SHORT PRESENTATIONS ON POSTERS

PV01 HBV AND LIVER TRANSPLANTATION – THREE DECADES OF EXPERIENCE

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Introduction and Background: In the past, there were different strategies to prevent HBV-reinfection after liver transplantation (LT) for HBV-associated liver disease. The aim of the analysis was compare different modes and to sum up the results of 30 years at a high volume transplant center.
Methods: Demographic, clinical, biochemical and histological data of 372 LTs performed for the HBV-induced liver disease in 352 patients were extracted from a prospective database. The incidence of HBV-reinfection was determined according to the transplant period and the mode of HBV-prophylaxis. Survival rates were determined in patients with successful prophylaxis, untreated and controlled HBV-reinfection.
Results and Conclusions: Lower prevalence of HBV-reinfection was observed in patients undergoing LT for an acute HBV-associated liver failure (9.4 vs. 30.9%; $p = 0.008$). Significantly lower HBV-reinfection rate was observed with a concomitant HCV-infection (14.3 vs. 30.6%; $p = 0.049$). No significant differences in the distribution of HBV-reinfection was observed in patients with HCC (24.7 vs. 30.1; $p = 0.388$) and HDV-co-infection (23.3 vs. 29.8%; $p = 0.474$). HBV-associated mortality increased in the first years after LT and later became comparable between the groups. Controlled HBV-reinfection did not demonstrate any fibrosis progression during a median histological follow-up of 13 years. Reinfection stopped to be significant for the survival in patients who received NUCs and HBIG ($p = 0.233$) compared to patients who received HBIG or nothing at all ($p = 0.004$). HBIG-discontinuation initiated in 55 patients did not result in HBV-recurrence.

Uncontrolled HBV-reinfection does not occur any more. Even in the formal presence of Hbs-Ag transplant fibrosis does not develop in a long-term follow up. The most reliable mode to prevent HBV-recurrence is still the combination of NUCs with a high genetic barrier. HBIG may be safely discontinued after LT.

PV02 SOFOSBUVIR IMPAIRS PROLIFERATION OF HEPATOCYTES *IN VITRO* AND *IN VIVO*

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Introduction and Background: The introduction of direct acting antivirals (DAAs) as highly effective treatments for hepatitis C virus infection (HCV) promised a decreasing incidence of hepatocellular carcinoma (HCC). However, recently an increased risk of HCC recurrence after DAA treatment was reported by some groups while others could not confirm this finding. Therefore we investigated whether Sofosbuvir (SOF) may have an influence on cell growth, apoptosis and cell proliferation of hepatocytes *in vitro* and *in vivo*.
Methods: Cell proliferation *in vitro* was measured by BrdU-ELISA, viability by MTT-assay and apoptosis by caspase assay in human HUH7 cells and the HCV GT1b-replicon cell line Con1 after treatment with SOF. Gene expression analysis was performed by qRT-PCR. Cell proliferation *in vivo* was determined by immunohistochemical staining of Ki67 in explanted liver tissue of 37 patients who underwent liver transplantation (LT) due to HCV cirrhosis. Of these, 25 had received SOF-based DAA therapy before LT and 12 patients did not.
Results and Conclusions: SOF significantly decreased HUH7 proliferation to 32% after 96 h ($p \leq 0.001$) compared to untreated cells. Proliferation of Con1 cells was reduced to 15% ($p \leq 0.001$). Furthermore, SOF treatment resulted in a significant reduction of actin gene expression by 65% ($p \leq 0.028$) in HUH7 and 55% ($p \leq 0.041$) in Con1 cells after only 48 h. Apoptosis was not affected by SOF in HUH7 and Con1 cells. The analysis of liver tissue confirmed our *in vitro* findings. Patients who received DAAs before LT show significantly less Ki67 positive hepatocytes ($p \leq 0.015$) in the explanted liver (Median 3.3, Range: 0.8–3.7) than patients who did not (Median: 1.4, Range: 0.4–3.5). Our herein presented results suggest an antiproliferative effect of SOF in hepatocytes *in vivo* and *in vitro* and identify a possible association of this effect to cytoskeletal processes.

PV04 CHRONIC GRAFT INJURY AND LONG-TERM OUTCOME AFTER PAEDIATRIC LIVER TRANSPLANTATION

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Introduction and Background: The prevalence of allograft fibrosis and hepatitis in asymptomatic paediatric liver transplant (LT) recipients is well documented. However, their impact on long-term outcome remains unclear.
Methods: We reviewed clinical data and long-term outcomes of 289 asymptomatic (ALT < 50 IU/l) children who underwent 10-year (±2 years) protocol biopsies in 8 international centres. Histological findings were correlated with outcomes including re-transplantation and survival. The median follow-up was 17 (8–24) years after LT.
Results and Conclusions: In the 10-year biopsies, normal or near normal histology was reported in 24%; periportal or central fibrosis without bridging in 47%; 20% had bridging fibrosis and 9% had cirrhosis. Inflammation was found in 52% of 10-year protocol biopsies.

In a subgroup of $n = 115$ patients, 5-year protocol biopsies were available and reviewed. To avoid confounders, we focused on the cohort of patients who had normal liver histology without fibrosis at both times (22%). Significant predictors of no fibrosis at 5 and 10 years include shorter cold ischaemic time ($p < 0.01$), no prior history of graft hepatitis ($p < 0.001$) and negative serum autoantibody status ($p = 0.014$).

A Kaplan-Meier analysis for patient and allograft survival did not demonstrate reduced allograft survival in patients with periportal/central fibrosis and bridging fibrosis in comparison to patients without fibrosis at 10-year biopsy. However, patients with cirrhosis at 10 years had a significantly ($p = 0.028$) higher risk of death (2 out of 27 patients) or re-transplantation (3 out of 27 patients) by the end of the second decade after LT.

76% of patients transplanted in childhood developed fibrosis in protocol liver biopsies 10 years post LT, which is potentially progressive in most cases. While many patients with fibrosis are stable, severe fibrosis or cirrhosis on 10-year protocol biopsy may lead to graft loss or mortality by the end of second decade post paediatric LT.

PV05 CHRONIC NEUROTOXICITY OF CALCINEURIN INHIBITORS IN PATIENTS AFTER LIVER TRANSPLANTATION

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Introduction and Background: Calcineurin inhibitors (CNI) frequently induce neurological complications early after orthotopic liver transplantation (OLT). We hypothesize that long-term CNI therapy after OLT causes dose-dependent cognitive dysfunction and alteration of brain structure.
Methods: Eighty-five OLT patients (20 with CNI free, 35 with CNI low dose and 30 with standard dose CNI immunosuppression) underwent psychometric

testing and cerebral magnetic resonance tomography about 10 years after OLT to assess brain function and structural brain alterations. Thirty-three healthy subjects adjusted for age, gender and education served as controls.
Results and Conclusions: Patients receiving CNI showed a significantly worse visuospatial/constructional ability compared to controls ($p \leq 0.04$). Furthermore, patients on low dose CNI therapy had an overall impaired cognitive function compared to controls ($p = 0.01$). The tacrolimus total dose and mean trough level were negatively correlated to cognitive function. CNI doses had been adjusted in 91% of the patients in the low dose and CNI free group in the past due to CNI induced kidney damage. Patients treated with CNI showed significantly more white matter hyperintensities (WMH) than patients on CNI free immunosuppression and controls ($p < 0.05$). Both, the mean cyclosporine A and tacrolimus trough levels correlated significantly with WMH.

Long-term CNI therapy is associated with cognitive dysfunction and structural brain alterations. Continuation of CNI therapy after the occurrence of nephrotoxic side effects – even in a low dose – carries the risk for cognitive alterations in the long-term, indicating an increased susceptibility against toxic CNI effects in this subgroup of patients. Patients showing CNI toxicity early after OLT might benefit from a change to CNI free immunosuppression.

PV07 DONOR SPECIFIC ANTIBODIES ARE ASSOCIATED WITH HIGHER INFLAMMATORY ACTIVITY, MORE FIBROSIS AND HIGHER EXPRESSION OF REJECTION ASSOCIATED TRANSCRIPTS IN SUBCLINICAL REJECTED HUMAN LIVER ALLOGRAFTS

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Introduction and Background: Subclinical rejection (SCR) is a common event after liver transplantation and has a good medium-term prognosis even if left untreated. We recently found hints for an intrahepatic regulation of cytotoxic T cells by regulatory T cells in SCR. Donor-specific antibodies (DSA) have not been investigated in this setting.
Methods: We included all virus negative patients from our biopsy program. Acute cellular rejection (ACR) was defined as: rejection activity index (RAI) $\geq$3 and liver enzymes (ALT, AST, AP) >2x upper limit of normal (ULN), SCR as RAI $\geq$3 and liver enzymes $\leq$2x ULN, and no histological rejection (NHR) as RAI<2, liver enzymes normal. RT-PCR was performed from 80 liver biopsies with gene panels using 90 genes for rejection, endothelial cell activation, operational tolerance, T cell exhaustion and immune regulation markers. DSA were detected with bead assays.
Results and Conclusions: On the transcriptional level SCR biopsies were more related to NHR than to ACR in a cluster analysis of RT-PCR results ($p < 0.05$ and $q < 0.08$). DSAs were found in paired blood samples in 28% of SCR, 8% of NHR and 24% of ACR biopsies, while the overall DSAs frequency was 22%. DSA+ SCR biopsies had significantly more lobular and portal inflammation, interface hepatitis, central perivenulitis and sinusoidal fibrosis compared to DSA- SCR. The expression of mostly rejection associated transcripts was higher in DSA+ SCR biopsies. 9% of SCR biopsies fulfilled the 2016 Banff criteria for possible chronic antibody mediated rejection (AMR). The gene expression analysis of these possible AMR biopsies is currently ongoing.

SCR is transcriptionally more related to biopsies without rejection. However, the appearance of DSA seems to mark SCR biopsies with more inflammation and fibrosis. The combination of SCR in biopsies with DSA positivity might therefore identify patients with more pronounced graft inflammation, which might require a change in immunosuppression.

