. The primary indication for LT was a chronic cholestatic disease in 82% of cases (biliary atresia in 58%). 95% received a ciclosporine based primary immunosuppressive regimen. 50% had a past history of acute rejection (AR) and 17% had a prior liver biopsy (LB) showing signs of CR. All patients underwent a percutaneous 10 yr-LB. Histologic diagnosis of CR was based on ductopenia and/ or bile duct epithelium dystrophy and/ or extensive central fibrosis with perivenular fibrosis. Liver function tests (LFT) were analysed at the time of the 10 yr-LB.
Results: While LFT were normal in 145 patients (68%) at the time of the 10yr-LB, 70% had graft abnormalities, mainly signs of CR in 38%, bile flow obstruction in 12% and chronic active hepatitis in 7%. Normal LFT were associated with normal histology in 57 patients, but 88 patients with normal LFT had histological abnormalities. Noteworthy, 64% of the patients with a CR diagnosis had normal LFT. The sensitivity and the specificity of LFT for the detection of histologic abnormalities were 87% and only 76% respectively.
Conclusion: In conclusion, 88 patients clearly benefited from the 10 yr-protocol liver biopsy. These results argue in favor of long term protocol liver biopsies, especially in adolescents with poor therapeutic compliance.

O-326 CONVERSION FROM PROGRAF TO ADVAGRAF IN ADOLESCENTS WITH NORMAL GRAFT FUNCTION AFTER LIVER TRANSPLANTATION

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Aims: Study of the pharmacokinetics (PK) of the extended-release formulation of tacrolimus (Advagraf) once daily, compared to tacrolimus (Prograf) twice-a-day.
Methods: The study was approved by the Institutional Review Board. Twenty adolescents (9 males; age: 12-17 years) fulfilled selection criteria: normal graft function, no rejection in preceding months, informed consent. Median time from OLT was 11.7 years (range: 1.4-15.5). Present immunosuppression consisted of prednisolone (19 patients, median: 4 mg every other day), plus tacrolimus. Four patients received Mycophenolate 11.5-25 mg/kg/day.
After 7 days taking their current doses of tacrolimus bid they were admitted for PK (samples at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11.5, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 20, 24 h). On day-8 they were converted to Advagraf on a 1:1 (mg/mg) basis for their total daily dose, given once daily. On day-14 a PK study of Advagraf was done (samples at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, 24 h).
Pharmacokinetics analysis was performed using a non-compartmental approach (WinNonlin 2.0). The relative bioavailability was assessed by the ratio: Area under the concentration–time curve (AUC) of Advagraf/ AUC of Prograf and its corresponding 90% confidence interval.
Results (Tacrolimus levels in ng/mL):
Day 7: PK of Prograf: Cmax of the afternoon dose was lower than Cmax of the morning dose. Mean values were C0: 7.09 C12: 7.08 Cmax: 19.5 AUC: 234.8 ng/ml·h
Day 14: PK of Advagraf: Mean values were C0: 7.09 Cmax: 18.9 AUC: 238.5 ng/ml·h
The mean ratio between formulations ($AUC_{Advagraf}/AUC_{Prograf}$) was 101% (90% CI: 91.3-111.85%)
The correlation of trough level with AUC was r^2: 0.72 (Prograf) and r^2: 0.74 (Advagraf)
Patients were assessed 1 month after conversion. Dose was modified after day-14 in 5/20 patients. Trough levels at 1 month were: 6.3$\pm$2.2. Renal and graft function did not show changes compared to baseline. Patients were satisfied with the once daily administration of the drug.
Conclusions: In adolescents with normal graft function, tacrolimus (Prograf) bid and extended-release tacrolimus (Advagraf) once daily are bioequivalent.

O-327 OPTIMAL LONG TERM GRAFT ACCEPTANCE FOLLOWING PEDIATRIC LIVER TRANSPLANTATION WITH STEROID-FREE TACROLIMUS-BASED IMMUNOSUPPRESSION

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Long-term immunosuppressive therapy (IS) is required for most pediatric liver transplant (LT) recipients. As defined by Calne, prope (almost) tolerance may constitute an optimal condition combining graft acceptance with very low IS load and minimal IS-related toxicity.
Methods: We reviewed 171 pediatric (median age at LT: 1.3 y; range: 0.3-14.0y) long-term survivors after LT, transplanted between 04/1999 and 06/2007 under tacrolimus-based regimens (deceased donors n=97, 57%; living donors: n=74, 43%), with a median follow-up post-LT of 6.0 y (range: 1.6-9.2 y). Their current status regarding IS therapy was analysed and correlated with the initial IS immunoprophylaxis. Prope tolerance was defined as tacrolimus monotherapy, with mean trough blood levels $<$ 4ng/ml during the preceding year of follow-up, combined with normal liver function tests.

Results: The 66 children transplanted before April 2001 received a standard tacrolimus-steroids regimen. Beyond April 2001, the subsequent 105 patients received steroid-free tacrolimus-basiliximab or -daclizumab immunoprophylaxis. In the latter group, 43 (41%) never experienced any acute rejection episode and, consequently, never received steroids. In the long term, a total of 79 recipients (47%) developed prope tolerance (n=73) or IS-free operational tolerance (n=6), 27 of them belonging to the 43 steroid-free patients (63%). In contrast, only 52/128 (41%) children treated with steroids subsequently developed prope/operational tolerance. Correlation between initial immunoprophylaxis and current IS therapy showed that prope/operational tolerance was significantly associated with steroid avoidance during the whole transplant follow-up (p=0.012).
Conclusion: Steroid-free tacrolimus-based IS seems to promote long term graft acceptance under minimal/no IS. If confirmed, these results constitute the first evidence that minimization of IS, including steroid avoidance, might be tolerogenic in the long term after pediatric LT.

