O1 LONG-TERM RESULTS OF ISLET ALLOGENIC TRANSPLANTATION AND PRIMARY GRAFT FUNCTION IMPACT

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Background: Islet allogenic transplantation is an eligible cell therapy for Type 1 Diabetes (T1D) patients with hypoglycemia unawareness or with previous Kidney transplantation. We report 10 years long-term results of Islet allogenic Transplantation in Lille. Patients and
Methods: Since 2003, 33 T1D were enrolled in this single-center phase 2 clinical trial. 19 TD1 received an allogenic Islet Transplantation Alone (ITA) with multiple radiologic or surgical intra-hepatic infusions and 14 T1D received an allogenic Islet After Kidney (IAK) Transplantation for end-stage renal disease with an immunosuppressive regimen according to the Edmonton protocol (Daclizumab, Sirolimus, Tacrolimus).
Results: 33 patients received mean Islet cells mass of 13 544 ± 511 IEQ per kg of body weight in two or three sequential infusions. 26 patients presented a functional transplant at follow-up (fasting C-peptide >0.3 ng/mL). 32 T1D patients achieved insulin independence within 121 ± 15 days (Kaplan-Meier estimate of 20% at 10 years). β-score is a simple and validated score to assess transplanted β-cell function (0–8). The primary graft function (PGF) was estimated 1 month after the last infusion with the β-score and was correlated to insulin independence duration ($p < 0.0001$; $r^2 = 0.56$). Thus, PGF was optimal (β-score ≥7) in 17 T1D patients and 10 years KM estimates of insulin independence was 40%, close to whole-pancreas transplantation functional results. There was no death related to transplant procedure and procedure-related complications significantly impaired primary graft function ($p < 0.05$).
Conclusion: Islet Allogenic Transplantation is a safe therapy and optimal PGF was associated with prolonged graft survival and better metabolic control after islet transplantation.

O2 EFFECT OF TIME ON DIALYSIS BEFORE LIVING DONOR KIDNEY TRANSPLANTATION ON QUALITY OF LIFE AND OCCUPATIONAL REHABILITATION OF RECIPIENTS

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Living-donor (LD) kidney transplantation is currently the best treatment for end-stage renal failure (ESRF), both in terms of quality-of-life and life expectancy. Preemptive transplantation before the terminal phase of chronic renal failure can be proposed.

The main objective of this study was to compare quality-of-life (QoL) and occupational rehabilitation in two populations: preemptive living-donor kidney transplant recipients (Pre-LDR) versus post-dialysis living-donor kidney transplant recipients (PD-LDR).

A self-administred questionnaire (SF-36 for QoL) was mailed to the home of all patients from seven French transplantation centers who had received a LD kidney from April 1, 2004 to December 31, 2011 and who had a functioning transplant on March 31, 2012. Social and occupational data were collected for four time points: before onset of ESRF; during dialysis (PD-LDR group); during the first post-transplantation year; at the time of the study.

The questionnaire was sent to 534 patients and 355 responded. Demographic data were similar in the two groups. While the two groups were not significantly different regarding social and familial items at the different time points, changes in occupational items revealed a difference between the Pre-LDR and the PD-LDR group. Patients in the Pre-LDR group had a stable occupational situation more often (89.3% vs 56.7%), definitive loss of occupational activity less often (4.8% vs 11.3%), and long-term sick leave less often (19.2% vs 29.8%). Factors associated with QoL were: educational level; Groll co-morbidity index; certain side effects. Having been on dialysis before kidney transplantation had no impact on QoL, but longer time on dialysis had a deleterious effect on the physical dimension ($p < 0.0001$), and the mental dimension ($p = 0.09$).

Dialysis before LD kidney transplantation has a significant impact on occupational rehabilitation and the duration of pre-transplantation dialysis significantly affects the QoL.

O3 EXOME SEQUENCING AND PREDICTION OF LONG-TERM KIDNEY ALLOGRAFT FUNCTION

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Current strategies to prevent long-term graft failure in kidney transplantation consider information at the HLA loci. Here, we used exome sequencing of DNA from ABO compatible kidney graft recipients and their living donors to determine recipient and donor mismatches at the amino acid level over entire exomes. The number of mismatches that are more likely to induce an immune response in the recipient was computationally estimated and designated as the allogenomics mismatch score (AMS). The AMS can be measured prior to transplantation with DNA from potential donor and recipient pairs. We examined the degree of relationship between the AMS and post-transplant kidney allograft function by linear regression. In a discovery cohort, we found a significant inverse correlation between the AMS and kidney graft function at 36 months post-transplantation ($n = 10$; 20 exomes) ($r^2 \geq 0.57$, $p < 0.05$). This relationship was confirmed in an independent and similar validation cohort ($n = 24$; 48 exomes) ($r^2 \geq 0.39$, $p < 0.005$). In a third cohort of living, intra-familial related donors ($n = 19$, 38 exomes), we found a weak trend in the direction observed in the first two cohorts, suggesting that the approach is more predictive in unrelated living donor transplantation. A model that controls for donor age, HLA mismatches and time post-transplantation yields a consistent AMS effect across these three independent cohorts ($p < 0.05$). The predictive ability of the AMS persists when the score is restricted to regions outside of the HLA loci. Taken together, these results show that the AMS is a predictor of long-term graft function in kidney transplant recipients.

O4 ASSOCIATION BETWEEN GFR DECLINE AND LONG TERM OUTCOME IN RENAL TRANSPLANTATION

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In renal transplantation, GFR decline is strongly associated to graft failure and patient death and thus could be an interesting proxy for clinical research. GFR estimating equations are known to underestimate GFR decline. Consequently, the threshold usually retained for the GFR decline is very high, around 50% (corresponding to a doubling in serum creatinine). Such a decline is a rare and delayed event limiting its relevance as a criterion of jugdement. A decline of 30% has recently been proposed as an acceptable alternative in CKD patients with native kidneys. We aimed at evaluating the validity of the 30% threshold in renal transplantation and the ability of the CKD-EPI equation to detect this threshold.

Monocentric analysis of patients transplanted from 1989 to 2000 with a functioning graft 5 years post-tx and an evaluation of GFR with inulin and CKD-EPI equation available at 1 and 5 years post-tx. Association between GFR decline and graft failure and patient death was anlysed with a competing-risk COX model.