PV08 ACUTE LIVER FAILURE – INCIDENCE AND AETIOLOGY ESTIMATED FROM A POPULATION BASED STUDY OF 25 MILLION PEOPLE IN GERMANY

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Introduction and Background: Acute liver failure (ALF) is an infrequent but life-threatening event and has a high mortality rate without liver transplantation. Currently, only estimations of incidence based on cohorts are available, whereas population based data are rare. We report the incidence of ALF in Germany using the account data of the largest statutory health insurance organization, the Federal Association of AOK, representing 25 million people.
Methods: The analysis included all patients insured by AOK uninterruptedly between 2010 until 2014. Coding of patients with ICD-10 and OPS were used to identify cases of ALF including concomitant diagnoses and liver transplantation (LT). Also age, sex, deaths were recorded. Data were extrapolated with age and sex adjustment to all people insured within the German statutory health insurance.
Results and Conclusions: The incidence of ALF in Germany was 1.59/ 100 000 person years in the investigated period. Peak incidence of ALV occurred in the 8th decade of life (27%). Of all patients with ALF 47% were male. Overall mortality rate was 66%, 69% in men and 63% in women. Evaluation of liver transplantation was encoded for 3.1% of patients and liver transplantation was performed in 3.5%. From transplanted patients with ALF 36% were male. One-year overall mortality rate after LT was 29%, 33% in men and 27% in women.

In conclusion, this analysis based on public health insurance data of 25 million insurants indicates a remarkably high incidence of ALF in Germany with only a low rate of consecutively performed liver transplantations despite a high mortality.

PV09 IMPACT OF DIRECT-ACTING ANTIVIRAL THERAPY ON THE NEED FOR LIVER TRANSPLANTATION RELATED TO HEPATITIS C IN GERMANY

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Introduction and Background: Interferon (IFN)-free therapies of chronic hepatitis C virus (HCV) infection have been approved by EMA since January 2014. Subsequently, HCV therapy has tremendously improved in effectiveness and tolerance. This development might have changed the need for liver transplantation (LT) due to HCV and, thus, the prevalence of other indications for LT on the waiting list.
Methods: Data on indications for LT, number of patients who received LT with or without HCV, patients who were treated for HCV on the waiting list, and treatment outcome were collected from 11 German transplant centres for the years 2010–2016. More than 55% of all liver transplantations performed in Germany were covered by our analysis.
Results and Conclusions: Absolute numbers of adult cadaveric liver transplants decreased in all centres between 2010 ($n = 610$) and 2016 ($n = 488$), indicating the widening gap between donor organ supply and demand. However, the ratio of patients with actively replicating HCV infection at time of listing decreased in the same time from 18% to 9%. Similarly, the percentage of patients transplanted with active HCV infection declined from 20% to 14%. HCV treatment on the waiting list was successful in less than half of the patients before the introduction of DAAs, while in 2015 and 2016 almost all patients who received HCV treatment on the waiting list achieved sustained viral response. Moreover, while almost 30% of patients used to stop treatment due to side effects before 2014, none of the patients who underwent HCV therapy on the waiting list had to stop treatment ever since.

The introduction of IFN-free DAA therapies was associated with a decrease in the proportion of HCV patients listed for LT as well as HCV patients requiring LT. Treatment of HCV on the LT waiting list became significantly more effective and tolerable.

PV10 BILIARY STRICTURES AFTER WHOLE LIVER TRANSPLANTATION WITH DUCT-TO-DUCT BILIARY ANASTOMOSIS: RETROSPECTIVE ANALYSIS AT TRANSPLANT CENTRE OF UNIVERSITY HOSPITAL TÜBINGEN

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Introduction and background: Biliary strictures (BS) are common complications after Liver Transplantation (LT) with an incidence up to 25%. Most of the literature about this topic is limited to pre-MELD-Era and with only few risk factors analysed. Aim of this study is to determine main risk factors influencing the occurrence of BS in the MELD-Era.
Methods: Data of patients who underwent Whole-LT with duct-to-duct anastomosis from January 2009 to December 2013 at the University Hospital Tübingen were retrospectively collected. Almost 450 possible risk factors for BS related to donor, graft, recipient, surgery and the post-transplant course were analysed.
Results and conclusions: 189 LTs were considered. Median F-UP was 71 months (IQR, 30–115). 59 BS, including 27 anastomotic (AS) and 32 non-anastomotic (NAS), were diagnosed in 42 cases. Median time of occurrence for BS was 271 days (96–5723). Recipient's correlated risk factors were chronic liver failure, alcohol, active HBV, portal hypertension and hepatorenal syndrome, cardiovascular disease and DM. Within donor's profile, trauma as cause of death, male sex (AS), overweight, and age > 50 years and weight > 50 kg (NAS) were associated with higher risk. A longer cold perfusion-hepatectomy time was associated with BS, whereas a longer heparin-hepatectomy time just with AS. Suboptimal quality liver was a risk factor for BS. Single interrupted suture for the posterior wall was the only technical aspect significantly associated with BS. Immunosuppression with Tacrolimus was protective against all type of biliary strictures. The following postoperative complications were significantly associated to BS: PVT, CMV reactivation, bleeding, kidney failure, rejection and graft loss, previous cholangitis or biliary obstruction.

PV11 DOES DONOR GENDER IMPACT ON LOWER URINARY TRACT INFECTIONS AFTER RENAL TRANSPLANTATION?

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Introduction and Background: Urinary tract infection (UTI) is the most common infection after renal transplantation (RTx) and can threaten graft and patient survival. Although female gender is a well-known risk factor for the development of UTI after RTx, the role of the donor gender in this context remains unclear. We herein aimed to clarify the impact of the donor gender on the development of UTI after RTx.
Methods: This study included 102 RTx outpatients with lower UTI and pathogen identification. 102 patients presenting at our RTx outpatient clinics during the same time period without UTI served as controls. In a second cohort (58 kidney recipients and 16 controls), we assessed the immunological response of leukocytes to lipopolysaccharide (LPS).
Results and Conclusions: UTI infections occurred noticeably frequent in patients with female gender, minor height and weight (all $p < 0.001$), advanced age ($p = 0.018$), deceased donor transplantation ($p = 0.024$) and male kidney allograft gender ($p = 0.035$). After identification by univariate analysis, multivariate logistic regression analysis indicated female gender ($p < 0.001$), minor height ($p = 0.040$), advanced age ($p = 0.026$) and male kidney allograft gender ($p = 0.029$) as potential risk factors for the occurrence of UTI after RTx. Immunosuppressive therapy impaired the IL1ß-, S100A8/S100A9- and IL8-dependent leukocyte response to LPS. This impairment was independent from recipient and donor gender.

Male kidney allograft gender is a potential novel risk factor for the occurrence of UTI after RTx. Donor gender did not influence the response of leukocytes to LPS. Further prospective studies are needed to identify the underlying mechanisms of higher male kidney donor dependent UTI.

PV12 IMPACT OF HEPATITIS B AFTER RENAL TRANSPLANTATION

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Introduction and Background: Hepatitis B (HepB) is more frequent in dialysis patients than in the normal population. Renal Transplantation is the best choice of treatment for end-stage renal disease. Patients with chronic HepB are known for worse long term patient and graft survival.
Methods: In our retrospective analysis of 1405 renal transplanted recipients we investigated the outcome of HepB positive patients prior to transplantation.
Results and Conclusions: From 1405 patients were 1211 with negative HBsAg (naïve group), 126 with negative HBsAg and positive HBc-antibodies and 68 patients with positive HBsAg. Kaplan-Meier-analysis showed a 5-year graft survival (censored for death) 89.5% in naïve group, 87.6% in HBc positive patients and 89.0% in HBsAg positive patients ($p = 0.699$). Patient survival after 5 years was 87.9% in naïve group, 82.8% in HBc positive patients and 80.0% in HBsAg positive patients ($p = 0.067$). Overall 5-year-survival of patients with a functional graft was 81.3% in naïve Hepatitis B patients, 75.6 in HBc positive and 71.2% in HBsAg positive respectively ($p = 0.045$). The 10-year patient survival was 78.6% in naïve group, 70.4% in HBc positive patients and 80.3% in HBsAg positive patients respectively ($p = 0.275$). The 10-year-death censored graft survival was 73.0% in naïve group, 65.7% in HBc positive patients and 63.6% in HBsAg positive patients ($p = 0.045$). The 10-year-graft survival rate (incl. death) was 62.6% in naïve Hepatitis B patients, 49.7% in HBc positive and 55.1% in HBsAg positive patients ($p = 0.016$). While hepatitis B had no impact on 5 year survival our data indicate inferior long-term survival after hepatitis B infection irrespective of serostatus. Further analyses have to look into causes of graft loss and potential confounding factors as well as treatment effect in modern era.

PV13 PROVISION OF HIGHLY SPECIALIZED AFTERCARE BY THE TRANSPLANT CENTER STRONGLY IMPROVES PATIENT AND ALLOGRAFT SURVIVAL IN LONG-TERM FOLLOW-UP AFTER KIDNEY TRANSPLANTATION

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Introduction and Background: Despite rapid medical advancements in the field of transplantation, mean kidney allograft survival remained at a standstill. If and to what extent a highly specialized and experienced aftercare of kidney transplant recipients (KTRs) impacts patient and allograft outcomes remains unknown.
Methods: We retrospectively analysed 1328 KTRs transplanted between 1998 and 2015. KTRs treated regularly in our transplant centre were compared with KTRs followed by local nephrologists. KTRs that make no use of the transplant centre provided aftercare were assessed by a questionnaire-based survey with respect to allograft survival and their reasons not to make use of it.
Results and Conclusions: In total 824 KTRs (62.0%) were followed in our transplant center and 504 KTRs (38.0%) were followed by local nephrologists. Multivariate analysis identified shorter distance to the transplant centre ($p < 0.001$), living donation ($p < 0.001$), early registration to the waiting list ($p = 0.009$), and shorter initial hospital stay ($p = 0.004$) as independent factors for strong adherence to the transplant centre. KTRs followed in our transplant centre showed a significantly better patient survival (72.7% vs. 50.4% after 15 years; $p = 0.001$) and death-censored allograft survival (85.0% vs. 64.4% after 15 years; $p < 0.001$) compared to KTRs followed by local nephrologists. These differences were equally observed in deceased and living donor KTRs. Reasons not to make use of the transplant centre provided aftercare included distance (47%), prohibitively expensive costs (37%), no identifiable advantages (34%), and negative experiences (7%).

Our data strongly indicate that provision of aftercare by the transplant centre is highly associated with superior patient and allograft survival. The observed wide differences may be attributed to highly specialized immunological and infectious screening protocols, careful and critical guidance of immunosuppression, and more comprehensive medical care. Transplant centres, local nephrologists, and health insurances must encourage patients to make use of transplant centre provided aftercare.