O-328 IMPROVED SURVIVAL FOLLOWING PEDIATRIC LIVER TRANSPLANTATION, TOWARD A 100% SURVIVAL PROSPECT?

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Purpose: When compared to post-mortem donors (PMD), pediatric liver transplantation (PLT) with living-related donors (LRD) provides lower pre-transplant mortality and, as recently published, similar patient and graft outcome post-transplantation (Am J Transplant 2007; 7: 440-447). Despite technical difficulties, LRD could even be associated with a significantly better post-transplant survival than PMD. The technical, immunological and overall outcome of PLT performed at our center since the initiation of the LRD program was analyzed.
Method: Between 7/1993 and 1/2008, 376 children received a primary PLT from a LRD (n=163) or a PMD (n=213). Both groups were compared and the putative impact of surgical and immunological variables on post-transplant outcome was studied using a multivariate analysis.
Results: Patient and graft survivals in this serie are given in the Table for LRD and PMD. Graft and patient survival in LRD and whole PMD transplant were statistically better when compared to transplant using reduced-size or split liver graft. Neither mortality nor significant morbidity was encountered in the 163 living donors. Moreover the learning curve analysis showed a 15% improvement of one year patient survival between 1993-1994 era (one year patient survival: 85%) and 2007-2008 (one year patient survival: 100%).

Post-transplant survival	LRD (n=163)	PMD (n=13)			Statistical significance
		Whole (n=89)	Reduced-size (n=77)	Split (n=47)	
Patient survival					
5 Years	93,66%	92,99%	81,24%	86,17%	
10 Years	92,76%	89,89%	81,24%	86,17%	p=0,035
Graft survival					
5 Years	91,15%	85,12%	73,72%	75,46%	
10 Years	90,22%	80,10%	73,72%	75,46%	p=0,001

Conclusion: Our results suggest that 100% patient survival might become gold standard in children undergoing liver transplantation at high-turnover centers. The implementation of a LRD program might largely contribute to reach this objective.

O-329 FAVORABLE LONG-TERM EFFECTS OF MYCOPHENOLATE MOFETIL (CellCept®) INTRODUCTION IN PEDIATRIC RENAL TRANSPLANT PATIENTS

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Purpose: Positive effect of mycophenolate mofetil (MMF) introduction on renal function of chronic renal transplant patients has been reported in several studies. An interim report on TranCept, a large prospective multicenter multinational clinical study of patients of ages >2 years started on MMF more than 6 months post-transplant, with or without CNI minimization showed a significant improvement of GFR upon MMF introduction. Here we report the effect of MMF introduction on the pediatric subpopulation (age <18years).
Methods: An interim analysis was performed on the pediatric subpopulation (n=109) where the effect of MMF introduction on eGFR (Schwartz formula) was assessed by comparing the slopes of the linear regression lines of eGFR before and after MMF introduction.
The results were compared descriptively to that of the whole population (n=2215).
Results: Median age at enrollment was 13.8 years. At time of interim analysis, the average follow up time was 24.5 months. Most MMF introductions were done between 2 and 5 years after transplantation. At 100 days after MMF introduction, CNI reduction was reported only in 16.7% CsA patients and 5.4% Tac patients. Box and whiskers plot for baseline corrected eGFR showed an upward trend after MMF introduction (figure 1). Change in slope of the baseline corrected linear regression lines of eGFR before and after MMF introduction was 3.43 ml/min/1.73m^2 per year (p<0.0001) in this pediatric subpopulation. In comparison, the slope change for the whole population was 2.03 ml/min/1.73m^2 per year.

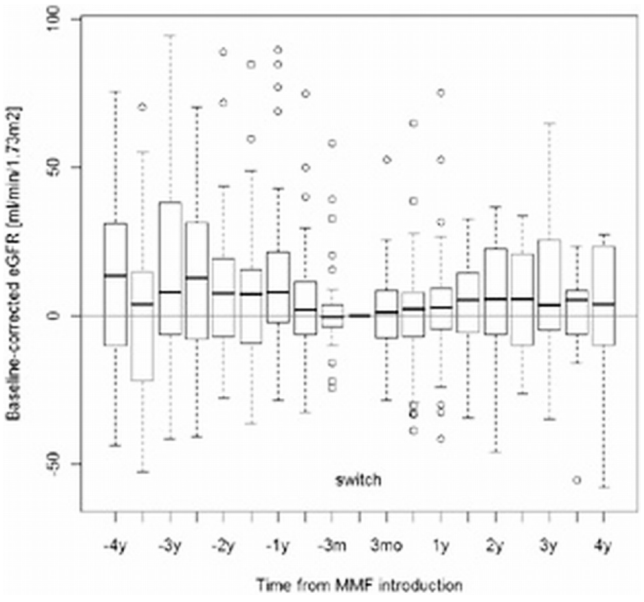

Figure 1

Improvement in eGFR was also observed in pediatric patients introducing MMF several years after transplantation.
Conclusion: Pediatric patients whose immunosuppressive regimen was changed to include MMF experienced a statistically significant renal function improvement comparable to that observed in the overall population.