Out of the 416 analysed patients, 156 lost their graft et 135 died during the follow-up. At the 30%-threshold of GFR decline, concordance between inuline and CKD-EPI was 53%. Association between GFR-inulin decline and graft failure remained significant regardless of the considered threshold (HR of 2.5 [1.6–3.8] and of 5.8 [3.4–10.0] for a threshold of 30 and 50%, respectively). A CKD-EPI-decline of 30% was similarly associated to graft failure (HR de 3.1 [1.9–4.9]). Similar results were observed for patient death.

A GFR decline of 30% between 1 and 5 years post-tx might be a valid surrogate for long term outcome in renal transplantation. Despite a poor concordance between inulin and CKD-EPI, utilization of CKD-EPI equation does not seem to impair the association between GFR decline and graft/patient survival.

O5 PREDICTIVE FACTORS FOR RENAL FUNCTION AFTER KIDNEY TRANSPLANTATION FROM UNCONTROLLED DONORS AFTER CIRCULATORY DEATH

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Introduction: Recipients, donors selection, preservation technique, are now well codified in most centres for kidney transplantation from donors after circulatory death (Maastricht I-II uDCD), but the predictive factors for renal function remain to be determined.
Methods: This monocentric, prospective cohort study was designed to determine the predictive factors of a poor renal function at 3 month after kidney transplantation from uDCD. Low renal function was defined as an estimated glomerular filtration rate (eGFR) lower than 40 mL/min.
Results: From August 2008 and October 2014, 88 patients received a uDCD kidney transplant. Four of those were excluded (death before 3 months and veinous thrombosis), and 84 were included in the study: group 1 (n = 26) with eGFR <40 mL/min/1.73 m² and group 2 (n = 58) with eGFR ≥40 mL/min/1.73 m². Both groups were similars in terms of recipient and donor age, HLA mismatches and pretransplant hemodialysis duration. In the univariate analysis, significant predictive factors for eGFR <40 mL/mIn/1.73 m^2 at 3 months were body mass index (BMI) (p = 0.0755), donor BMI (p = 0.0195), and donor eGFR (p = 0.0033). In preimplantatory biopsies, the histological factors from the Banff score cpt (p = 0.0842), ct (p = 0.0147), cv (p = 0.0441), and the combination cv + ct (0, 0183), ci + ct (p = 0.0416), ci + cv (p = 0.0825), ci + cv + ct (p = 0.0171) were also significants. In the multivariate analysis, significant factors were donor eGFR (OR: 0.931 (95%CI 0.884–0.981), and the histological combined factor cv + ct (OR: 2.3 (95% CI 1.245 – 4.252). Cold ischaemic time, delayed graft function were not significatively different between the 2 groups.
Conclusion: Donor eGFR, and the histological factor cv + ct on preimplantatory biopsies are predictive factors for recipient eGFR 3 months after a kidney transplantation from uDCD.

O6 KIDNEY GRAFT SURVIVAL IN 'VALVE BLADDER' PATIENT

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Objective: To study the survey of kidney transplants in patients with posterior urethral valve (PUV).
Methods: Between 1983 and 2013, 10 patients with PUV [2.2 to 17.4 years aged] were transplanted in our centre. Criteria of study were graft survival, graft renal function, number of acute rejection (AR) and of acute graft pyelonephritis (AGPN) and pre/post-transplant urodynamic evaluation (UE).
Results: Dialysis was initiated an average age of 7.5 years for an average duration of 20 months. Mean age at transplantation was 9 years. At the review, 6 patients were still transplanted with a second graft for 2 of them. Two to 4 AR in 3 patients were observed. Five patients presented at least one AGPN. Graft survival rate (n = 12) was 91.7% at 1 year, 82.5% at 5 years and 61.9% at 10 years. Mean serum creatinine was 140 mmol/L at 1 year, 95 mmol/L at 5 years and 137 mmol/L at 10 years. Before transplantation, UE was disturbed in 5/8 cases with bladder capacity (BC) ≤80% of expected BC in 6/8 cases and abnormal flowmetry in 4/7 cases. Before transplantation, one patient required bladder augmentation and a patient needed clean intermittent catheterization (CIC). After transplantation, BC increased in 5/6 cases with low pre-transplant BC. At the review, the flowmetry was normal in 9 patients; one patient still required the CIC.
Conclusion: Graft survival after renal transplant in valve bladder was not different compared to those described in patients without abnormalities of low urinary tract. New increase of creatinine levels appeared 10 years after transplant. Pre-transplant but also post-transplant UE is essential for urodynamic disorders and prevent complications of the graft.

O7 IMPACT OF DONOR AGE ON OUTCOMES AFTER HEART TRANSPLANTATION IN THE MODERN ERA

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Introduction: The average age of organ donors rose from 37.8 to 57.7 years old over the last fifteen years in France. We sought to investigate the effect of donor age on long-term outcomes after heart transplantation (HT).
Methods: A single-center retrospective review included 261 consecutive HT from January 1996 to March 2013. Donor characteristics were collected from the French national database of the Agence de la Biomedecine. The incidence of primary graft failure (PGF) and cardiac allograft vasculopathy (CAV), and the overall survival were compared in HT recipients between 1996 and 2004 (group A, n = 120) and 2005–2013 (group B, n = 141). Comparison of survival curves was performed using the log-rank test.
Results: Median follow up was 53 months. The mean age of organ donor was 34 ± 12 y-o in group A vs. 42 ± 13 y-o in group B (p < 0.001). Donors in group B shared a higher body mass index (23 ± 2 vs. 26 ± 5 kg.m², p < 0.001) and were more exposed to tobacco (29.6% vs. 52.9%, p < 0.001). One-year and 5-year survival rates were not significantly different between groups, respectively 79% and 63% in group A vs. 80% and 62% in group B (p = 0.551). The rate of PGF was 36% in group A vs. 40% in group B (p = 0.092). Freedom from CAV at 5 years was 98% and 95% respectively (p = 0.367).
Conclusion: In this retrospective single-center study, we suggest that the selection of older allografts does not impair the mid-term outcomes after HT.

O8 SYSTEMATIC BIOPSIES OF RENAL TRANSPLANTS AT M3 IN PEDIATRICS: SECURITY AND USEFULNESS

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Introduction: Subclinical rejection is one of the issues in renal transplantation. Adaptation of immunosuppressive treatment is mandatory for long-term graft survival. No recommendations are published about usefulness of systematic biopsies. We evaluated results of routine biopsies performed 3 months post transplant.
Methodology: We compared the cohort of renal paediatric transplant 2005–2014 (systematic biopsy to M3 (cases)), 57 grafts, with renal paediatric transplant 1995–2004 (control) (biopsies for cause), 43 transplants. Complications of the biopsy, renal function at 3 months, 1 and 5 years, graft survival at 1 and 5 years and the characteristics of the rejection were studied.
Results: No complications occurred in the context of systematic biopsies. At 3 months post transplant, the average GFR is 71 mL/min/1.73 m² in group cases versus 56 mL/min/1.73 m^2 in controls (p = 0. 01). This difference remains significant at 1 year but not at 5 years.