PV14 DETECTION OF ACUTE CELLULAR RENAL ALLOGRAFT REJECTION VIA URINE METABOLITES – THE RENALTX-SCORE-U100

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Introduction and Background: Post-transplant surveillance for acute rejection is mainly based on regular monitoring of serum creatinine levels and consecutive biopsies upon functional renal impairment. Recently, we developed a novel method to detect kidney allograft rejection via urine metabolomic panels investigated by nuclear magnetic resonance spectroscopy (NMR).
Methods: Within the prospective Umbrella study performed at the University Hospital Regensburg 2479 urine specimens from 109 consecutive kidney-graft recipients from day 1 through month 12 after transplantation were collected. The specimens were analysed using the numares AXINON NMR system and the results were compared to the allograft-rejection status according to the biopsy results.
Results and Conclusions: The metabolomic panel was able to detect acute cellular allograft rejection during outpatient phase (≥day 15 after

transplantation, area under the curve (AUC) 0.75, [95% confidence interval (CI) 0.68 to 0.83], $p < 0.001$). A combination of the metabolomic signature and eGFR significantly improved the overall test performance (AUC 0.84).

In conclusion, the metabolomic signature in combination with eGFR appears to be the first reliable non-invasive test which can be easily used for post-transplant outpatient monitoring. To confirm the results from the previous Umbrella study we have now started a European multicenter study. The novel test system was meanwhile licensed as renalTX-SCORE-U100.

PV15 MONITORING OF DONOR-REACTIVE T CELLS USING DONOR SPLEEN CELLS AND/OR IFNG-BASED ASSAYS MIGHT UNDERESTIMATE DONOR-REACTIVE T CELL IMMUNITY

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Introduction and Background: Donor reactive T cells (DRT) are known to cause acute cellular rejection. IFNg-based assays have been previously established to assess the frequencies and the role of DRT as biomarkers for rejection prediction. To this end, peripheral blood cells are stimulated by antigen sources expressing donor human leukocyte antigen (HLA) molecules, most frequently using donor spleen cells (DSC). Although the data on predictive value of DRT is encouraging, some studies report on relevant number of false negative and/or false positive results. Previously, some authors suggested importance of graft cell-derived peptides for the stimulation of DRT. Recently, we established a new method for monitoring DRT using donor urine-derived tubulo-epithelial cells (TEC) as an allograft tissue specific source. The aim of the current study was to compare stimulatory capacity of TEC and DSC for the monitoring of donor-reactive T cells.
Methods: For this, a small renal transplant patient cohort including patient with acute cellular rejection and patient with stable graft function as control were analysed.
Results and Conclusions: Using 15-colour flow cytometry we performed in-depth functional and phenotypic characterization of DRT upon stimulation either by TEC or DSC. Using TEC as an allogenic source, we observed a significantly higher frequency of DRT as compared to DSC. In addition, our multi-parameter analyses revealed dominance of Th17 phenotype within donor-reactive $CD4^+$ cells, while granzyme B was the most pronounced cytokine within $CD8^+$ cells. Interestingly, functional characterization of DRT showed almost no IFNg production by DRT in both stimulation approaches.

In summary, our data demonstrate the superiority of our novel donor TEC-based approach reflecting significance of previously proposed graft organ cell specificity for DRT monitoring. In addition, IFNg as a read out parameter for DRT monitoring might underestimate the magnitude of cellular allo-sensitization.

PV16 METABOLISM RATE OF EXTENDED-RELEASE TACROLIMUS (ADVAGRAF®) AND RENAL DYSFUNCTION AFTER KIDNEY TRANSPLANTATION

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Introduction and Background: The metabolism rate of immediate release tacrolimus (Prograf®) is defined as the ratio of tacrolimus blood concentration (C) and daily tacrolimus dose (D). Fast Prograf® metabolism (C/D ratio <1.05 ng/ml $\times$ 1/ml) is associated with impairment of kidney function after renal transplantation (RTx). We hypothesized that a fast metabolism rate of extended-release tacrolimus (Advagraf®) is analogously associated with kidney dysfunction after RTx.
Methods: In our study we included patients that underwent RTx between 2007 and 2016 and received an initial immunosuppressive regimen with Advagraf®, mycophenolate, prednisolone and an induction with basiliximab as induction. Patients with a C/D Ratio <0.75 ng/ml $\times$ 1/ml (according to the overall median) one month after RTx were defined as fast Advagraf® metabolizers, a C/D ratio ≥ 0.75 ng/ml $\times$ 1/ml defined slow metabolizers. Renal function (s-creatinine) and the switch of immunosuppression were analysed in a 36-months follow-up.
Results and Conclusions: 84 RTx patients on Advagraf® (41 fast metabolizers and 43 slow metabolizers) were included in our study. Ten days, 1, 2, 3, 6, 12, 24 and 36 months after RTx fast metabolizers showed a reduced renal function compared to slow metabolizers (mean creatinine: 2.7 vs. 1.8 mg/dl after ten days ($p = 0.006$); 1.3 vs. 1.1 mg/dl after 36 months, respectively; $p = 0.039$). Interestingly, more fast than slow metabolizers were switched from Advagraf® to an alternative immunosuppressive drug (49% vs. 30%; n.s.).

In a 3-year follow-up renal function after RTx was better in slow than in fast Advagraf® metabolizers. Thus, calculation of the Advagraf® C/D ratio early after RTx may be a key tool in the individualization of the immunosuppressive regimen.

PV17 ATHENA STUDY: OUTCOMES ON ALLOGRAFT FUNCTION AFTER 12 MONTHS OF MODERN EVEROLIMUS-BASED VS. CONSERVATIVE TACROLIMUS-MPA REGIMEN IN *DE NOVO* RENAL TRANSPLANT RECIPIENTS

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Introduction and Background: ATHENA was designed to compare efficacy, safety and outcomes on renal function [GFR] of everolimus [EVR] in combination with tacrolimus [TAC] or cyclosporine A [CyA] vs. a standard regimen of mycophenolic acid [MPA] +TAC in *de novo* kidney transplant recipients [KTxR].
Methods: In this 12 months [M], prospective, controlled multi-centre study with 15 German and 12 French sites, 612 patients [pts] were randomized [rdz] 1:1:1 at time of Tx to either a) EVR (target: 3–8 ng/ml M1-M12) +TAC (4–8 ng/ml M1-M3; 3–5 ng/ml M3-M12), b) EVR(3–8 ng/ml M1–M12) + CyA (75–125 ng/ml M1-M3; 50–100 ng/ml M3-M12) or c) control TAC (4–8 ng/ml M1-M3; 3–5 ng/ml M3–M12) +MPA. All pts continued on steroids. Here we report M12 outcomes on allograft function from full analysis set: 208EVR+TAC pts, 199EVR+CyA pts, 205TAC+MPA pts.
Results and Conclusions: From rdz to M12 allograft recovery was good in all three treatment groups with increase in GFR (Nankivell) as ΔeGFR M1-M12: a) EVR+TAC +6.6 ml/min, b) EVR+CyA +9.6 ml/min, c) TAC+MPA +7.6 ml/min (not significantly different). Analysis of donor age categories [<35; 35–49; 50–64; >65 years] showed that donor age >65 years had worst renal allograft outcomes, regardless of treatment. Urinary protein excretion at M12 was not different between groups with a category analysis showing only 3.7%of TAC+MPA vs. 1.3% of TAC+EVR vs. 0.7% of CyA+EVR pts had proteinuria in nephrotic range [>339 mg/mmol] at M12.

ATHENA, the largest European KTx study, showed that renal allograft function improved comparably in all treatment groups with no differences in measured urinary protein excretion after 12 Mo drug exposure. Additionally, strongest impact on post Tx GFR appears to be determined by donor age, which is shown herein for the first time in a large prospective study.

PV18 12 MONTHS DATA FROM ATHENA STUDY SHOW COMPARABLE SAFETY AND EFFICACY OF MODERN EVEROLIMUS-BASED REGIMEN VS. CONSERVATIVE TACROLIMUS-MPA-BASED REGIMEN IN *DE NOVO* RENAL TRANSPLANT RECIPIENTS

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[1]*Athena Study Group, Germany;* [2]*Athena Study Group, France;* [3]*Novartis Pharma, Nürnberg, Germany*

Introduction and Background: ATHENA study was designed to compare everolimus [EVR] in combination with tacrolimus [TAC] or cyclosporine A [CyA] vs. mycophenolic acid [MPA] and TAC in *de novo* kidney transplant recipients [KTxR].
Methods: In this 12 months [M], prospective, controlled multi-centre study, 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR(3–8 ng/ml) +TAC(M1-M3:4–8 ng/ml;M3-M5:3–5 ng/ml), or EVR(3–8 ng/ml) +CyA(M1-M3:75–125 ng/ml;M3–M5:50–100 ng/ml) or TAC (M1-M3:4–8 ng/ml;M3–M5:3–5 ng/ml)+MPA. Here we report M12 outcomes on efficacy and safety from ITT set ($n = 208$ EVR+TAC, 199 EVR+CyA, 205 TAC+MPA pts).
Results and Conclusions: At M12 tBPAR KM-estimates were 6.7% for EVR+TAC, 17.6% for EVR+CyA and 3.9% for TAC+MPA, most events BANFF IA (1.9%; 9%; 1.5%), only 1.5%, 2% vs. 0.5% BANFF IIB/III. 5pts in EVR+TAC, 5 in EVR+CyA and 6pts in TAC+MPA died. Graft losses were few: 10(4.8%) in EVR+TAC, 13(6.5%) EVR+CyA and 6(2.9%) in TAC+MPA group, including 5 primary non-functioning grafts in each EVR-group and 1 in TAC+MPA arm. Safety profiles were comparable with incidences of AEs/infections leading to study drug discontinuation or dose adjustment/interruption of 56.7% in EVR+TAC, 55.5% in EVR+CyA vs. 61.3% in TAC+MPA arm. Primary reasons for changes were infections (7.1% EVR+TAC, 4.5% EVR+CyA, 23.5% TAC control) as well as lympho-/leucopenia (3.3%, 3.5%, 13.2%). No differences in AEs on wound complications were found (sum-incidences: 41.9% in EVR+TAC, 38.9% in EVR+CyA, 43.2% in TAC+MPA).

ATHENA as largest European KTx study confirmed good efficacy and event rates well within international standards for all 3 groups and no unexpected safety events for this indication and population. There were no differences in reported AE wound healing and less leucopenia with EVR-based regimen.