O-330 KIDNEY TRANSPLANTATION FROM PEDIATRIC DONORS AFTER CARDIAC DEATH (DCD): 25 YEAR EXPERIENCE IN THE NETHERLANDS

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Introduction: DCD kidney transplantation is a well accepted method to expand the donor pool. However, there is general reluctance to use DCD kidneys from less ideal donors such as old aged donors and children. The results of pediatric DCD renal transplantation are largely unknown.
Methods: All 91 pediatric (age < 18 years) DCD kidneys transplanted in the Netherlands from 1980 to 2006 were included in the study. Their outcome was compared to 405 pediatric donors after brain death (DBD) kidneys. Short and long term outcome were compared using multivariable regression analyses. Graft and patient survival were compared using the log rank test. In the DCD group, risk factors for primary non function (PNF) were identified with univariable and multivariable regression analyses.
Results: Median donor age was 13 years and 14 years in the DCD and DBD group, respectively. PNF and DGF in the DCD group was higher than in the DBD group (9% vs. 2%; p<0.01 and 48% vs. 8%; p<0.001). DCD kidneys were associated with inferior glomerular filtration rates (GFR) after 3 months (52 vs. 45 ml/min, p=0.034) but with similar GFR after 1, 2, and 5 years. Death-censored graft survival, including PNF kidneys, at one and five year was 84% and 78% in the DCD group and comparable in the DBD group (p=0.56). In the DCD group, warm ischemia time (WIT) ≥ 25 minutes was a significant predictor for PNF with an odds ratio of 13 (95 CI: 1.6-115; p=0.02).
Conclusion: The incidence of PNF and DGF is higher in pediatric DCD kidney transplantation than in pediatric DBD kidney transplantation. This, however, has no effect on graft and patient survival. Despite 9% never functioning grafts, pediatric DCD kidneys are a valuable extension of the donor pool.

Session 41. Belatacept in kidney transplantation

O-331 PRIMARY OUTCOMES FROM A RANDOMIZED, PHASE III STUDY OF BELATACEPT VS CYCLOSPORINE IN KIDNEY TRANSPLANT RECIPIENTS (BENEFIT STUDY)

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Introduction: Belatacept, a co-stimulation blocker, is being developed as an immunosuppressant for kidney transplant recipients to avoid the renal and extra-renal toxicities of calcineurin inhibitors (CNIs) that impact long-term patient/graft survival. BENEFIT assessed belatacept-based regimens vs a cyclosporine (CsA)-based regimen in kidney transplant recipients.
Methods: BENEFIT is a 3-year, randomized, Phase III study in adults receiving a kidney transplant from a living or deceased donor, with an anticipated cold ischemia time <24 hours. Patients were randomized 1:1:1 to a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids. Co-primary endpoints were composite patient/graft survival, composite renal function (measured GFR (mGFR) <60 mL/min/1.73 m^2 at Month 12 or a decrease in mGFR ≥10 mL/min/1.73 m^2 from Month 3 to Month 12), and incidence of acute rejection (AR).
Results: 666 patients were randomized and transplanted. 58% received living donor transplants, 42% from deceased donors. Patient/graft survival with belatacept regimens was non-inferior to CsA at Month 12.

	Belatacept MI (n=219)	Belatacept LI (N=226)	CsA (n=221)
Composite patient/graft survival, n (%)	209 (95%)	218 (97%)	205 (93%)
Composite renal function impairment endpoint, n (%)	115 (55%) [p<0.0001 vs CsA]	116 (54%) [p<0.0001 vs CsA]	166 (78%)
Mean measured GFR, mL/min (SD)	65.0 (30.0) [p<0.0001 vs CsA]	63.4 (27.7) [p<0.0001 vs CsA]	50.4 (18.7)
Acute rejection, n (%)	48 (22%)	39 (17%)	16 (7%)

The incidence of AR in the LI regimen was non-inferior to CsA. AR in belatacept patients had limited impact on graft survival and on the relative renal benefit of belatacept. Infection and overall malignancy rates were similar across arms; PTLD was observed in 1 (0.5%), 2 (0.9%), and 1 (0.5%) patients in the MI, LI, and CsA groups in the first 12 months.
Conclusions: At 12 months, belatacept regimens demonstrated superior renal function and similar patient/graft survival vs CsA, despite an increase in AR in the early post-transplant period. Belatacept represents a promising, non-nephrotoxic therapy option in kidney transplant patients.

O-332 PRIMARY OUTCOMES FROM A RANDOMIZED, PHASE III STUDY OF BELATACEPT VS CYCLOSPORINE IN ECD KIDNEY TRANSPLANTS (BENEFIT-EXT STUDY)

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Introduction: Belatacept, a selective co-stimulation blocker, is being evaluated as an immunosuppressant in renal allograft recipients to avoid the renal and extra-renal toxicities of calcineurin inhibitors. As recipients of extended criteria donor (ECD) kidneys at elevated risk of graft dysfunction and loss, they may particularly benefit from a non-nephrotoxic option such as belatacept.
Methods: BENEFIT-EXT is a 3-year, randomized, Phase III study in adults receiving an ECD kidney transplant. Patients were randomized 1:1:1 to receive a more intensive (MI) or less intensive (LI) regimen of belatacept or cyclosporine (CsA); all patients received basiliximab induction, MMF, and corticosteroids. The two co-primary endpoints were: composite patient/graft survival at 12 months and composite renal function (measured GFR <60 mL/min/1.73 m^2 at Month 12 or a decrease in measured glomerular filtration rate (GFR) ≥10 mL/min/1.73 m^2 from Month 3 to Month 12. Secondary endpoints included the incidence of acute rejection (AR).
Results: 543 patients were randomized and transplanted. Patient/graft survival with belatacept was non-inferior to CsA at Month 12.