Altogether (100 grafts), 196 biopsies were performed, 52 grafts have presented at least a rejection with 25% (13) subclinical, all belong to the case (p = 0, 021). Among 57 systematic biopsies, 13 showed subclinical lesions, 12 led to an increase of immunosuppression.

In the case group, the GFR was significantly lower after 2 rejections (77 mL/min/1, 73 m² of 0 to 2 rejections versus 23 mL/min/1.73 m^2 after 3 rejections). The survival of the graft was not significantly different between both groups at 1 year (92.7% for cases versus 92.3% for controls) and 5 years (82.8% for versus 87.2% cases).
Conclusion: Systematic biopsy at M3 is a safe procedure. It allows early adaptation of immunosuppressive drugs wich results in significant improvement in kidney function the first year post transplant.

O9 COMPARATIVE HEALTH-RELATED QUALITY-OF-LIFE AMONG HEART TRANSPLANT VS. LONG-TERM MECHANICAL CIRCULATORY SUPPORT RECIPIENTS

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Introduction: Due to shortage of donors, implantation of long-term mechanical circulatory support (MCS) devices is increasingly used either as bridge to heart transplantation or as destination therapy. Although the one-year survival is comparable among transplanted (HTx) patients and MCS recipients, little is known about their health-related quality-of-life.
Methods: In a single-center study, we prospectively followed-up 47 heart transplant and 34 long-term mechanical circulatory support recipients (devices were HeartMate II in 61.8%, HVAD in 14.7%, Jarvik2000 in 14.7% and Syncardia TAH in 8.8%). Health-related quality-of-life was evaluated through the SF-36 and the Minnesota Living with Heart Failure (MILHF) questionnaires at baseline, at the 6th, 12th and 24th postoperative month.
Results: At baseline, HTx and MCS patients showed similar average SF-36 physical summary component (PSC) and mental summary component (MSC) scores; MCS patients had significantly higher average MILHF score (p = 0.03). We observed a statistically significant improvement in average PSC, MSC and MILHF scores from the baseline to the postoperative timepoints for both the MCS and HTx groups. Nonetheless, MCS patient presented lower average PCS score at the 6th, 12th and 24th postoperative month (p < 0.001, p = 0.002 and p = 0.023, respectively) and higher average MILHF score at the 6th postoperative month (p = 0.03). Average MILHF at the remaining timepoints and MSC scores were not statistically different among MCS and HTx patients.

Conclusions: MCS employment allows an improvement in health-related quality-of-life similarly to HTx. Nonetheless, MCS recipients present worse average scores at corresponding postoperative timepoints than HTx patients. Technological improvements in MCS devices are required to improve patients' tolerance to therapy.

O10 TRANSPLANT PROTOCOL FROM DECEASED DONORS AFTER CIRCULATORY ARREST CATEGORIE 2 OF MAASTRICHT. RESULTS TO 8 YEARS AND RISK FACTORS FOR GRAFT FAILURE

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The national protocol for the uDCD program restricts donor age <55 y, no flow period <30 min and total warm ischemia time (WIT) <150 min. In situ kidney perfusion was performed either in hypothermia with a double-balloon catheter (ISP) or in normothermia (nRP). Machine Perfusion was mandatory. Only non-sensitized recipients awaiting a 1st transplant were eligible. 374 kidney transplants from 2007 to 2012) were analyzed. nRP was performed in 35% of the cases, mean WIT was 135 min and mean cold ischemia time (CIT) was 14 h.

Risk factors analysis of primary non function (PNF, n = 33) and graft failure (eGFR <30 mL/min or graft loss at 1 year, n = 55) were performed by logistic regression.

PNF risk factor was paradoxically donor age <35 year [OR = 4.24, p = 0.007]. Sensibility analysis shown a center effect.

Graft failure risk factors (excluding PNF) were donor age and BMI, in situ organ perfusion modalities, ISP duration, HLA mismatch, CIT in univariate analysis ($p < 0.2$). No effect of donor age, no flow period, WIT or CIT were found in multivariate analysis. A significant risk of graft failure was associated with high donor BMI [OR = 1.12, <0.001] and ISP >155 min (compared to nRP) [OR = 2.16, IC = [1.04; 4.49]].

One and 3-year graft survival (without censuring deaths) were significantly different according to donor type: 87% and 79% for uDCD, 87% and 78% for DBD ECD and 94% and 89% for DBD-SCD. After adjustment on recipient age in a Cox model, a significant higher risk of failure at 1 year remained in uDCD recipients compared to optimal DBD [HR = 0.537].

In conclusion, uDCD kidneys represent an additional source of valuable transplants. The use of nRP decreased the graft failure rate, probably through mechanisms close to those described in preconditioning experiments.

O11 IL-33 IS REQUIRED FOR KIDNEY ISCHEMIA-REPERFUSION-INDUCED INJURY IN MICE

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Introduction: Ischemia-reperfusion (IR) injury during kidney transplantation induces necrosis of renal cells and the release of "alarmins" such as IL-33 that can activate the innate immune system, thereby triggering an inflammatory response and tissue damage leading to renal failure, dysfunction or rejection. The aim of this study was to investigate the contribution of IL-33 in kidney IR injury.
Methods: 10–12-week-old wild-type (WT) and IL-33-deficient (IL-33Gt/Gt) male C57/Bl6 mice were subjected to 32 min of unilateral kidney ischemia or a Sham operation. After 24 h, kidneys were harvested and leucocyte infiltration (macrophages, neutrophils, NK and NKT cells) was analyzed by flow cytometry. Renal injury was assessed by measurement of plasma creatinine and histological grading.
Results: Plasma creatinine level and tissue damage were significantly increased after renal IR in WT mice, as compared with Sham-operated animals, a difference that disappeared when WT mice were replaced by IL-33Gt/Gt mice. As expected, intra-renal neutrophils and macrophages, which are generally considered as two main effector populations of IR injury, were significantly increased 24 h-post IR. Surprisingly, such a phenomenon was maintained in IL-33Gt/Gt mice despite their lower sensitivity to kidney injury. On the other hand, NK and NKT cells, also known for their deleterious effect during renal IR injury, and which are targeted by IL-33, seemed to be less recruited 24 h-post IR in IL-33Gt/Gt mice compared with WT mice.
Conclusion: IL-33Gt/Gt mice do not recruit NK and NKT cells and are less sensitive to kidney damage 24 h-post IR, consistent with an NKT/NK cell-dependent deleterious effect of IL-33 during renal IR injury. This study underlines a new possible role of IL-33 as an innate-immune mediator during kidney IR injury.