PV19 RESULTS AFTER RENAL TRANSPLANTATION FROM DECEASED DONORS WITH ACUTE KIDNEY INJURY

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Introduction and Background: Acceptance of organs from deceased donors with acute kidney injury (AKI) is still controversial mainly due to uncertainty regarding outcomes.
Methods: This is a retrospective, monocentric study of 642 renal transplant patients who received a renal allograft between 2005–2016. Eighty-nine patients received a kidney transplant from an AKI donor defined as having serum creatinine (SCr) >2 mg/dl (group 1). They were compared with a group of 214 patients with donor SCr of 1.1–2 mg/dl (group 2) and 339 patients with normal kidney function donors (SCr <1.1 mg/dl, group 3). Data collected from donor medical records included age, gender, BMI, cause of death, hypertension or diabetes history, SCr, extended criteria donor and cardiac arrest. Patient- and graft survival, SCr, estimated glomerular filtration rate (eGFR) and rate of delayed graft function (DGF) were analysed.
Results and Conclusions: Donors with AKI were younger (group 1: 49.31 ± 16.34; group 2: 56.91 ± 15.68, group 3: 55.28 ± 16.08 years, $p = 0.001$) and had a higher BMI (29.76 ± 6.9; 27.81 ± 4.65;25.91 ± 4.13 kg/m^2, $p < 0.001$) compared to the other groups. Cumulative 1-year patient- and graft survival were 92.1% / 83.1% in group 1, 94.4% / 79.0% in group 2 and 96.5% / 88.5% in group 3, log rank $p = 0.248$. Cumulative 3-years patient- and graft survival were 87.3% / 78.2% in group 1, 87.3 % / 71.4 % in group 2 and 92.9% / 79.1% in group 3, log rank $p = 0.255$. Mean SCr and mean eGFR after 1 year were 2.0 ± 1.57 mg/dl and 56.3 ± 24.7 ml/min in group 1, 2.11 ± 1.74 mg/dl and 50.2 ± 23.0 ml/min in group 2, and 1.81 ± 1.14 mg/dl and 56.8 ± 22.7 ml/min in group 3, $p = 0.043$. Mean SCr and mean eGFR after 3 years were 2.41 ± 2.48 mg/dl and 55.8 ± 29.0 ml/min in group 1, 2.22 ± 2.18 mg/dl and 51.67 ± 22.8 ml/min in group 2, and 1.65 ± 0.78 mg/dl and 59.15 ± 26.5 ml/min in group 3, $p = 0.001$. Incidence of DGF was 38.2% (group 1), 26.6% (group 2) and 22.1% (group 3). In this cohort of patients, kidneys from donors with AKI can be used safely with reasonable early outcomes.

PV20 INCREASED EXPRESSION OF THE COINHIBITORS PD-1 AND BTLA ON CMV-SPECIFIC T-CELLS IS ASSOCIATED WITH SYMPTOMATIC CMV INFECTION IN RENAL TRANSPLANT PATIENTS

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Introduction and Background: Cytomegalovirus (CMV) infections occur frequently in renal transplant patients due to immunosuppressive therapy. It was the aim of this study to investigate if the expression of co-inhibitory molecules on CMV-specific T-cells is associated with the clinical course of renal transplant patients.
Methods: 30 renal transplant patients were recruited. Peripheral blood was sampled and stimulated with CMV lysate in presence of anti-CD28/CD49d. After 6 h of stimulation, CD154 expression was determined by flow cytometry on CD3$^+$ T-cells. The co-inhibitors PD-1 and BTLA were determined on CD154$^+$ CD3$^+$ T-cells. Symptomatic CMV infection was defined as CMV syndrome or tissue invasive disease. Asymptomatic CMV infection was defined as detectable CMV replication in peripheral blood and absence of signs indicating CMV syndrome/tissue invasive disease.
Results and Conclusions: Two renal transplant patients were at low risk for CMV infection as determined by donor /recipient CMV IgG sero-status at the time of transplantation (D-/R-). Seven patients were at high risk (D$^+$/R$^-$) and the remaining 21 patients were confined to the intermediate risk group (D$^+$/R$^+$ or D$^-$/R$^+$). PD-1 expression was significantly enhanced on CMV-specific CD3$^+$ T-cells in patients with a history of symptomatic CMV infection ($n = 6$) as compared to patients with asymptomatic CMV ($n = 14$) infection (CD3$^+$ CD154$^+$: %PD-1 + 63.8 ± 16.0% vs. 37.2 ± 19.4%, $p = 0.006$). Likewise, expression of BTLA on CMV-specific T-cells was significantly increased in patients with symptomatic vs. asymptomatic CMV infection (CD3$^+$ CD154$^+$: %BTLA$^+$ 89.3 ± 9.5% vs. 66.0 ± 22.0%, $p = 0.003$).

PD-1/BTLA was upregulated on virus-specific T-cells in patients with symptomatic CMV infection. The co-inhibitors PD-1/BTLA usually promote T-cell suppression. Therefore, increased expression of PD-1/BTLA on CMV-specific T-cells may compromise viral control and could serve as biomarker to stratify patients at risk.

PV23 MTOR-INHIBITOR EFFECT ON TUMOR OCCURRENCE, BPAR AND MORTALITY IN SOLID ORGAN TRANSPLANTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction and Background: mTOR-Is positively influence the occurrence and course of certain tumors after solid organ transplantation. The effect of mTOR-Is on the overall incidence of tumors irrespective of their origin is not entirely clear.
Methods: The current literature was searched for prospective randomized controlled trials in solid organ transplantation. There were 1356 trials screened of which 32 could be included (pts. = 12 367). Meta-analyses were performed regarding tumor incidence, BPAR and mortality.
Results and Conclusions: A significant reduction of malignancy under mTOR-Is was seen long term (RR 0.65, CI 0.48–0.87, $p = 0.004$). This effect remained stable when combined with CNIs (RR 0.70, CI 0.52–0.94, $p = 0.02$). When NMSCs were excluded the risk for malignancy remained significantly reduced under mTOR-I therapy (mono and combi) (RR 0.43, CI 0.24–0.77, $p = 0.005$). Combination of mTOR-Is and CNIs had the lowest incidence of BPARs (1 year: RR 0.75, CI 0.59–0.97, $p = 0.03$; long term: RR 0.76, CI 0.58–0.98, $p = 0.04$). Mortality was not increased under mTOR-I regimen.

Posttransplant patients have a lower incidence of malignancy when treated with an mTOR-I no matter if it is used in combination with CNIs or not. This beneficial effect remains significant even when NMSCs are excluded. The combination of mTOR-Is and CNIs renders the best protection against BPARs without increasing the risk of mortality.

PV24 DETECTION OF PATIENTS ON INCREASED RISK OF ACUTE REJECTIONS AND CMV REPLICATION BY SPECIFIC MONITORING OF NFAT-REGULATED GENE EXPRESSION

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Introduction and Background: The transcriptional activity of nuclear factor of activated T-cells (NFAT)-regulated genes in the peripheral blood has been suggested as a potentially useful immune monitoring method to individualize calcineurin inhibitor therapy. The aim of the present study was to characterize the possibility and clinical utility of monitoring of residual NFAT-regulated gene expression in renal allograft recipients in a multicentre approach.
Methods: *De novo* renal allograft recipients were recruited in this prospective non-interventional 6-month trial. Immunosuppression consisted of tacrolimus (Tac), mycophenolic acid and low-dose steroids. Residual expression (RE) of NFAT-regulated genes (IL-2, IFNy, GM-CSF) was measured by quantitative real-time PCR at C0 and C1.5 after Tac intake.
Results and Conclusions: In total, 64 patients were enrolled from three European transplant centres. Mean age was 48 ± 12 years (41 male, 30 living donation). NFAT-RE showed a high inter-individual variability. Mean NFAT-RE increased from day 14 to month 6 (15 ± 16 to 40 ± 26%). Low inhibition of NFAT-regulated genes (NFAT-RE>40%) within the first three months after transplantation was associated with an increased risk of acute rejection episodes. Patients with CMV infections ($n = 10$) showed significantly higher inhibition of NFAT-regulated genes compared to patients without CMV replication (NFAT-RE month 2: 16 ± 13 vs. 39 ± 30%, $p = 0.013$).

A high immunosuppressive load is an important risk factor to develop infections as CMV viremia after renal transplantation, whereas a low inhibition of T-cell associated genes as IL2 is a risk factor for acute rejections. Monitoring of NFAT regulated gene expression in Tac treated transplant recipients is supposed to be a supporting tool to detect patients on risk of viral replication, acute rejections and provides an individual profile of response to calcineurin inhibitors that facilitates individual dose adjustments of this drug.

PV26 PRESERVATION OF RENAL FUNCTION WITH EVEROLIMUS PLUS REDUCED TACROLIMUS AND CORTICOSTEROID WITHDRAWAL-BASED REGIMEN IN *DE NOVO* PEDIATRIC RENAL TRANSPLANT RECIPIENTS: 12-MONTHS RESULTS: THE CRADLE STUDY

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Introduction and Background: CRADLE (NCT01544491) study evaluates the efficacy and safety of everolimus with reduced tacrolimus (EVR+rTAC) and early corticosteroid (CS) withdrawal regimen in pediatric renal transplant recipients (pRTxR). Here, we present the 12-month (M) renal function outcomes.
Methods: In this 36 M, multicentre, open-label study, pRTxR (1 to <18 years) on mycophenolate mofetil (MMF)+standard-exposure TAC (sTAC)+CS were randomized (1:1) at 4–6 weeks post-Tx to either EVR+rTAC with CS withdrawal at 6 M (EVR C0:3–8 ng/ml; TAC C0: randomization [RND] to M3:4–6 ng/ml; after M4: 2–4 ng/ml) or sTAC+MMF+CS (TAC C0:RND to M3:7–10 ng/ml; from M4 to 5–8 ng/ml). Co-primary objectives were renal function (eGFR updated Schwartz formula) and composite efficacy (BPAR, graft loss or death) at M12.
Results and Conclusions: Of 106 (EVR+rTAC; $N = 52$ and MMF+sTAC; $N = 54$) randomized patients, 65.4% in EVR+rTAC arm and 87.0% in MMF+sTAC arm completed M12 on study treatment. More patients were above TAC target C0 in the EVR+rTAC than the MMF+sTAC arm (38.9 vs. 17.8%). Renal function in EVR+rTAC arm was numerically better than in MMF+sTAC arm: difference in mean eGFR: 3.8 ml/min/1.73 m^2; eGFR increased from RND in EVR+rTAC arm, whereas it decreased in MMF+sTAC arm (+3 vs. -5 ml/min/1.73 m^2). Overall safety and rates of BPAR were comparable between arms with 100% renal graft and patient survival. No new safety signals were identified. AE leading to study drug discontinuation were higher in EVR+rTAC vs. MMF+sTAC arm. Most patients (EVR+rTAC vs. MMF+sTAC 72.5 vs. 78.3%) had mildly increased urinary protein/creatinine ratio at M12, comparable between groups. Despite poor adherence to TAC C0, EVR+rTAC and CS withdrawal regimen preserved renal function while maintaining efficacy and safety up to 12 M post-TX.