	Belatacept MI (n=184)	Belatacept LI (n = 175)	CsA (n=184)
Composite patient/graft survival, n (%)	158 (86%)	154 (88%)	156 (85%)
Composite renal function impairment endpoint, n (%)	124 (71%) [p=0.002 cs CsA]	129 (76%) [p=0.06 vs CsA]	151 (85%)
Mean measured GFR, mL/min (SD)	52.1 (21.91) [p=0.008 vs CsA]	49.5 (25.35) [p=0.10 vs CsA]	45.2 (21.08)
Acute rejection, n (%)	32 (17%)	31 (18%)	26 (14%)

The overall rates of infection and malignancy were similar between groups. Post-transplant lymphoproliferative disorder (PTLD) was observed in one (0.5%) and two (0.9%) patients in the MI and LI groups, respectively, and in none in the CsA group in the first 12 months.
Conclusions: Belatacept regimens demonstrated better renal function, with similar patient/graft survival and AR compared with a CsA-based regimen in ECD kidney transplant recipients. Belatacept represents a promising immunosuppressant therapy in ECD kidney transplant recipients.

O-333 BELATACEPT IS ASSOCIATED WITH PRESERVATION OF RENAL FUNCTION AND STRUCTURE AT 1 YEAR COMPARED TO CYCLOSPORINE IN EXTENDED CRITERIA DONOR (ECD) KIDNEY TRANSPLANT PATIENTS (BENEFIT-EXT STUDY)

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Introduction: Calcineurin inhibitors (CNIs) contribute to diminished renal function and chronic allograft nephropathy, which impact long-term graft survival in kidney transplant recipients. A belatacept-based immunosuppressive regimen that replaces CNIs may improve renal function and structure in extended criteria donor (ECD) kidney recipients. This abstract focuses on renal endpoints.
Methods: BENEFIT-EXT is a 3-year, randomized, Phase III study in adults receiving an ECD kidney transplant. Patients were randomized 1:1:1 to receive a more intensive (MI) or less intensive (LI) regimen of belatacept or cyclosporine (CsA); all patients received basiliximab induction, MMF, and corticosteroids. The primary renal endpoint was composite renal function (measured GFR [mGFR] of <60 mL/min/1.73 m^2 at Month 12 or a decrease in mGFR ≥10 mL/min/1.73 m^2 from Month 3 to Month 12). Secondary renal endpoints at Month 12 included mGFR, calculated (cGFR) GFR, and protocol biopsies to assess for chronic allograft nephropathy (CAN).
Results: 543 patients were randomized and transplanted. 71% of patients in the MI group, 76% in the LI group, and 85% in the CsA group met the composite renal function non-inferiority endpoint.

	Belatacept MI (n=184)	Belatacept LI (n=175)	CsA (n=184)
Composite renal function impairment endpoint, n (%)	124 (71%) [p=0.002 vs CsA]	129 (76%) [p=0.06 vs CsA]	151 (85%)
Mean mGFR, mL/min (SD)	52.1 (21.9) [p=0.008 vs CsA]	49.5 (25.4) [p=0.10 vs CsA]	45.2 (21.1)
Mean cGFR, mL/min (SD)	50.1 (17.2) [p<0.01 vs CsA]	49.5 (16.7) [p<0.01 vs CsA]	42.7 (15.9)
CAN prevalence, n (%)	82 (44.8%) [p=NS vs CsA]	80 (46.0%) [p=NS cs CsA]	95 (51.6%)

Differences in cGFR occurred as early as the first month post-transplant and continued through 12 months.
Conclusions: Belatacept demonstrated better renal function in ECD kidney transplant recipients, with differences that occurred in the early post-transplant period and were maintained through the first year. Whether trends for lower CAN with belatacept will magnify differences in renal function over time will be assessed in this 3-year trial.

O-334 BELATACEPT IS ASSOCIATED WITH IMPROVED CARDIOVASCULAR AND METABOLIC RISK FACTORS COMPARED TO CYCLOSPORINE IN KIDNEY TRANSPLANT PATIENTS (BENEFIT AND BENEFIT-EXT STUDIES)

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Introduction: Hypertension, dyslipidemia, and diabetes are common comorbidities in kidney transplant recipients, which impact patient survival and can be exacerbated by certain immunosuppressive agents. Belatacept is a selective co-stimulation blocker that may avoid extra-renal toxicities associated with calcineurin inhibitors.
Methods: BENEFIT assessed belatacept in patients receiving a kidney transplant from a living or deceased donor; BENEFIT-EXT in extended criteria donor (ECD) recipients. Each assessed belatacept in more intensive (MI) and less intensive (LI) regimens vs cyclosporine (CsA). All patients received basiliximab, MMF, and corticosteroids. Secondary endpoints included changes in systolic (SBP) and diastolic (DBP) blood pressure, intensity of anti-hypertensive treatment; mean changes in non-HDL, total-, LDL-, and HDL-cholesterol and serum triglycerides; the intensity of lipid-lowering medication use, and the incidence of new onset diabetes mellitus (NODM). Endpoints through Month 12 are presented.
Results: 1209 patients were randomized and transplanted across the two studies (n=666 in BENEFIT; n=543 in BENEFIT-EXT). Mean SBP was 6–8 mmHg lower and mean DBP was 3–4 mmHg lower in the MI and LI groups vs CsA ($P \leq 0.02$) in ECD or non-ECD recipients. More CsA patients used ≥ 3 anti-hypertensive medications compared with LI patients ($P < 0.02$ LI vs CsA in each study).