O12 HYPERCHOLESTEROLEMIA PROMOTES RENAL MICROVASCULAR REMODELING IN A PORCINE AUTO-TRANSPLANTED KIDNEY GRAFT MODEL

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Introduction: The organ shortage in renal transplantation increases the number of recipients with a higher prevalence of comorbidity factors such as dyslipidemia. The transplant procedure induces vascular lesions limited by induction of regeneration processes. The goal of our study was to characterize the role a diet-induced increase in plasma oxidized LDL on the kidney cortex vascular remodeling after in a renal auto-transplantation model.
Methods: We used three months old pigs following a kidney auto transplantation procedure: left kidneys were removed and cold stored for 24 h at 4°C in University of Wisconsin solution and autotransplanted. A contralateral nephrectomy was performed to mimic renal mass in clinical situation. Two experimental groups were studied: kidneys graft removed 3 months after surgery either from animals exposed to a standard diet (Normal diet, n = 5) or from animals fed a high-fat diet started immediately after weaning (High-fat diet, n = 5). We characterized the cortical microvascularization by microcomputed tomography and histological injury analysis 3 months post-surgery.
Results: Increased plasma oxidized LDL levels at three months promoted concomitant microvascular rarefaction for small vascular segments with diameter inferior to 40 μm particularly in the middle cortex (vascular density as a percentage of vessels expressed as mean ± SEM: 0.46 ± 0.21 in high-fat diet vs 1.61 ± 0.45 in normo-diet pigs) and a decrease of vascular segment diameter average (52.11 ± 4.05 vs. 85.63 ± 5.58 μm in outer cortex, 69.75 ± 4.69 vs. 117.79 ± 11.21 μm in middle cortex, 74.70 ± 2.73 vs.128.76 ± 13.96 μm in inner cortex). This was associated with a monocyte infiltration and interstitial fibrosis tubular atrophy.
Conclusion: These results underline that high fat-diet induces a microvascular rarefaction which worsen the vascular remodeling induced by ischemia-reperfusion and suggest to control hypercholesterolemia in recipient at the early stage of renal transplantation.

O13 INFLUENCE OF COLD ISCHEMIA DURATION ON MICROVASCULAR REMODELING IN A RENAL PORCINE AUTOTRANSPLANTATION MODEL: PRELIMINARY STUDY BY MICROSCANNER

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Introduction: Ischemia-reperfusion in organ transplantation is responsible for a pathophysiological process targeting graft vascular network. The goal of this preliminary work is to characterize the changes of renal cortex vascular network related to the duration of the hypothermic preservation in a porcine auto-transplanted kidney model.
Materials and methods: Three months old male pigs were used. Left kidneys were harvested and preserved in UW solution at 4°C for 24 h (n = 5) or for 48 h (n = 4). A contralateral nephrectomy was performed to mimic the nephron mass in the transplanted human recipient. The auto-transplanted animals were followed for 3 months (M3). At M3, kidney grafts were perfused with a radio-opaque silicone polymer and the cortical part was studied by X-ray micro-computed tomography. Vascular morphology is studied by a three-dimensional analysis of images from the cortex.
Results: At M3, the hypothermic preservation for 48 h of grafts compared to 24 h induced a significant increase of the cortical area thickness

(13.98 ± 0.79 mm vs 11.41 ± 0.39 mm, p = 0.03), associated to a drastic decrease of microvessels contrasting with an increase in the percentage of vessels with a diameter >120 μm. These results are accompanied by an impairment of renal function and histological lesions characterized by tubulointerstitial fibrosis and tubular atrophy in UW48 group.
Conclusion: These preliminary results suggest that the renal function in grafts subjected to long preservation duration could be associated with chronic hypoxia and fibrosis related to microvascular rarefaction.

O14 HYPOTHERMIC PULSATILE PRESERVATION OF KIDNEYS FROM UNCONTROLLED DECEASED DONORS AFTER CARDIAC ARREST

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Background: Kidneys from uncontrolled donors after cardiac arrest (uDCD) suffer from a period of warm ischemia between cardiac arrest and cold flushing. The present study was performed to evaluate renal outcomes in machine perfused uDCD grafts and the influence of resistive index (RI) on graft function and survival.
Materials: Forty-four kidneys from uDCD were included in this study. The potential donors (Maastricht category I and II) underwent cardiopulmonary resuscitation by assisted ventilation and chest compression; the organs were preserved with in situ cold perfusion (IGL-1 solution) using an aortic double-balloon triple-lumen catheter ("Gillot sonde") or a normothermic subdiaphragmatic extracorporeal membrane oxygenation. All the harvested kidneys were machine perfused using hypothermic (1–4°C) pulsatile perfusion (RM3, Waters Medical System). Kidneys with RI³0.5 mmHg/mL/min after 6 h of perfusion were discarded.
Results: There was one PNF, while 37 recipients (84.1%) experienced DGF. Graft survival at two years was 97.6%. The incidence of acute rejection episodes was 18.18%

A linear regression model showed that RI values at the end of perfusion were associated with MDRD variations at 3 and 6 months after transplantation (p = 0.049 and p = 0.01, respectively) and with inuline clearance at 1 year (p = 0.03). RI at the beginning of perfusion was significantly influenced by the in situ cold perfusion procedure, donor smoking, warm ischemia time; at the end of the perfusion it was influenced by the in situ cold perfusion procedure, donor sex and donor serum creatinine values.
Conclusions: Machine perfusion allows to prevent the deleterious effects of warm ischemia in uDCD grafts and RI values are correlated to graft function.