PV27 DISTINCT MORPHOLOGICAL FEATURES OF ACUTE TUBULAR INJURY IN RENAL ALLOGRAFTS CORRELATE WITH CLINICAL OUTCOME

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Introduction and Background: Acute tubular injury (ATI) is common in renal allografts and is related to inferior long-term allograft function. However, it is unknown which of the morphological features of ATI can predict outcome and how they should be graded. Here, we examine features of ATI systematically in protocol biopsies and biopsies for cause to define the most predictive features for allograft outcome.
Methods: Analyses included 521 protocol biopsies taken at 6 weeks, 3 and 6 months after transplantation and 141 biopsies for cause from 204 patients. Features of ATI included brush border loss, tubular epithelial lucency, flattening, pyknosis, nuclei loss and luminal debris, each graded semi-quantitatively. Additional immunohistochemical stainings were performed for markers of cell injury (NGAL), cell death (cleaved caspase-3, FACL4) and proliferation (Ki-67).
Results and Conclusions: Inter-observer reproducibility was good for pyknosis, flattening, brush border loss, fair for lucency and poor for nuclei loss and luminal debris. In protocol biopsies between 6 weeks and 6 months, the degree of ATI remained virtually unchanged. Biopsies for cause had generally higher injury scores. Deceased donor source, delayed graft function, ganciclovir/valganciclovir treatment and urinary tract infection correlated with ATI. The degree of brush border loss, lucency, pyknosis, and FACL4 expression correlated best with impaired allograft function. Only in patients with tubular Ki-67 expression long-term allograft function improved.

Reliable assessment of ATI is possible by semi-quantitative grading of tubular epithelial cell brush border loss, lucency and pyknosis, and the novel ferroptosis marker FACL4. Examination of Ki-67 expression can help determine the potential for recovery from this damage.

PV28 ONE-YEAR RESULTS OF THE EUROPEAN ROBOTIC KIDNEY TRANSPLANTATION PROGRAMME

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Introduction and Background: In order to reduce the morbidity of the open surgery, a robotic assisted approach has been recently introduced. We present the one-year results from the ERUS Robotic Kidney Transplantation Group common prospective recruitment database of Robotic assisted kidney transplants (RAKT) on 69 cases.
Methods: A common prospective recruitment database of RAKT performed at 8 different European Centers was therefore created in July 2015. Functional and surgical data were analyzed and herein reported.
Results and Conclusions: Patients demographics: 29 adult females and 40 males, mean age 42 years (range: 25–64), mean BMI 26 kg/m^2 (range: 22–33), and mean pre-transplant GFR: 10.4 ml/min per 1.73 m^2 (range: 3–29). There were no vascular and ureteral anomalies in the cases included. The mean ASA score were 2. Overall surgical time was 324 min (range: 220–430) with vascular suture time of 42 min (range: 32–48), and estimated blood loss < 80 ml. Overall ischemia time (including warm ischemia, cold ischemia and rewarming time) was 98.9 min (range: 84–140). The average rewarming time was 55 min (range 51–58). Two patients were converted to open transplantation. There were two cases (3%) of transplantectomy for a massive arterial thrombosis on POD 2. One case of intraperitoneal hematoma occurred on POD 1, and was successfully managed laparoscopically. The mean post-operative serum creatinine level was 204 μmol/l (range: 81–479) on post-operative day (POD) 7. The mean hospital stay was 6 ± 1 days (range 4–8 days). The mean time of ureteral catheter was 15 days (range: 14–16) after the surgery. There were five cases (7%) of delayed graft function although at 1 month follow up. Furthermore, no arterial nor ureteral strictures occurred.

RAKT with regional hypothermia appears to be a safe and reproducible surgical procedure in a properly selected group of patient. One mayor potential advantage of RAKT is related to the quality of the vascular anastomosis, and lower surgical trauma.

PV31 NORMOTHERMIC DONOR LUNG PRESERVATION WITH PORTABLE EVLP SIGNIFICANTLY REDUCES ISCHEMIA/REPERFUSION INJURY IN LUNG RECIPIENTS BY PROMOTING CYTOKINE ANTAGONISTS

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Introduction and Background: The INSPIRE trial revealed significant reduction of PGD grade 3 using the Organ Care System (OCS) compared to the standard of care (SOC) lung preservation. To investigate immunological mechanisms initiated by cold vs. normothermic preservation, blood and perfusate samples were assessed for immune response proteins. We hypothesized that OCS preservation supports tissue integrity and anti-inflammatory milieu.
Methods: Blood plasma and perfusion solutions from 33 patients with OCS and 26 patients with SOC-preserved lungs were analysed for 95 plasma proteins by multiplex assays. Donor, recipient demographics, cold ischemic times (CIT), PGD scores at T0 were assessed and correlated with cytokines.
Results and Conclusions: Clinical evaluation (OCS/SOC) revealed mean recipient age of 50/49y, diagnoses: idiopathic fibrosis ($n = 17/10$), cystic fibrosis ($n = 7/8$), idiopathic pulmonary hypertension ($n = 3/3$), emphysema

(n = 6/5), mean total cold ischemic times (258 vs. 549 min $p < 0.0001$). In the OCS group, no cumulative PGD score >2 was seen compared to 19% PGD3 in SOC ($p = 0.035$). IL-6, CXCL8-10, sICAM-1 plasma levels at T0 were significantly reduced in OCS patients (all $p < 0.01$). IL-6 plasma levels at T0 in SOC recipients showed the strongest correlation to CIT ($p = 0.031$), PaO2/FiO2 ratio ($p = 0.092$) and PGD at T0 ($p < 0.05$). Significantly higher levels were observed in OCS vs. SOC perfusates (all $p < 0.001$). We propose a new mechanism of modulating IRI by induction of cytokine antagonists like IL-1RA and IL-31 that correlated with IFN-g ($p = 0.001$) in OCS perfusates.

Recipients of OCS-preserved lungs show significantly reduced IRI by reduced levels of pro-inflammatory factors. The strong correlation of IL-6 with PGD score, PF and CIT in SOC but not OCS patients argues for an impact of inflammation on early graft function. As potential mechanism, we propose the induction of cytokine antagonists. Thus, portable EVLP may have the potential to ameliorate IRI and improve clinical outcome.

PV32 THE PERSISTENCE OF DONOR SPECIFIC HLA-ANTIBODIES HAS A DETRIMENTAL IMPACT ON PATIENTS' SURVIVAL AFTER LUNG TRANSPLANTATION

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Introduction and Background: The impact of *de novo* donor-specific (DSA) anti-HLA antibodies diagnosed by solid-phase assays on outcome in lung transplant recipients is still a matter of debate. We hypothesize that differentiating DSA by persistent and transient appearance may offer an additional risk assessment.
Methods: The clinical relevance of HLA-antibodies was investigated prospectively in 169 recipients who were transplanted between 2013 and 2017. The presence of HLA-antibodies was analyzed by Single Antigen Bead assay regular prior and after (3 weeks, 3, 6, 12, 18, 24, 30, 36 months) transplantation. Patient survival and risk factors for the development of DSA were assessed within a mean follow-up of 20 months.
Results and Conclusions: In 61 patients (36.1%) *de novo* DSA were detected at least once. In 30 out of 61 patients (49.2%) DSA disappeared and were classified as transient if they did not turn up again. In 31 patients (50.8%) DSA still remained over more than two time points. There was a trend for lower one-year-survival (88.1% vs. 92.2%; $p = 0.724$) and two-year-survival (83.7% vs. 93.6%; $p = 0.302$) in patients with DSA compared to patients without DSA. Remarkably, patients with persistent DSA had significantly reduced one-year-survival (76.7% vs. 100%; $p = 0.035$) and two-years-survival (64.0% vs. 100%; $p = 0.028$) compared with those with transient DSA.

Consistently detectable *de novo* DSA are associated with an increased risk for adverse survival. Dynamic monitoring of DSA could predict the risk of lung allograph dysfunction and might play a role for therapeutic strategies.

PV34 INCREASED PHOSPHORYLATION OF P70S6 KINASE IS ASSOCIATED WITH CMV REACTIVATION IN LUNG TRANSPLANT PATIENTS

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Introduction and Background: Lung transplant (LuTX) patients typically receive a triple immunosuppression consisting of a calcineurin inhibitor, a proliferation inhibitor and steroids. Patients at risk for cytomegalovirus (CMV) reactivation are usually being treated with antiviral agents in a prophylactic manner or monitored regularly to recognize and treat reactivation. CMV reactivation occurs despite these two strategies. CMV replication is dependent on the activity of the mammalian target of rapamycin (mTOR) pathway. It was studied whether mTOR activity (indicated by phosphorylation status of p70s6 in T-cells) is associated with CMV reactivation in patients.
Methods: 18 female LuTX patients and 18 male LuTX patients were recruited. 21 patients were at intermediate risk for CMV infection (CMV IgG serostatus donor (D)−/recipient (R)+ or D+/R+), 6 patients had low risk (D−/R−) and 9 patients had a high risk for CMV infection (D+/R−). The age of the patients ranged from 22 to 71 years. Peripheral blood was collected and phosphorylation of p70S6 kinase in T-cells was determined by flow cytometry.
Results and Conclusions: 12 patients had at least one episode of CMV reactivation in the past. Seven of these patients belonged to the high risk group and the remaining five patients belonged to the intermediate risk group. Comparing high risk patients with history of CMV reactivation vs. without reactivation revealed no difference regarding p70s6 kinase phosphorylation. However, intermediate risk patients with CMV reactivation had significantly increased p70s6 phosphorylation in T-cells as compared to intermediate risk patients without CMV reactivation (p70s6 kinase phosphorylation in $CD4^+$ T-cells given as MFI: 196.5 ± 69.3 vs. 91.5 ± 54.5, $p = 0.006$). There was no difference in phosphorylation status of p70s6 kinase comparing patients with vs. without mTOR inhibitor.

Phosphorylation of p70s6 may serve as biomarker to stratify patients at risk for CMV reactivation.