	Belatacept MI	Belatacept LI	CsA
Mean non-HDL cholesterol, mg/dL (SD); BENEFIT			
Baseline	124.0 (40.0)	123.4 (47.2)	124.5 (39.4)
Month 12	132.1 (37.1)	131.8 (38.4)	142.4 (45.4)
Adjusted mean change (SE)	8.1 (2.8)	8.0 (2.8)	18.3 (2.8)
p-value	0.0115	0.0104	–
Mean non-HDL cholesterol, mg/dL (SD); BENEFIT-EXT			
Baseline	121.0 (40.5)	122.9 (44.8)	125.9 (38.1)
Month 12	135.0 (45.0)	134.2 (40.7)	153.4 (46.7)
Adjusted mean change (SE)	12.6 (3.6)	11.2 (3.6)	29.3 (3.8)
p-value	0.0016	0.0006	–
Mean triglycerides, mg/dL (SD); BENEFIT			
Baseline	173.3 (125.9)	164.5 (94.7)	177.8 (158.7)
Month 12	155.2 (86.5)	149.0 (82.8)	179.8 (103.0)
Adjusted mean change (SE)	-17.0 (7.0)	-21.2 (6.9)	6.6 (6.9)
p-value	0.0165	0.0047	–
Mean triglycerides, mg/dL (SD); BENEFIT-EXT			
Baseline	170.9 (102.4)	167.3 (87.2)	186.4 (95.75)
Month 12	171.9 (129.8)	153.2 (70.0)	213.8 (113.1)
Adjusted mean change (SE)	-1.0 (9.5)	-18.2 (9.2)	34.5 (10.0)
p-value	0.0106	0.0001	–
Mean total cholesterol, mg/dL (SD); BENEFIT			
Baseline	168.9 (43.3)	169.1 (48.2)	168.2 (41.7)
Month 12	182.2 (40.3)	182.0 (40.3)	190.2 (47.7)
Adjusted mean change (SE)	13.4 (3.0)	13.2 (3.0)	21.6 (3.0)
p-value	0.054	0.0468	–
Mean total cholesterol, mg/dL (SD); BENEFIT-EXT			
Baseline	170.5 (43.5)	171.6 (46.8)	172.0 (39.9)
Month 12	184.2 (47.5)	184.1 (45.6)	201.3 (49.5)
Adjusted mean change (SE)	13.3 (3.8)	12.7 (3.8)	29.8 (4.1)
p-value	0.0033	0.0024	–

Changes in LDL- and HDL-cholesterol were not significant between belatacept and CsA regimens.
Conclusions: Belatacept regimens had a better cardiovascular and metabolic profile than the CsA regimen, with less hypertension, dyslipidemia, and NODM vs CsA. The differences in these cardiovascular and metabolic parameters will continue to be assessed over the 3-year trials.

O-335 ONE YEAR SAFETY PROFILE OF BELATACEPT IN KIDNEY TRANSPLANT PATIENTS FROM THE BENEFIT AND BENEFIT-EXT STUDIES

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Introduction: Belatacept demonstrated excellent patient/graft survival and better renal function in two Phase III trials of belatacept vs cyclosporine (CsA) regimens in kidney transplant recipients. The current analysis focuses on the safety profile of belatacept across the two pivotal studies, including notable events such as infections and malignancies.
Methods: BENEFIT assessed an immunosuppressive regimen of belatacept in patients receiving a kidney transplant from a living or deceased donor; BENEFIT-EXT in patients receiving an extended criteria donor kidney transplant. In both studies, patients were randomized to a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids.
Results: 1209 patients were randomized and transplanted across the two studies (n=666 BENEFIT; n=543 BENEFIT-EXT).

Events through month 12	Belatacept MI	Belatacept LI	CsA
All adverse events, n (%)			
BENEFIT (n=666)	218 (99.5)	225 (99.6)	219 (99.1)
BENEFIT-EXT (n=543)	182 (98.9)	174 (99.4)	184 (100)
All serious adverse events, n (%)			
BENEFIT (n=666)	112 (51.1)	100 (44.2)	126 (57.0)
BENEFIT-EXT (n=543)	129 (70.1)	113 (64.6)	130 (70.7)
Serious infectious adverse events, n (%)			
BENEFIT all events (n=666)	44 (20.1)	42 (18.6)	47 (21.3)
Urinary tract infection	10 (4.6)	9 (4.0)	15 (6.8)
CMV infection	9 (4.1)	10 (4.4)	6 (2.7)
Pneumonia	2 (0.9)	3 (1.3)	5 (2.3)
BENEFIT-EXT all events (n=543)	66 (35.9)	54 (30.9)	65 (35.3)
Urinary tract infection	13 (7.1)	15 (8.6)	11 (6.0)
CMV infection	12 (6.5)	14 (8.0)	12 (6.5)
Pneumonia	7 (3.8)	3 (1.7)	3 (1.6)

There were four cases of tuberculosis in the belatacept groups across the two studies (n=2 each MI and LI) and one in the CsA group in the first 12 months. The incidence of malignancies (excluding non-melanoma skin cancer) was similar among the three groups in BENEFIT-EXT (2–3%) and numerically higher in the belatacept arms in BENEFIT (1.8% LI; 2.3% MI) vs CsA (0.5%). PTLD occurred in seven patients within the first 12 months across both studies (n=2 MI; n=4 LI; n=1 CsA). Five PTLD cases were renal (n=1 MI; n=3 LI; n=1 CsA), and two were in the CNS (n=1 MI; n=1 LI). Risk factors for PTLD included: patients who were EBV negative, CMV disease, and T-cell depleting therapy. Updated safety information, including PTLD, will be presented.
Conclusions: Both belatacept regimens were associated with similar rates of adverse events, serious adverse events, and infection vs the CsA regimen. The incidence of PTLD may be higher in belatacept-treated patients, particularly those with known risk factors for PTLD.