O15 TRIMETAZIDINE IS PROTECTIVE DURING KIDNEY PRESERVATION WITH MACHINE PERFUSION

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Introduction: The use of machine perfusion for kideny preservation is recommended for the conservation of organs obtained from donors after cardiac arrest (warm ischemia) or from marginal donors. Preservation with machine perfusion allows organs evaluation and potential additon of drugs modifying the protocols with a predictive and therapeutic approach
Materials and methods: Two experimental groups of 6 animals were studied using Large White pigs. The left kidney was removed after 1 h of warm ischemia, washed by KPS-1® solution (group KPS) KPS-1® or with trimetazidine (KPS + T group) and then placed in perfusion machine. Kidneys were then transplanted in the same animal and contralateral kidney removed. Perfusion milieu was sampled for tissue infury markers. The recovery of glomerular and tubular function was studied every day for one week. A kidney biopsy was peformed at D7 to assess tissue injury. Markers of lesions (KIM-1, NGAL, AST and H-FABP), oxidative stress and innate immunity was evaluated. Three months after auto transplantation, animals were sacrificed and a histomorphological analysis and immunoblotting were performed
Results: The contribution of trimetizidine allows a significant improvement in recovery of function and limiting the oxidative stress in association with a reduction in tubular necrosis. This is also related to a significant limitation of tissue damage markers release during machine preservation. The expression of markers of innate immunity is also significantly limited. At 3 months, the glomerular filtration level is improved in the KPS + T group with a reduction of interstitial fibrosis and tubular atrophy
Conclusion: Kidney preservation with machine perfusion is potentially interesting for organ evaluation and potential addition of protective drug which could change protocole for patients.

O16 EXPLORING ISCHEMIA REPERFUSION MECHANISMS USING HIGH THROUGHPUT PROTEOMICS

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Objectives: Ischemia reperfusion lesions are an unavoidable consequence of organ transplantation. Research into novel therapeutics against these lesions requires an in depth characterization of the involved mechanisms.
Methods: Using a primary culture of human aortic endothelial cells, we compared the proteome of cells in normal culture conditions to cells subjected to an anoxic/hypothermic stress for 24 h in University of Wisconsin solution. Proteome comparisons analyses were performed on a nano LD MS MS (N = 3).
Results: Differential analysis of the normal/stresses samples revealed alterations in the expression profile of more than 500 proteins.

In order to clarify the results interpretation, a heatmap was produce which permitted us to divide our results into three categories: proteins remaining stable during the protocol, proteins which expression was lost, and proteins newly expressed.

We proceeded to a cultering analysis, grouping proteins and their ontology into cellular mechanisms. We used Cytoscape (ClueGo App). This analysis demonstrated that cold ischemia repressed the pathways commanding the expression and maturation of mRNAs and proteins, with an impact on the energy metabolism.

Newly expressed proteins were involved in recycling and endocytosis pathways, close to autophagy, and proteins expressed at the cellular membrane. However, the cell maintained the expression of proteins involved in pathways such as stress resistance (antioxidant defenses, RedOx balance), gene transcription and translation, as well and cytoskeleton regulation.
Conclusions: Our data clearly highlights that cold ischemia is an essential step at the cellular level in regards to the major regulatory pathways and the lesion pathways involved at reperfusion. Ischemia thus induces an in depth reprogramming of the cell, surprisingly including the expression of novel proteins whereas hypothermia and hypoxia are typically associated with a global inhibitory influence on the metabolism.

O17 ALVEOLAR AND CIRCULATING MICROPARTICLES CORRELATE WITH INFLAMMATORY ISCHEMIA REPERFUSION ACTIVATION IN A RODENT MODEL FOR EX VIVO LUNG PERFUSION

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Introduction: Following to lung transplantation, lung ischemia reperfusion injury is only graded by means of radiological and oxymetric characteristics. There is no actual relevant biomarker of ischemic insult in lungs. Microparticles (MPs) are submicronic fragments shed from stimulated and stressed cells measured as biomarkers of cell injury. We aimed at assessment of MPs released during ischemic lung injury in an ex vivo rat lung perfusion model (EVrLP).
Method: Following anesthesia, lungs were harvested from adult male Wistar rats. Lungs were placed in the EVrLP model either immediately (no ischemia [NI]; n = 6) either following 1 h cold ischemia ([IC1]; n = 6), or following 20 h cold ischemia ([IC20]; n = 6), or following 1 h warm ischemia ([WI]; n = 6). Lungs were ventilated, and perfused with acellular Perfadex® for 1 h. Lung function was assessed with hemodynamic and oxymetric criteria. Alveolar and circulating MPs, as well as inflammatory cytokines were assessed in the broncho-alveolar lavage and in the perfusate respectively. Oxidative stress expression was searched for in the lung parenchyma with a western blot assay.
Results: Lungs submitted to ischemia present with significantly higher amounts of MPs in the perfusate and in the BAL. Pulmonary artery pressure and wet to dry weight ratio are significantly higher in [WI] and [IC20]. Inflammatory cytokines and oxidative stress proteins expression witness for ischemia injury activation.
Conclusion: The production of alveolar and circulating MPs correlates with inflammatory ischemia reperfusion injury activation. MPs do reveal as relevant biomarkers for lung ischemia related injury in an experimental model of rodent ex vivo perfusion.

O18 MYELOID HEME OXYGENASE-1 CONTROLS RENAL ISCHEMIA-REPERFUSION INJURY

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Background: Renal ischemia reperfusion injury (IRI) leads to major organ and cell damages by at least the activation of innate immunity. The heme oxygenase-1 (HO-1), a stress-responsive enzyme, protects kidney from renal IRI through multiple mechanisms. In kidneys, HO-1 can be expressed by many cellular sources among which tubular epithelial cells and myeloid cells. The aim of this study was to understand the role of the myeloid HO-1 in the natural control of renal IRI and after pharmacological induction of HO-1 by hemin.
Materials and methods: Myeloid HO-1 KO mice (HO-1M-KO mice), specifically deficient for HO-1 in myeloid cells, littermate (LT) control mice, and wild-type (WT) C57/Bl6 mice underwent bilateral renal IRI for 26 min. After 24 h of reperfusion, plasma and kidneys were harvested. WT mice were treated with hemin 5 mg/kg or saline 24 h prior ischemia. Renal IRI was evaluated by plasma creatinine and histology. Renal inflammation, leukocytes influx and oxidative stress were assessed by ELISA, immunostaining and nitrotyrosine levels respectively. HO-1 expression in renal leukocytes was assessed by FACS.
Results: Renal damages were worsened in HO-1M-KO compared to LT mice (i.e., higher creatinine levels and tubular necrosis). Intra-renal cytokine expression (i.e., IL-6, MCP-1 and KC), oxidative stress and neutrophil/macrophages influx were also enhanced. In WT mice, the protective effect of hemin pretreatment (i.e., plasma creatinine levels, tubular necrosis) was associated with a specific upregulation of HO-1 within myeloid CD11b+F4/80lo renal cells before IRI and a higher proportion of these HO-1 producing myeloid cells upon IRI. A subsequent dampened renal inflammation was found in hemin-treated mice (i.e. IL-6, MCP-1 and KC).
Conclusion: Our results demonstrate that myeloid-derived HO-1 in CD11b+ F4/80lo renal cells significantly controls the magnitude of renal IRI. Targeting myeloid HO-1 might represent a promising approach for transplantation.