PV35 NORMOTHERMIC *EX VIVO* LUNG PERFUSION – PRELIMINARY RESULTS

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Introduction and Background: Recently the number of lung transplantations in Germany dropped dramatically. In this situation it is of utmost importance to use every potential transplantable organ. Normothermic *ex vivo* lung perfusion (EVLP) offers the possibility to reevaluate donor lungs that previously were deemed untransplantable.
Methods: Since April 2016 we performed 40 lung transplants. In this period 10 lungs with no standard criteria were evaluated by use of EVLP, their results were compared with recipients after standard LuTx (controls). According to the Toronto protocol the lungs were reconditioned for 4 h. Lungs after EVLP were accepted for transplantation if they then met a pO2/ FiO2 more than 350 mmHg.
Results and Conclusions: 8 out of 10 donor lungs were successfully transplanted after EVLP. Recipient age in EVLP group was 55 ± 7 years vs. 51 ± 11 years in controls, donor age EVLP 57 ± 10 years and controls 54 ± 14 years (n.s.). Best pO2 on FiO2 1.0 /PEEP 5: EVLP 332 ± 77 mmHg vs. controls 463 ± 108 mmHg ($p < 0.05$). Donor ventilation time EVLP: 146 ± 100, controls: 155 ± 89 h (n.s.) Lungs were transplanted with a mean out of body time after implantation of the second lung of 716 ± 152 min EVLP group and 374 ± 103 min controls ($p < 0.05$). Postoperative ventilation time was 284 ± 353 h for EVLP and 218 ± 362 h for controls (n.s.). Length of intensive care stay was 291 ± 330 h for EVLP and 259 ± 368 for controls. In hospital stay was 33 ± 20 days for EVLP and 21 ± 10 days for controls (n.s.). 30 day mortality was 12% for EVLP vs. none for controls.

Normothermic EVLP procedure can safely be used in the evaluation of lungs initially considered unacceptable. This initial experience from a single centre shows that primary outcome was unaffected. 8 out of 10 lungs initially not suitable for transplantation were successfully processed and later transplanted, and total ischemic time was safely prolonged. Use of EVLP potentially results in a reduction of waiting list mortality.

PV36 "OLD-FOR-OLD" IN LUNG TRANSPLANTATION – IS IT POSSIBLE? A COMPARATIVE STUDY USING THE INTERNATIONAL SOCIETY OF HEART AND LUNG TRANSPLANTATION DATABASE

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Introduction and Background: The number of lung transplants is limited by the scarcity of suitable donor organs. Currently, the use of lungs from donors <55 years are recommended, which markedly limits the available donor pool. In this study, we assessed how outcomes in recipients from older donors differ from those of donors <55 years and to evaluate the interaction with older recipients.
Methods: The Registry of the International Society for Heart and Lung Transplantation (ISHLT) was queried. All adult primary lung transplants performed between 1988 and 2012 were included. All donors and recipients were divided into three groups based on age <55, 55–64, and >64 years. Kaplan-Meier analysis was used for survival post-transplant and adjustment for covariates was performed using Cox proportional regression analysis.
Results and Conclusions: 43 155 adult primary lung transplants were analysed. In this cohort, 37 887 donors were <55 years, 4499 were 55–64 years, and 769 donors were >64 years old. 2497 transplants (15.5%) in recipients aged 55–64 years derived from donors >55 years with significantly older donors and recipients in Europe ($p < 0.001$). 5-year survival in recipients aged 55–64 years was comparable for donors <55 years and 55–64 years and lower for those from >64 years ($p = 0.0166$). In recipients >64 years no significant difference in 5-year survival was observed for all donor age groups ($p = 0.6166$). In donors <55 years and 55–64 years significantly better survival for double compared to single lung transplants was observed ($p < 0.001$). No difference was seen in donors >64 years ($p = 0.1321$).

Recipients of 55–64 years showed comparable survival after lung transplantation from donors <55 years and 55–64 years. Survival in recipients and donors >65 years was comparable. Therefore, the introduction of an "old-for-old" program for recipients >55 years from donors outside the standard age criteria seems feasible.

PV37 VASOACTIVE-INOTROPIC SCORE AS PREDICTOR OF OUTCOME AFTER HIGH-URGENT LISTING FOR CARDIAC TRANSPLANTATION

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Introduction and Background: Vasoactive-inotropic score (VIS) is used as surrogate marker to predict early postoperative outcome in paediatric cardiac surgery. Its use in ESHF patients on the waiting list is unknown. The objective of this study was to assess the association between VIS and clinical outcomes of high urgent (HU) listed patients for heart transplantation (HTx).
Methods: 447 HU patients between 12/2005 and 05/2016 were analysed. The VIS was evaluated for predicting adverse events during the waiting time (death, urgent VAD implant, delisting due to bad condition) of these patients. Baseline characteristics, 5-year survival and 1-year post-HTx survival were compared.
Results and Conclusions: Of the 447 pts, 120 suffered from adverse events (FAIL group) whereas 320 (HTx group) underwent HTx after HU listing. 7 pts did not undergo HTx or suffered from adverse events and where therefore not included in the analysis.6 pts were censored at the time of delisting because of good condition. Adverse events occurred because of death in 14 pts (FAIL death group), VAD-implant ($n = 90$) and bad condition ($n = 10$). During follow up, of those, 46 underwent secondary HTx thereafter (FAIL secondary HTx group), and the remaining 68 pts did not undergo HTx (FAIL destination group). An increasing VIS score was associated with a significantly increased risk for adverse events (OR 1.16, 95% CI 1.09–1.23, $p < 0.001$). Estimated 5-year survival was similar in the HTx and FAIL secondary HTx groups ($p = 0.56$), while survival was impaired in the FAIL destination and FAIL death groups. The 1-year post-HTx survival was similar between HTX group and FAIL secondary HTx group ($p = 0.78$).

Elevated VIS at time of HU listing is associated with increased incidence of adverse events during waiting time. Adverse events did not affect 1-year post-HTx survival. The usefulness of VIS as a predictor of clinical outcome in HU pts may have important implications for optimized selection and decision for early VAD-implant or HU listing.

PV39 EXPERIENCE WITH MULTIPLE ORGAN HEART TRANSPLANTATION

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Introduction and Background: Multi organ transplantation in combination with the heart represents a therapeutic option in selected patients with additional organ failures. Some studies provide evidence for a protective immunological effect in long-term follow-up after simultaneous combined organ transplantation from the same donor. Aim of this study was to review our outcomes in patients undergoing heart (HTX) or multi organ transplantation (MOTX) including the heart.
Methods: We assessed outcome of all patients who received either isolated heart transplantations (HTX, $n = 133$) or heart transplantations plus other organs (MOTX, $n = 21$) between 1999 and 2015. MOTX included 11 heart-lung, 4 heart-liver, 1 heart-lung-liver and 5 heart-kidney transplantations.
Results and Conclusions: MOTX patients showed significantly higher risk profile due to their multi-organ failure, critical status (High Urgent: HTX: 67.7%; MOTX 95.2%, $p < 0.05$) and complexity of the procedure with an extended ischemic time (222 ± 44 vs. 256 ± 52 min, $p < 0.05$). Kaplan Meier shows estimations of both groups. While perioperative survival was worse in MOTX, survival at 6 years was identical. Rejection rates (HTX: 34.6% vs. MOTX 28.6%; $p = 0.59$), antibody mediated rejections (HTX: 15.0%; MOTX 19.0%; $p = 0.64$) and development of antibodies (HTX: 21.1%; MOTX 28.6%; $p = 0.44$) was similar in the two groups. However, MOTX was associated with significantly less malignancies (12.0% vs. 0%; $p = 0.09$) and cardiac allograft vasculopathy (CAV: 53.4% vs. 23.8%; $p < 0.05$).

Combined heart transplantation represents a valid therapeutic option in selected patients with additional organ failures despite elevated perioperative risk. Similar long-term survival in MOTX compared to HTX may be related to lower rates of cardiac allograft vasculopathy and malignancies. There was no visible effect of MOTX on the rate of acute rejections.

PV40 CD40MAB OR CD40L COSTIMULATION BLOCKADE AND XENOGRAFT PRESERVATION USING "STEENS" CARDIOPLEGIA IN ORTHOTOPIC CARDIAC XENOTRANSPLANTATION OF TG PIG HEARTS IN A PIG-TO-BABOON MODEL (40 DAYS SURVIVAL)

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Introduction and Background: We introduced a non-toxic immunosuppression (IS) based on CD40/CD40L co-stimulation blockade in group G1 and to improve primary xenograft function in a group G2 we added a new non-ischemic myocardial preservation technique in a life-supporting cardiac xenotransplantation model (pig-to-baboon).
Methods: Nine orthotopic (OHXTx) heart transplantations were performed in baboons with genetically-modified GalKO/hCD46/hTM transgenic pig hearts. The IS consisted of ATG, rituximab, MMF, cortisone and CD40 antibody or PASylated Fab-CD40L. "Perioperative cardiac xenograft dysfunction" (PCXD) often caused by cardioplegia with crystalloid solution (Bretschneider solution (BS), 50 ml/kg; G1: $n = 5$) was replaced in G2 ($n = 4$) by Steen´s "non-ischemic preservation technique" with a 8°C cold myocardial perfusion solution (modified Krebs-Henseleit solution with albumin, 10% erythrocytes, hormones and vasoactive agents (Steen et al, 2016). Hereby hearts were constantly perfused during explantation and storage time, intermittently during implantation, using an independent portable heart-lung-machine.
Results and Conclusions: The ischemic time ranged from 112–128 min. Survival in G1 with BS was 3, 1, 30, 1 and 1 day(s) with PCXD in 3 cases. In G2 no PCXD was observed and the recipients survived 18, 1**, 27 and 40 days. Cause of death were mostly respiratory problems, renal and hepatic failure, one with neurological deficit** and one with V. cava thrombosis, but no hyperacute or delayed xenograft rejection occurred. Baboons in G2 were in good general conditions, but after 3 weeks a donor organ (over)growth was found.

With conventional crystalloid cardioplegia perioperative cardiac xenograft dysfunction plays a detrimental role after orthotopic xHTx. This could now be prevented with the Steen's "non-ischemic preservation technique. This is an important step on the way to a long-term survival of 2 -3 months, which is necessary for clinical cardiac xenotransplantation.

PV41 ALLOANTIBODIES IN A MIXED CELLULAR AND ANTIBODY MEDIATED REJECTION MODEL IN MICE

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Introduction and Background: In the clinical setting mixed T-cell and antibody mediated rejection (TCMR, ABMR) are relevant since they are difficult to treat. To study T- and B-cell interactions we studied a translational mouse model of allogenic kidney transplant (ktx) rejection and characterized lymphocyte kinetics in correlation to MHC alloantibody production.
Methods: For allogenic ktx Balb/C (H-2d) donor kidneys were transplanted into a completely mismatched C57Bl/6 (B6) (H-2b) male recipients and control isogenic ktx was performed with B6 donors and recipients. Ischemia times were standardized to 45 min cold and 30 min warm. Blood was drawn weekly and flow-cross match was performed with Balb/C splenocytes. At the designated endpoints at 2, 3 and 6 weeks after ktx work up of the renal tissue was done. Flow cytometry at 3 and 10 days as well as after 6 weeks was performed to

characterize infiltrating leukocyte subsets of the graft, the blood, the spleen and the regional lymph nodes.
Results and Conclusions: MHC-alloantibodies were detected as early as 7 days after allogenic ktx. Elevated plasma cell levels were detected in the graft, the regional lymph nodes and spleen after allogenic ktx. Furthermore, T-killer cells showed higher expression in the allograft but not in regional lymph nodes, spleen or circulating blood compared to isogenic ktx. Histology revealed signs of acute rejection with severe inflammation and CD3 positive cellular infiltrates. Furthermore, endothelial neutrophil infiltration was detected mainly in medium-sized vessels.