O-336 IMMUNOSUPPRESSION WITH BELATACEPT-BASED, CNI-FREE, STEROID-AVOIDING REGIMENS IN KIDNEY TRANSPLANT RECIPIENTS: 6 MONTH, INTERIM RESULTS

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Introduction: Strategies to avoid both CNIs and steroids in the same regimen have not been successful in de novo kidney transplant patients. This study was designed to assess two belatacept-based regimens vs a tacrolimus-based regimen in kidney transplant recipients as potential CNI-free, steroid-avoiding immunosuppression.
Methods: This is a Phase II, 1-year, randomized, open-label, exploratory, multicenter study in EBV seropositive adults receiving a primary kidney trans-

plant. Patients were randomized 1:1:1 to receive belatacept+MMF, belatacept+sirolimus (SRL), or tacrolimus (TAC)+MMF. All patients received induction with thymoglobulin (6 mg/kg max) and four associated doses of corticosteroids. The primary endpoint was the incidence of acute rejection (AR) at 6 months. Additional endpoints at 6 months included percent of subjects surviving with a functioning graft, percent of subjects steroid-free, and calculated glomerular filtration rate (cGFR) using the modification of diet in renal disease (MDRD) formula.
Results: 89 patients were randomized and transplanted; 51% received an organ from a deceased donor.

Outcome (month 6)	Bela + MMF (n=33)	Bela + SRL (n=26)	TAC + MMF (n=30)
Acute rejection, n (%)	4 (12)	1 (4)	1 (3)
Patient and graft survival, n (%)	31 (94)	25 (96)	30 (100)
Patient survival, n (%)	32 (97)	26 (100)	30 (100)
Graft survival, n (%)	32 (97)	25 (96)	30 (100)
Steroid-free patients, n (%)	27 (82)	23 (89)	28 (93)
CNI-free patients, n (%)	28 (85)	21 (81)	–
Mean cGFR, mL/min/1.73m^2 (SD)	57.5 (14.8)	58.7 (29.7)	50.8 (18.2)
Serious infections, n (%)	6 (18)	2 (8)	4 (13)
Oral ulcers, n (%)	1 (3)	6 (23)	0
Tremors, n (%)	1 (3)	0	7 (23)
Lymphocele, n (%)	1 (3)	1 (4)	0

Most AR occurred within the first 3 months. Overall safety was similar across groups. Other notable events were one case of skin cancer in the belatacept+SRL group, and one CMV viremia in the TAC+MMF group.
Conclusions: Belatacept, as part of a CNI-free, steroid-avoiding regimen, provided similar patient/graft survival and AR incidence, acceptable safety, and a trend towards superior renal function vs a TAC-based regimen at 6 months post-transplant. The study demonstrates promise for the use of belatacept in combination with thymoglobulin and either MMF or sirolimus.

Session 42. Late Breaking

LB-1 CYCLOSPORINE (CyA) VERY LOW DOSE WITH EVEROLIMUS (E) HIGH DOSE IS ASSOCIATED WITH BETTER OUTCOMES IN RENAL TRANSPLANT PATIENTS WITH RESPECT TO STANDARD TREATMENT WITH EC-MPS (M)

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Aim of the study was to compare efficacy of CyA very low dose with E high dose with respect to CyA standard dose with M therapy.
In a randomised, prospective, monocenter, open study, patients were enrolled to receive either E (C0 8-10 ng/ml) + CyA (C2 250-300 ng/ml) + steroids or M (1440 mg/day) + Cya (C2 500-700 ng/ml) + steroids. 56 pateints were enrolled in group E, 50 in group M. Efficacy was evaluated at 3 and 12 months. Data analysis has been made per protocol and statistics were made by t-test, χ^2 and Kaplan-Meier when appropriate.
Characteristics of groups were similar. BPAR (E 18.8% vs M 18.2%) were similar in both groups. E patients had lower incidence of DGF than M patients (22.6% vs 40.9%; $p<0.05$; RR 0.65).1-year graft survival was 95% in group E and 88% in group; p=NS. CyA dose at 1 year was lower in group E (1.52±0.67 vs 2.55±0.79 mg/kg;$p<0.0001$). eGFR (Cockcroft-Gault) was higher in group E (81.64±32.67 vs 62.62±22.81 ml/min; $p<0.001$).Systolic blood pressure was lower in group E (124.9±14.64 vs 131.1±13.23 mmHg; p=0.03). Hemoglobin blood levels were slightly lower in group E (12.62±1.42 vs 13.01±1.3 g/L; p=NS; RR for anemia1.302).Serum cholesterol was similar in both groups (E 219.1±47.20 vs M 207.2±38.8 mg/dl; p=NS) but E patients used more statins (RR=1.49). 24 hours proteinuria was higher in group E (519.7±77.31 vs 296.7±33.42 mg/24 hours; p=0.01).
E regimen compared to M regimen is associated with DGF lower incidence, slightly better 1-year graft survival rate, a significantly higher eGFR and lower systolic blood pressure.

LB-2 RANDOMISED CONTROLLED TRIAL OF ALEMTUZUMAB-TACROLIMUS MONOTHERAPY WITH DACLIZUMAB-TACROLIMUS-MYCOPHENOLATE MOFETIL IN RENAL TRANSPLANTATION