O19 IMPACT OF EVEROLIMUS, AN MTORC1 INHIBITOR, ON HEPATOCELLULAR CARCINOMA RECURRENCE AFTER LIVER TRANSPLANTATION: RESULTS FROM THE H2304 STUDY

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Background: In patients undergoing liver transplantation (LTx) due to hepatocellular carcinoma (HCC), immunosuppression plays a major role in HCC recurrence post-LTx. Pre-clinical, retrospective, and cohort studies suggests a protective role of everolimus (EVR), an approved antineoplastic agent, on recurrence of HCC after LTx. Here, we present HCC recurrence, patient outcome and impact of EVR treatment and exposure up to 36 months (M) post-LTx in a subgroup of 203 HCC patients from the H2304 (NCT00622869) study.
Methods: Data were retrieved from the core study and its extension, a 3-year randomized controlled trial in 719 de novo LTx recipients received EVR (C0 3–8 ng/mL) plus reduced tacrolimus (rTAC, C0 3–5 ng/mL) or EVR(C0 6–10 ng/mL) with TAC Withdrawal (TAC-WD) at M4 or standard TAC (TAC-C, C0 6–10 ng/mL). Milan criteria (prior/at Tx), number of tumor lesions, diameter of largest nodule, and total tumor diameter (TDD) as well as alpha fetoprotein (AFP) levels were assessed at time of Tx. Follow-up reporting was obtained at 12, 24, and at 36 M for patients entering into the extension phase.
Results: Baseline demographics and HCC characteristics were comparable between the EVR + rTac (n = 67), TAC-WD (n = 69) and TAC-C (n = 67) groups.Overall, HCC recurrence was observed in 2, 11, and 13 patients at M12, 24, and 36, respectively. Incidences of efficacy failure (BPAR: 7.6%, 22.6% and 12.6%; graft loss: 4.7%, 3.0% and 3.3%; death: 6.3%, 6.4% and 4.9% for EVR + rTAC, TAC-WD and TAC-C, respectively) and evolution of renal function overtime were similar to overall population. Overall HCC recurrence rate was lower in patients treated with EVR vs TAC 2.2 vs 11.9% p = 0.007 at the end of the 24 M core study, and 2.9 vs 13.4% p = 0.012 at M36.
Conclusion: Similar to the overall population, HCC patients treated with EVR + rTAC had fewer rejections and better renal function compared to TAC-C. The observed reduced HCC recurrence rate seen in the EVR treated patients, warrants further investigation.

O20 OUTCOME OF RETRANSPLANTED PATIENTS AFTER POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS: A FRENCH NATIONWIDE STUDY

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Introduction: Post-transplant lymphoproliferative disorders (PTLD) are a serious complication with a mortality rate of 60% at 5 years in France. Among patients who survived, some lost their graft and return to dialysis. Retransplantation of these patients remains questioning because of the risk of recurrent PTLD with reintroduction of immunosuppression.
Patients and methods: Data were retrospectively collected in all adults who underwent kidney retransplantation after PTLD in France between 01/01/1998 and 01/09/2015, from patients' files and CRISTAL Database.
Results: A total of 46 adult patients, 29 men and 17 women, underwent kidney retransplantation after PTLD. Mean delay from PTLD to the retransplantation was 99 ± 44 months [28–215]. Regarding EBV Status at the time of retransplantation, 97% of patients were EBV seropositive (anti EBNA IgG positive in 86% of cases). Induction therapy was used in 39/46 retransplantations (85%). Four patients received Rotuximab and 53% were treated with anti-viral drug. Fourteen patients were treated with Thymoglobulins (30%) and 25 with IL2 receptor antagonists (54%). Association of calcineurin inhibitors (Tacrolimus in 38 patients, cyclosporine in 8 patients), mycophenolate mofetil and steroids was the most frequent maintenance immunosuppression regimen (89%). Only one patient was treated with Sirolimus de novo and seven were later switched from calcineurin inhibitor to a proliferation signal inhibitor.

One patient showed a recurrence 20 months after the subsequent transplantation (2%) and died of PTLD progression. 45 patients showed no recurrence of lymphoma after a mean delay of 76 ± 53 months, 4 died of independent cause than PTLD and 2 lost their graft.
Conclusion: Retransplantation after PTLD is safe in the French cohort of kidney recipients. The occurrence of one recurrent case raises the question of the better strategy to use to prevent relapse.

O21 A STRICT SELECTION OF OBESE PATIENTS MINIMIZES POST RENAL TRANSPLANT COMPLICATIONS BUT INCREASES WAITING TIME

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Access to kidney transplantation in obese subjects is still difficult. A body mass index (BMI) <35 is still imposed in our department.

We retrospectively studied data from 136 patients, kidney transplanted from Jan 2010 and Dec 2012 at the Clermont-Ferrand.University Hospital. Data from non-obese patients (NO group, n = 108) were compared with those from patients with a history of obesity (O, n = 28). In the group O, data from patients with more than 5 kg weight loss (OWL, n = 13) were compared to data from patients who did not lose weight (ONWL group, n = 8).

There is no difference in demographics, comorbidities and transplantation except a tendency to more cardiac history (21 vs 10%, p = 0.1) and diabetes (25 vs 14%, p = 0.16) in O / NO. O had a BMI = 31 + 2, only 6/28 had a BMI <30 at time to transplantation. There are no more medical or urological postoperative complications but more primary non-functions (18 vs. 4%, p = 0.012) and delayed graft functions (57 vs 20%, p < 0.01) in O / NO. Wound complications were not collected. The hot and cold ischemia times did not differ between O and NO groups. Demographic characteristics, comorbidities, transplantation characteristics and outcomes after surgery and albumin before transplantation were not different between OWL and ONWL. However, the OWL waiting period tends to be longer than that of ONWL (3 years 2 months vs 1 year 11 months, p = 0.15).