Cross-match in mice is a novel tool to characterize alloantibody response in mouse models for antibody-mediated rejection and correlates with enhanced plasma cell levels in the allograft, the regional lymph nodes and the spleen after ktx.

PV42 HUMAN PODOCYTES EXPRESS THE NEGATIVE COSTIMULATOR PDL-1 AND SUPPRESS T-CELL PROLIFERATION

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Introduction and Background: Podocytes are parenchymal renal cells that are part of the renal filtration barrier. On tissue level, parenchymal cells have mechanisms conferring protection against immunological damage during inflammation. Negative costimulation is one mechanism by which parenchymal cells escape local immune responses and thus avoid damage due to inflammation. It was the aim of this study to investigate if podocytes express negative costimulators and are able to suppress T-cell responses.
Methods: An immortalized human podocyte cell line was used. Human T-cells were isolated by negative magnetic sorting and labelled with CFSE to track proliferation. PDL-1 expression on podocytes was determined by flow cytometry and PCR. For coculture experiments, human T-cells were stimulated with anti-CD3/anti-CD28 in presence of human podocytes. PDL-1/PD-1 interaction was blocked by an anti-human PD-1 antibody.
Results and Conclusions: Podocytes constitutively expressed the negative costimulator PDL-1. Treatment with TNFa or IFNg enhanced PDL-1 expression on podocytes (given as mean fluorescence intensity (MFI) of PDL-1 expression; baseline: 145 $\pm$ 29 AU; TNFa: 155 $\pm$ 38 AU; IFNg: 191 $\pm$ 48 AU). Blocking PDL-1/PD-1 interaction resulted in significantly enhanced T-cell proliferation (calculated mean percentage of suppression: 20 $\pm$ 8%). The proliferated T-cell fraction (PF) was significantly different comparing conditions without blocking antibody vs. with blocking antibody (given as PF: 45 $\pm$ 10% vs. 57 $\pm$ 12%, $p < 0.05$).

A pro-inflammatory cytokine environment enhances PDL-1 expression on podocytes. PDL-1 expression is functional and confers immuno-regulatory capacity to podocytes.

PV43 VIREMIA CLEARANCE RATE CORRELATES WITH EXHAUSTION STATE BUT NOT RECEPTOR REPERTOIRE SHAPE OF BKV-SPECIFIC T-CELLS IN RENAL TRANSPLANT PATIENTS WITH SEVERE BKV INFECTION

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Introduction and Background: Reactivation of the BK polyomavirus is known to lead to severe complications in kidney transplant patients. The current treatment strategy relies on decreasing the immunosuppression to allow the immune system to clear the virus. Recently we demonstrated a clear association between the resolution of BKV reactivation and reconstitution of BKV-specific $CD4^+$ T-cells. However, the factors determining the duration of the clearance of the viral infection remain unknown.
Methods: We applied a combination of in-depth multiparametric flow cytometry and CDR3 beta chain receptor repertoire analysis of BKV specific T-cells to a cohort of 5 kidney transplant patients with BKV reactivation. In this manner, we were able to track the TCR repertoires at single clone levels during the clinical course of BKV infection.
Results and Conclusions: Neither the number of BKV-specific T-cells in peripheral blood nor the diversity of the T-cell receptor affected the duration of BKV infection. In contrast, the exhaustion status of BKV-specific T-cells correlated with the duration of viral clearance, such that the lack of PD1 and TIM-3 on BKV-specific T-cells is associated with short remission time. This duration was further found to be independent of hyperexpanded, immunodominant BKV-specific T-cell clones and of the overall magnitude of cellular immunity.

Our data demonstrate that the quality rather than quantity of BKV-specific T-cells determines the remission time after BKV reactivation.

PV44 FARNESYLTRANSFERASE-INHIBITORS EXERT IMMUNOSUPPRESSIVE CAPACITY BY INHIBITING PROLIFERATION OF HUMAN B-CELLS AND PRESERVING THE FUNCTION OF REGULATORY B-CELLS

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Introduction and Background: Prenylation of proteins is an important post-translational modification step. Farnesyltransferase inhibitors (FTI) have been shown to inhibit prenylation of proteins thereby interfering with cell growth and signaling. The potency of two different farnesyltransferase-inhibitors as immunosuppressive agents was investigated in this study. For this purpose, the effect of Tipifarnib and Lonafarnib on activated B-cells was studied.
Methods: Human B-cells were magnetically isolated from healthy controls. Isolated B-cells were labelled with CFSE to track proliferation and stimulated for 72 h with CpG in presence of IL-2. B-cells were cultured in presence of tipifarnib (Tipi), lonafarnib (Lona) or rapamycin (Rapa). The baseline values were determined on B-cells stimulated with CpG+IL-2 in absence of Tipi, Lona and Rapa. Proliferation, IL-10 and Granzyme B (GrB) production was assessed by flow cytometry.
Results and Conclusions: After 72 h of culture, the average proliferated fraction (PF) of B-cells was 55 $\pm$ 10% in the baseline condition. In presence of Tipi, the PF decreased significantly to 17 $\pm$ 6% (vs. baseline, $p < 0.0005$). Similarly, Lonafarnib decreased the PF to 25 $\pm$ 8% (vs. baseline, $p < 0.05$). Rapa showed the most potent capacity to suppress proliferation (vs. baseline, PF: 4 $\pm$ 4%, $p < 0.0005$). GrB production by B-cells was reduced by Rapa and by Lona and Tipi (% of GrB producing B-cells; baseline: 7.4 $\pm$ 5.5%; Rapa: 1.1 $\pm$ 0.7%; Lona: 3.7 $\pm$ 3.4%; Tipi: 2.9 $\pm$ 1.9%). In contrast, IL-10 production was not affected by Lona and Tipi (% of IL-10 producing B-cells; baseline: 6.7 $\pm$ 1.8%; Lona: 7.3 $\pm$ 1.1%; Tipi: 6.3 $\pm$ 0.8%) whereas Rapa treatment significantly reduced IL-10 production by B-cells (Rapa: 2.1 $\pm$ 0.4%, $p < 0.05$).

FTI suppress B-cell proliferation while preserving IL-10 production of regulatory B-cells. Thus, FTI have immunosuppressive capacity and may complement future therapeutic strategies in organ transplantation.

PV45 ASSESSMENT OF ISCHEMIA-REPERFUSION INJURY IN AN EXPERIMENTAL HUMAN PERFUSION MODEL AFTER TREATMENT WITH RATG

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Introduction and Background: The failure of translating results obtained in animal models into humans is a pivotal problem of research in transplantation. The aim of our study was to test the human placenta as an ischemia-reperfusion human model. Secondly, our aim was to study the modulation of leukocyte-endothelial reactions through immunosuppression with rabbit ATGs after ischemia-reperfusion by means of intravital microscopy.
Methods: Human placentas ($n = 12$) from elective caesarean deliveries were used after informed consent and IRB approval. All placentas were immediately connected to a monitored double perfusion system consisting of a two roller-pumps, reservoir, oxygenator, hemo-filter and bubble-trap. The placentas were reperfused with compatible human blood for 240 min after 60 min ischemia and treatment with ATG (1 mg/kg; Thymoglobulin, Sanofi, USA). Pressure, flow, and AVDO2 were investigated. Tissue expression of inflammation (IL-6, TNF-α) and adhesion-molecules (ICAM-1, PECAM, CD62E) was investigated by immunohistochemistry. Intravital Microscopy was performed to analyze adherence and infiltration of leukocytes.
Results and Conclusions: Our human placenta model could be validated for the study of inflammatory and vascular-endothelial reactions. The hemodynamic measurements were reproducible and the AVDO2 showed a continuous vitality of the perfused tissues. The blood cells counts were stable thorough the reperfusion. Morphological and immunohistochemical analyses confirmed a normal configuration of placental tissue and its endothelium after 4 h of reperfusion. Intravital microscopy was feasible and allowed quantification of adherent leukocytes, showing a reduction of the leukocyte adherence after Thymoglobulin treatment.

The isolated human placenta allows the study of functional human endothelium in a vascular structure. Our results confirm in a human model

the improvement of the microcirculation after induction of immunosuppression with rATG.

PV48 FATIGUE AND ITS IMPACT ON QUALITY OF LIFE IN PEDIATRIC LIVER TRANSPLANT RECIPIENTS

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Introduction and Background: Fatigue is one of the most prevalent symptoms in children with chronic conditions. Previous research has established that fatigue is associated with impaired health-related quality of life (HRQOL). Therefore, the aim of our study was to investigate the occurrence of fatigue in pediatric liver transplant (PLT) recipients and the impact on their HRQOL.
Methods: The Pediatric Quality of Life Multidimensional Fatigue Scale (MFS) was administered to 100 families of PLT recipients ages 2–18 years (71 child self-reports; 100 parent proxy-report) during their annual medical check-up. Participants also completed the PedsQL Generic Core Scales (PedsQL). The MFS encompasses 3 subscales: 1) General fatigue, 2) Sleep/rest fatigue, 3) Cognitive fatigue, and a Total fatigue score.
Results and Conclusions: Mean age of participants was 12.0 ± 4.5 years, and age at PLT was 2.5 ± 3.2 years. 53% were boys. Participants and their parents reported significantly more fatigue across all domains compared to healthy peers of a large MFS validation study. To examine the contribution of different domains of fatigue to child's HRQOL multiple regression analyses were conducted. For both child self-report and parent proxy-report, only two domains of fatigue, General and Cognitive fatigue, were significant predictors for child's HRQOL. There was no significant contribution of Sleep/rest fatigue. The regression models explained 66% of the variance of child self reported HRQOL ($R^2_{adjusted}$=0.659, $p < 0.001$), and 60% for parent proxy-report ($R^2_{adjusted}$=0.601, $p < 0.001$).

To our knowledge, this is the first study that exclusively investigates fatigue in PLT recipients. Present findings demonstrate significantly more fatigue among participants compared to healthy peers. Considering the high impact on HRQOL further research is urgently needed to better understand the underlying mechanisms of fatigue and to develop appropriate interventions to improve impaired HRQOL in PLT recipients due to fatigue.