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Purpose: We have previously shown that the cheap and simple combination of Alemtuzumab induction with low dose Tacrolimus and a steroid sparing regime is safe and effective. We have now completed a randomised controlled trial [RCT] of this regime compared with Daclizumab induction, conventional dose Tac and Mycophenolate Mofetil [MMF] in renal transplantation.
Follow-up to the primary end-point (survival with a functioning graft at one year) of this trial [ClinicalTrials.gov: NCT00246129] is now complete.
Methods: 82 patients [54m, 28f; mean age 47.3±13.36 years] received Alemtuzumab, low dose Tac [0.1mg/kg; target level 5-8 ng/mL] and 41 patients [27m, 14f; mean age 47.0+10.64 years] received Daclizumab, Tac [0.15mg/kg; target level 8-12 ng/mL] and MMF [target level: 1.5-3.0 mg/L]. Both groups received our steroid sparing regime [prednisolone 60mg daily day 1-3; 30mg daily day 4-7 and then stopped]
In the event of rejection, steroids and MMF were added to the Tac monotherapy group.
Results: One year patient and graft survival is similar in both groups [Alemtuzumab 100% and 97.6%; Daclizumab 97.5% and 97.6% respectively]
The incidence of biopsy proven allograft rejection at 1 year is lower in the Alemtuzumab group, 9% vs 18% in the Daclizumab group, but not statistically significant [p=0.13].
Allograft function [MDRD eGFR, mL/min/1.73m2] is similar at 6 and 12 months [Alemtuzumab 53.7±3.63, 56.8±4.01 vs Daclizumab 49.5±4.78, 50.7±5.80, $p>0.05$; mean±95%CI].
73.2% of the Alemtuzumab group remained on Tac monotherapy at 1 year.
Infection rates [positive bacterial and viral isolates, expressed as incidence/100 patient months] are similar in both groups.
Conclusions: This RCT shows that our simple regime of Alemtuzumab induction and low dose Tacrolimus monotherapy provides excellent patient and allograft survival with a low rate of rejection, infection and good function equivalent to a conventional Daclizumab, Tacrolimus and MMF protocol.

LB-3 BORTEZOMIB THERAPY FOR ACUTE HUMORAL REJECTION

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Purpose: Current therapies do not reduce donor specific anti-HLA antibodies (DSA) levels due to a lack of effect on plasma cells. This study describes plasma cell depletion via bortezomib, to abrogate DSA in transplant recipients with antibody mediated rejection (AMR) or mixed acute rejection (MAR).
Methods: 22 AMR or MAR episodes in 19 patients were treated with bortezomib (1.3 mg/m2/dose ×4). Serial measurements of HLA antibody were conducted before, during, & after treatment by Luminex single antigen beads (levels expressed as MESF). Immunodominant DSA (iDSA) is defined as DSA with highest MESF value at rejection diagnosis.
Results: Mean follow-up post-bortezomib was 181±138 days. 74% of patients experienced a late humoral rejection episode (>6 months post-transplant). 63% of patients were treated with bortezomib after failing primary therapy. Bortezomib therapy resulted in resolution or improvement in cellular rejection in all patients, and also improvement in inflammatory lesions in AMR. Therapeutic response was much better in early AMR than late AMR (ie, >6 months posttransplant). The mean reduction in iDSA after treatment with bortezomib was 55±28 percent, and the iDSA nadir occurred at 35±81 days post treatment. Six allografts were lost of which 3 were due to noncompliance with maintenance immunosuppression. Of compliant patients, 6 month and 12 month graft survival was 90% and 67% respectively. Treatment with bortezomib for AMR ± ACR is generally well tolerated. Adverse effects included transient thrombocytopenia and gastrointestinal complaints, and malignancies and opportunistic infection have not been observed.

	N = 19, (%)
Time Post Transplant to Rejection (months), Mean ± SD	31±44
Late Rejection (>6 Months Post Transplant)	13 (68)
SCr at Rejection Diagnosis, Mean ± SD	3.1±1.7
Pre-Bortezomib iDSA MESF level, Mean ± SD	784,455±427,069
iDSA MESF Level at Nadir, Mean ± SD	386,318±363,617
Percent Reduction in iDSA at Nadir, Mean ± SD	55±28
Percent Reduction in SCr (mg/dL) at Nadir, Mean ± SD	32±19
Time to iDSA Nadir (days), Mean ± SD	35±81
Post Treatment Follow-Up (days), Mean ± SD	181±138

Conclusions: Bortezomib therapy for AMR ± ACR effectively reduces DSA titers and results in a 67% graft survival rate at 12 months post treatment. Plasma cell depletion via bortezomib continues to provide a viable option for humoral rejection and is being evaluated in prospective trials.

LB-4 FASTING PROTECTS AGAINST HEPATIC ISCHEMIA/REPERFUSION INJURY VIA UPREGULATION OF HO-1 AND ANTIOXIDANT DEFENCE

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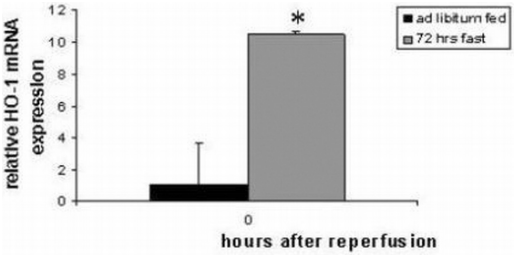
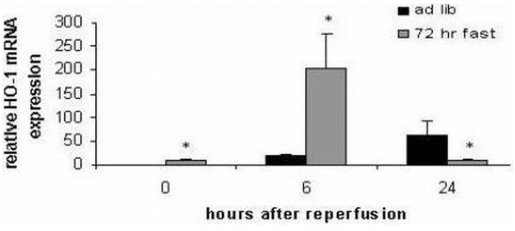
Ischemia reperfusion (I/R) injury is an important factor determining patient outcome after major liver surgery and transplantation. Release of reactive oxygen species contributes to reperfusion injury of the liver after ischemia. We have shown that 72 hours of fasting protects against hepatic I/R injury. To elucidate the protective mechanisms, we investigated the effect of fasting on mRNA expression levels of hepatic HO-1 and antioxidant defence genes.
Male C57BL/6 mice were fed ad libitum or fasted for 72 hours prior to surgery. The portal vein to the left and middle liver lobes (70%) was clamped for 75 minutes to induce I/R injury. Liver damage, neutrophil influx and mRNA levels of mitochondrial superoxide dismutase2, glutathione peroxidase1, and glutathione reductase were determined at 0, 6 and 24 hours after reperfusion.
At 24 hours post-reperfusion, significantly lower ALAT levels ($P<0.01$), significantly less hemorrhagic necrosis ($P<0.001$) and a significantly reduced number of infiltrating neutrophils ($P<0.05$) was observed in livers of fasted animals. Hepatic HO-1 mRNA expression levels were upregulated at baseline, with values significantly higher than the ad libitum fed group. The peak expression level was found 6 hours post-reperfusion in the fasted group while the control group peaked at 24 hours after reperfusion. Hepatic mRNA expression levels of mitochondrial superoxide dismutase 2, glutathione peroxidase 1 and glutathione reductase were all significantly upregulated at baseline in livers of 72 hours fasted animals.