The major limitation of the study is the small numbers of subjects but O seems to have not more urological and medical postoperative complications

that NO. However, O patients are very selected: no patient have a BMI >34 and they had only few comorbidities. If O patients must lose weight, they expected a longer waiting time. In the region, 20% of dialysis patients are obese. This selection could affect their access to transplantation.

O22 LONG-TERM EVOLUTION LIVER TUMORIGENESIS, STEATOSIS AND FIBROSIS SCORES AFTER INTRAPORTAL ISLET TRANSPLANTATION IN TYPE 1 DIABETES

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The carbohydrate antigen 19.9 (CA19.9), a mucin circulating glycoprotein, is a proliferation marker of the liver and pancreatic duct cells. Used as a marker of pancreatic adeno-carcinoma, it also increases in unbalanced diabetes, cholestasis, liver fibrosis and renal insufficiency. Besides beta cells, preparations for islet transplantation include ductal cells. The percentage of these ductal cells is inversely correlated to the purity of the preparation. CA19.9 is thought to be a biomarker of these cells, fate of which is poorly understood: destruction, neogenesis, favourable impact on islet implantation or even tumorigenesis.

The aim of this prospective study was to describe the evolution of CA19.9 in a cohort of islet-transplanted type 1 diabetic patients and to determine the factors influencing its variation.

Patients: 43 C-peptide negative type 1 diabetic patients (15 islet-after-kidney transplantation (IAK), 28 islet transplantation alone (ITA), transplanted between 2003 and 2013 in a single center were included with a median follow-up of 6 years. All patients had normal CA19-9 level before islet transplantation.

Methods: Blood CA19-9 and alphafoetoprotein levels, metabolic, renal and liver parameters, betascore and daily insulin need were measured before and yearly after transplantation. The mean purity and viability of the 2 or 3 islet preparations received by each patient was calculated. The percentage of liver steatosis assessed with MRI, and a score of liver fibrosis assessed with Fibroscan were prospectively recorded. The linear mixed model taking the effect time into account was used to compare the kinetics of CA19-9.

Results: The 10-year percentage of insulin independence was 22% and of detectable C-peptide of 75%. After transplantation, CA19.9 levels increased above the normal threshold in 30% of the patients, especially during the first 3 years, without clinical or morphological evidence of exocrine pancreatic disease. At 10 years, CA19.9 levels were significantly correlated with liver enzymes (OR = 0.20; $p < 0.0001$), the degree of purity of islets (OR = −1.25; $p = 0.0001$), the daily insulin dose (OR = −0.15; $p = 0.03$) with a tendency for the βscore. CA19.9 levels were neither correlated with the liver fibrosis score, nor to the alphafoetoprotein level, nor to HbA1c or renal parameters.

In conclusion, Ca19-9 increases in a third of the patients after islet transplantation. This increase is strongly and inversely correlated with the islet purity and to a lesser extent with the quality of the metabolic results. These results suggest that the presence of ductal cells in islet preparations could have a beneficial effect through environmental factors or neogenesis. Otherwise neither liver tumorigenesis, steatosis nor fibrosis was observed more than 10 years after intraportal islet transplantation.

O23 EARLY SIGNS OF ENDOCRINE PANCREAS ABNORMALITIES AND SENESCENCE IN MIDDLE AGE RATS WITH NORMAL VASCULAR FUNCTION: IMPACT FOR PANCREATIC ISLET TRANSPLANTATION

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Introduction: Because major ischemia reperfusion occurs at the onset of islets transplantation, that is associated with early aging of the graft, we investigated whether the age of the donor could itself contribute to pancreatic islet alteration and loss of grafted islets.

Materials and Methods: Pancreas were harvested from 12 or 52 weeks wistar rats (n = 8 each). The morphology of islets was examined by Haematoxylin & Eosin and Gomori's trichrome. The area of cells secreting insulin or glucagon was measured by immunofluorescence. Protein extracts from frozen pancreatic tissues were analyzed by western blots to study senescence, tissue factor (TF) expression and indicators of oxidative stress (ROS). Circulating microparticles (Mps) were also measured as surrogates of vascular cell injury origin. In addition, vascular function was studied in mesenteric artery rings in response to acetylcholine and phenylephrine.

Results: A higher proportion of small diameter islets was measured in aged vs. young rats (91% vs. 87%). Larger islets were twice in young rats. In middle age rats a higher amount of collagen fibers surrounding the islets and around the blood capillaries was observed between the endocrine cells of the islets. The glucagon /islets surface ratio increased by 40%. Western blots showed up-regulated p53 (2-fold increase), p21 (four fold increase), p16 (2-fold increase), trend to increase of TF and down regulated eNOS (2-fold decrease). ROS increased significantly (2-fold increase). No sign of vascular injury (MPs) or dysfunction (vascular reactivity) was evidenced.

Conclusion: Morphological pancreatic islet alterations are detected in middle age rats before any measurement of vascular aging. The early raise of pancreas senescence in the process of ageing suggests the determinant role of donor age in pancreatic islet transplantation.

O24 IS SYSTEMATIC CARDIOPULMONARY EXERCISE TESTING FOR PATIENTS AWAITING KIDNEY TRANSPLANTATION USEFUL?

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Renal pre-transplant assessment must select candidates for renal transplantation to minimize postoperative risks. The cardiopulmonary exercise testing (CPET) is an interesting tool to measure exercise aerobic capacity. The aim of this study was to evaluate the interest of CPET in the pre-transplant kidney assessment.

This prospective, open, single-centre study includes all candidates sent to our center between July 2011 and July 2013 for inclusion on the kidney transplant list. CPET was performed on a cycle ergometry, and aerobic capacity as measured by VO2 peak was evaluated. Main clinical and laboratory data were collected, and the Charlson Comorbidity Index was calculated. Univariate and multiple linear regression analyses were used to identify demographic and clinical correlates of peak exercise oxygen uptake <5 METs (or <17.5 mL/kg/min). The Cox proportional hazards model was used to determine parameters that best predicted the duration on temporary contraindication list.

233 patients were finally included and VO2 peak was seriously impaired in 37% of patients (VO2 peak <5 METs). VO2 peak median was 19.2 mL/kg/min [16.0; 23.5]. Multivariate analysis revealed Comorbidity Charlson Index (CCI) (OR 1.31 [1.05, 1.65], $p < 0.001$) and Body Mass Index (OR 1.17 [1.09; 1.27], $p < 0.001$) as independent predictors of VO2 peak <5 METs. CCI (OR 0.87 [0.77, 0.97], $p = 0.02$), a VO2 peak ≥5 METs (OR 1.53 [1.08; 2.18], $p = 0.02$) and B blood group (OR 0.46 [1.28; 3.66], $p < 0.05$) were significantly associated with the duration of temporary contraindication.