PV51 EVEROLIMUS WITH REDUCED TACROLIMUS MAINTAINS EFFICACY FOLLOWING LIVING-DONOR LIVER TRANSPLANTATION (LDLT): 12-MONTH RESULTS FROM AN INTERNATIONAL RANDOMIZED TRIAL (NCT01888432)

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Introduction and Background: Everolimus (EVR) with reduced-exposure tacrolimus (rTAC) after deceased-donor liver transplantation has been shown to be effective but trials in LDLT are lacking.
Methods: In an international, open-label, phase III trial (H2307), adult primary LDLT patients were randomized at day 30 post-Tx to continue standard tacrolimus (TAC-Control) or to EVR+rTAC, both ± corticosteroids. Here, we present efficacy data from the study.
Results and Conclusions: 284 patients were randomized (mean 54 years, 72% male, 79% Asian, mean [SD] MELD score 14 [5.5]; 42% hepatocellular carcinoma [HCC], 30% positive for hepatitis B virus). Mean TAC trough concentration at month 12 was 36% lower with EVR+rTAC than TAC-Control. The primary endpoint, a composite of graft loss (GL), death or treated biopsy-proven acute rejection (tBPAR) at month 12 post-Tx, was similar with EVR+rTAC or TAC-Control (n [Kaplan-Meier%]): primary endpoint 7 (5.1%) vs. 8 (5.8%). No GL occurred and patient survival was comparable in both groups. Although tBPAR rates were similar in EVR+rTAC [3 (2.2%)] and TAC-Control [5 (3.6%)], moderate or severe episodes occurred only with TAC-Control. Mean estimated GFR (eGFR, MDRD-4) was numerically higher with EVR+rTAC up to Month 12. HCC recurrence was seen only in 5 patients in TAC-Control group. Study drug withdrawal due to adverse events (AEs) was similar in both groups. Withdrawal was similar with EVR+rTAC or TAC-Control: 18 (12.7%) vs. 15 (10.6%).

Early initiation of EVR+rTAC after LDLT demonstrated comparable efficacy and numerically better renal function at M12 compared to TAC-Control. HCC recurrence was not observed in the EVR+rTAC cohort but affected only TAC-Control patients, a finding that merits further investigation.

PV52 EFFECT OF EVEROLIMUS WITH REDUCED TACROLIMUS ON RENAL FUNCTION (RF) AFTER LIVING-DONOR LIVER TRANSPLANTATION (LDLT): 12-MONTH RESULTS FROM AN INTERNATIONAL RANDOMIZED TRIAL (NCT01888432)

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Introduction and Background: Everolimus with reduced tacrolimus (EVR+r-TAC) has been shown to offer a renal advantage vs. standard TAC (TAC-Control) in deceased-donor LTx but data are lacking after LDLT.
Methods: In a multicenter, 24 M, open-label phase III study (H2307), patients were randomized at day 30 post-LDLT to start EVR+rTAC or continue standard TAC, both ± steroids. Here, we present the RF results from the study.
Results and Conclusions: 284 patients were randomized (142 EVR+rTAC, 142 TAC-Control; mean [SD] MELD score 14 [5.5]). Mean TAC trough concentration in the EVR+rTAC group exceeded target range until month 6 and remained close to the upper threshold thereafter. Efficacy at month 12 was similar with EVR+rTAC or TAC-Control. Mean estimated GFR (eGFR, MDRD-4) at randomization was 90 ml/min/1.73 m^2 in both groups. Observed mean eGFR was numerically higher with EVR+rTAC to month 12. The EVR+rTAC group was non-inferior to TAC-Control for the key endpoint of change in eGFR from randomization to month 12 post-Tx: mean (SE) −8.0 (1.8) vs. −12.1 (1.8) ml/min/1.73 m^2; mean difference 4.2 ml/min/1.73 m^2; $p < 0.001$ for non-inferiority. Among patients who remained on study drug (120 EVR+rTAC, 116 TAC-Control), change in eGFR was in favor of EVR+rTAC: mean (SE) −8.0 (1.9) vs. −13.3 (1.9) ml/min/1.73 m^2 with TAC-Control, a mean difference of 5.3 ml/min/1.73 m^2 ($p = 0.046$). At month 12, urine protein:creatinine ratio was ≥3000 mg/g in 1.6% and 0% of EVR+rTAC and TAC-Control patients, respectively; no patient required renal replacement therapy.

Mean eGFR was numerically higher to month 12 after starting EVR+rTAC vs. TAC-Control. These data show that in LDLT, even in the setting of excellent renal function, EVR with low-exposure tacrolimus offers a renal advantage.

PV53 URINARY PROTEINS IN LONG-TERM FOLLOW UP AFTER LIVING DONATION

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Introduction and Background: In a previous study, it was found that about 2/3 of the living donors showed abnormal urinary protein findings one year after donor nephrectomy. We wanted to know if and how they change in a long-term follow up.
Methods: Within the ambulant follow-up the glomerular (immunoglobulin G, albumin and transferrin) and the tubular (a1-microglobulin, retinol-binding protein, ß2-microglobulin) urinary proteins, the urinary enzyme N-acetyl-β-glucosaminidase and the total protein of 63 living donors were determined. A comparison with the results one year after living donation was made to check to what extent the number and patterns of urinary proteins changed in the long-term follow-up. Therefore, the urine results of the patients were divided into 4 groups depending on the time after donor nephrectomy: <1 year (group 1), 1 to 5 years (group 2), 5 to 10 years (group 3) and >10 years (group 4) after living donation.
Results and Conclusions: While one year after donor nephrectomy 2/3 ($n = 27/40$) of the patients still show an abnormal protein pattern, there are only 50% ($n = 15/30$) in group 2, 45% ($n = 10/22$) in group 3 and 40% (4/10) in group 4. One year after living donation, the tubular urinary protein patterns (38%, $n = 15/40$) have been dominated. In the following years, the glomerular urinary proteins were more often detected, about 20% in groups 2 to 4. After more than 10 years, we found no pure tubular urinary protein pattern anymore.

On the one hand, our results show that there is an improvement of the condition of the donor's solitary kidney in the long-term course, which speaks for living donation as a type of treatment of renal insufficiency. On the other hand, the determination of urinary proteins could provide an early indication of a possible kidney damage, thus enabling an early therapeutic intervention. A claim to the universal validity of these results cannot be obtained because of the low number of cases.

PV54 RETROPERITONEOSCOPIC DONOR NEPHRECTOMY REDUCES OPERATION TIME, HOSPITAL STAY, AND SURGICAL COMPLICATIONS COMPARED TO A MINI OPEN PROCEDURE

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Introduction and Background: A major goal in living kidney transplantation is to reduce the burden of the living donor (LD). It has been shown that laparoscopic and retroperitoneoscopic techniques are safe for the LD and the recipient, but comprehensive data regarding the latter procedure are still rare.
Methods: We analysed the impact of the switch from a mini open nephrectomy (MON) to a retroperitoneoscopic donor nephrectomy (RPDN) in our centre. We compared the last 50 MON to the first 100 RPDN regarding operation time, complications, length of hospital stay, and patients" own rating of the surgical burden. All LD between 2009 and 2015 were included. The patients" rating of the surgical strain was assessed 3 months after nephrectomy in both groups.
Results and Conclusions: LD demographics were not different between the groups (mean age 52 y in MON and 54 y in RPDN; mean BMI 25 in MON and 26 in RPDN). The mean operation time was shorter in RPDN (118 min vs. 175 min, $p < 0.001$). Patients were discharged from hospital earlier (5.0 d vs. 6.3 d, $p < 0.001$). 17 surgical complications occurred in the MON group (34%). Most complications were mild (Clavien grade I or II, e.g. postoperative pain, UTI). In two donors, severe complications occurred: lung embolism and bowel injury (grade IV) and a granuloma on the vocal cord needing operative resection (grade IIIb). In the RPDN group, 15 complications occurred (15%). They were mild in 14 patients. In one patient, open conversion was needed due to bleeding (no transfusion, grade IIIb). There were significantly less complications in the RPDN group ($p = 0.01$). Three months after nephrectomy, RPDN patients reported less physical strain ($p = 0.008$), less post-operative pain ($p < 0.001$), and felt less bothered by the surgical scar ($p = 0.02$).

In summary, RPDN can be performed safely with short operation time. Patients profit from earlier discharge and fewer complications, and they report less surgical strain. We recommend switching to RPDN to reduce the physical burden of the LD.

PV55 EFFICACY AND SAFETY OF EVEROLIMUS WITH REDUCED TACROLIMUS IN LIVING-DONOR LIVER TRANSPLANT RECIPIENTS WITH HEPATOCELLULAR CARCINOMA: SUBGROUP ANALYSIS FROM THE H2307-STUDY (NCT01888432)

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Introduction and Background: The use of the mammalian target of rapamycin inhibitor (mTORi) has been reported to reduce hepatocellular carcinoma (HCC) recurrence post-LTx. We report 12 M results of everolimus plus reduced tacrolimus (EVR+rTAC) vs. standard tacrolimus (sTAC) in living-donor liver transplant (LDLT) recipients with HCC.
Methods: H2307 is a 24 M, multicenter, open-label, controlled study in which LDLT recipients were randomized to EVR+rTAC ($N = 142$) or sTAC ($N = 142$) after a run-in period of 30 ± 5 days post-LTx. 119 had HCC of which 56 patients were randomized to EVR+rTAC arm and 63 to sTAC. Outcome measurements included assessment of renal function (estimated glomerular filtration rate [eGFR] as assessed by modification of diet in renal disease [MDRD4]); the incidence of composite efficacy failure (CEF: treated biopsy proven acute rejection [tBPAR], graft loss [GL] or death); and HCC recurrence in patients transplanted for HCC disease.
Results and Conclusions: Baseline HCC-related parameters were comparable between EVR+rTAC and sTAC arms. At M12, mean eGFR was significantly higher for EVR+rTAC vs. sTAC in the HCC subpopulation (88.3 ± 30.8 vs. 74.0 ± 21.1 ml/min/1.73 m^2, $p = 0.01$). CEF and its components at M12 were comparable for EVR+rTAC vs. sTAC (CEF in %: 7.1 vs. 4.8; tBPAR: 3.6 vs. 1.6; GL/death: 3.6 vs. 3.2; $p > 0.05$). At M12, no recurrence of HCC (0%) was reported in EVR+rTAC arm whereas 5 patients (8.1%) in the sTAC arm had developed recurrent HCC ($p = 0.059$), 3 of them outside Milan criteria.

In HCC subpopulation of the H2307 trial, patients who received EVR+rTAC vs. sTAC regimen had better renal function with comparable efficacy and a reduced incidence of recurrent HCC. The use of EVR+rTAC in preventing recurrence needs to be confirmed with longer follow-up.