Data expressed as mean ± SEM; *p<0.05 vs ad libitum fed animals on the indicated time point.



Data expressed as mean ± SEM; *p<0.05 vs ad libitum fed animals on the indicated time point.

Short-term preoperative fasting protects against hepatic I/R injury. Fasting induces baseline upregulation of HO-1 and antioxidant mRNA expression levels. Maximum HO-1 levels were significantly higher and achieved earlier after I/R injury in the fasted group. This leads to improved antioxidant defence and reduced organ damage. In analogy to ischemic preconditioning we coin the term nutritional preconditioning for the beneficial effects induced by fasting.

LB-5 PRELIMINARY RESULTS OF A STUDY FOR LIVER DONOR QUALITY WITHIN THE EUROTRANSPLANT DATABASE: STRIKING DIFFERENCES WITH THE UNOS LIVER DONOR QUALITY!

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Introduction: The scarcity of optimal liver donors led to the idea of using livers from extended-criteria-donors (ECD). To give an objective score for donor liver quality and help in the process of organ allocation, a donor-risk-index (DRI) was created within UNOS. Because of differences between the UNOS and Eurotransplant donor pool, it is not clear whether the same DRI would apply in the European setting.
Purpose: To validate the UNOS-DRI within Eurotransplant.
Method: Retrospective analysis of the Eurotransplant database regarding donor characteristics. All 6521 deceased liver donors between January 1st2003 and December 31st2007 are included. Donor and transplant data from the Eurotransplant database are compared to UNOS data, obtained from the article by Feng (AJT 2006;6:783-790), describing all 20.023 deceased liver donors between January 1st1998 and December 31st2002.
Results: Differences were seen between the UNOS and Eurotransplant (ETI) populations in: mean age (UNOS: 39yrs; ETI: 46yrs), death-by-cerebral vascular accidents (UNOS: 44%; ETI: 61%), death-by-trauma (UNOS: 45%; ETI: 28%), donation-after-cardiac-death (UNOS: 1.1%; ETI: 2.0%) and split livers (UNOS: 2.0%; ETI: 7.5%). These differences lead to a remarkable higher mean DRI within Eurotransplant (DRI 1.7) as compared to UNOS (DRI 1.3).
Conclusions: These preliminary results demonstrate striking differences in several factors of the DRI as well as the mean DRI between the Eurotransplant and UNOS region. This suggests a higher willingness to transplant ECD livers in Eurotransplant than in the US. Outcome data of liver transplantation should be interpreted in the light of the local mean DRI. Comparison of transplantation results between regions with different mean DRI may help to disclose regions where more liberal use of ECD livers can be performed safely.
This is a study supported by the Eurotransplant Liver and Intestine Advisory Committee (ELIAC).

LB-6 PANCREAS TRANSPLANTATION FROM NON-HEART BEATING DONORS IN THE UNITED KINGDOM

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Purpose: To review the early experience of NHBD pancreas transplantation in the UK to correlate donor, recipient and graft characteristics with early outcome
Methods: Data were obtained on 74 transplants (39 SPK, 19 PAK, 16 PTA) from Maastricht category 3 and 4 NHBD performed at 6 centres between July 2005 and March 2009 from the National Transplant Database. Pancreases were procured if donor asystole occurred within 60 minutes of treatment withdrawal. There was no pre-mortem cannulation or pharmacologic intervention. UW solution was used in all cases. Results: Mean (±SD) donor age & BMI was 28±13yrs & 23±6kg/m2. Causes of donor death were trauma (34%), CVA (27%), hypoxia (29%). Mean recipient age was 42±8. Median HLA mismatch was 4. Seven recipients had >50% allosensitization. Median time to transplant was 100 days (0-1448). All grafts had caval (93%) or portal (7%) venous drainage and enteric (90%) or bladder (10%) exocrine drainage. Median cold ischemia was 837min (316-1320). All centres used antibody induction with depleting (54%) or non-depleting (46%) antibodies and maintenance with tacrolimus (80%) or cyclosporine (20%) and mycophenolate with (49%) or without (51%) corticosteroids. Median f/u was 10 months (0-45). Delayed graft function occurred in 23% (kidney), and in 5% pancreases. Overall patient & pancreas survival was 96 & 80% (SPK 87%, PTA 81%, PAK 63%). Thrombosis (10.8%), anastomotic leak (2.7%), death with functioning graft (4%) and rejection (1.3%) caused graft loss. Donor BMI >27 (p=0.058), HLA mismatch >4 (p=0.08), HLA sensitization >50% (p=0.006), PAK vs. SPK (p=0.048) increased risk of early graft loss
Conclusion: Most early pancreas losses are due to thrombosis. Graft survival in SPK & PTA is better than in PAK. Higher donor BMI is associated with increased risk of early graft loss. The role of histocompatibility and allosensitization needs further investigation.