This is the first prospective study to demonstrate a significant association of the CCI and impaired aerobic capacity with an impact on the duration of the temporary contraindication. Therefore, the use of CPET seems to be relevant in the selection of dialysis patients candidates for inscription on kidney transplant list if the CCI is ≥3.

O25 EVEROLIMUS AND SKIN CANCER SECONDARY PREVENTION IN HEART TRANSPLANT PATIENTS. RESULTS OF THE MULTICENTER FRENCH OPEN RANDOMIZED STUDY CERTICOEUR; EVEROLIMUS VS. ANTICALCINEURINS

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CERTICOEUR compare the effect of two immunosuppressive strategies, (1) usual strategy (CNI) (anticalcineurins minimization), (2) replacement of CNI by everolimus (EVL) - on the number of new premalignant and malignant skin tumors (carcinoma cell carcinoma, keratoacanthoma, basal cell carcinoma, Bowen's disease and pre epitheliomatous keratosis) over 24 months in cardiac transplant patients having already developed one or more of these lesions. The study took place from 2008 to 2014. EVL (Certican): 0.75 mg/12 h and then trough level adjusted (3–8 ng/mL)) was associated with a 75% reduction in CNI dose followed by CNI discontinuation. The primary endpoint was the occurrence of new skin tumors per patient. Secondary outcomes were the number and histology of new lesions, the proportion of patients with new lesions, the time to onset of lesions, the occurrence of other skin cancers, the incidence of

non-skin cancers, changes in renal function, safety of EVL and description of the CNI reduction practices.
Results: 39 patients were included: 28 EVL and 11 CNI (175 were expected, 22% of target was achieved). Baseline characteristics were comparable between the two groups. 94 tumors occurred in the EVL group, 48 in the group "Usual Strategy". The CNI were discontinued in 11 of 28 EVL patients. Tumor recurrence occurred in 42% of EVL patients vs 80% if CNI. Despite the small study size, the recurrence-free survival analysis (ITT analysis) shows a trend in favor of EVL ($p = 0.073$; HR = 0.28). The distribution of tumors is comparable between the two groups. Renal function remained stable despite the reduction of exposure to CNI.
Conclusion: Everolimus may have a role in secondary prevention of skin tumors in cardiac transplant patients with a history of skin carcinoma.

O26 KIDNEY RETRANSPLANTATION IN PATIENTS HAVING PRESENTED AT LEAST ONE SQUAMOUS CELL CARCINOMA DURING A PREVIOUS TRANSPLANTATION PERIOD EXPOSES TO A HIGH RISK OF AGGRESSIVE SKIN SQUAMOUS CELL CARCINOMA

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Squamous cell carcinoma (SCC) is a frequent complication of the immunosuppression (IS). Nevertheless, there is no recommendation for re-transplantation (re-Tx) in patients having presented one or several SCC during a previous Tx.

We have done a retrospective and multicentric study, including 62 re-Tx patients, having presented at least one SCC during a previous Tx. The primary study endpoint is the number of aggressive SCC (local recurrence and/or metastasis) and the secondary criteria, the survival of the patient and of the graft, the number of skin tumors (histologically confirmed) observed during last Tx period. Finally we tried to estimate risk factors of aggressive SSC.

45/62 patients (72%) presented of new SCC after re-Tx with a number of SCC doubled compared with the period of previous Tx. 14 patients (23%) developed an aggressive SSC after re-Tx (4 local recurrences and 10 metastases) after an average of 48 months post re-Tx. Thirty patients (48%) died, among which 5 (12%) from a metastatic evolution of their SCC. The patient survival was of 88%, 79% and 55% at, respectively 3, 5 and 10 years after re-Tx. The risk factors of the aggressive SSC were, the clear phototype (I-II: 64 vs 35%) and a higher number of SCC during previous Tx (15 vs 7.2). The age of the patient, the total duration of the IS or of the dialysis before the last Tx and the delay between the last SCC and the re-Tx did not seem to influence the evolution.

This study confirms that kidney transplant recipients having had, at least, one SSC during a previous Tx are at high risk of aggressive SCC and in particular for those of clear phototype and/or with a high number of preliminary SCC (>10). The high risk of a fatal evolution needs to be underlined. The place of the mTOR inhibitors was not studied in our study but if the re-Tx is realized, this one, must be strictly supervised by a dermatological follow-up and by an adaptation of the IS.

O27 ASSOCIATION BETWEEN GUT MICROBIOTA MODIFICATIONS AND METABOLIC DISORDERS IN KIDNEY TRANSPLANTATION RECIPIENTS: THE METABIOTE-TR STUDY

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Introduction: Gut microbiota modifications (dysbiosis) have been observed during obesity and diabetes, with an underrepresentation of specific bacterial species. Kidney transplant recipients (KTR) are particularly exposed to the development of metabolic disorders, both before and after kidney transplantation (KT). Here, we investigated changes in gut microbiota composition in KTR with or without metabolic disorders.
Methods: A fecal sample was collected from KTR with or without metabolic disorders before and 2 to 12 months after KT. Fecal bacterial DNA was extracted from these samples. qPCR analysis was performed to explore 9 bacterial species or groups in the gut microbiota of diabetic, obese and control patients. The results were expressed as relative count to total bacteria and as absolute count per ng of stool DNA.
Results: 52 KTR were included: median age was 56 years, 35% of women. Before KT, there were 29% of diabetic patients (called "diabetic-pre") and 15% of obese patients. After KT, 27% of patients developed New Onset Diabetes ("NODAT") and 5% developed obesity. Before KT, the Firmicutes/Bacteroidetes ratio was increased in diabetic-pre, and Faecalibacterium prausnitzii relative and absolute counts were decreased in diabetic-pre and in NODAT patients, compared to controls. After transplantation, Lactobacillus relative and absolute counts were increased, and Akkermansia muciniphila relative and absolute counts were decreased in all diabetic and obese patients, compared to controls.
Conclusion: KTR who develop metabolic disorders show a dysbiosis, some characteristics of which are common with what have been described outside of the KT setting. The interest of specific bacteria as a marker (A. muciniphila) or a risk factor (F. prausnitzii) needs to be explored.

O28 EVEROLIMUS WITH REDUCED TACROLIMUS PRESERVES LONG-TERM RENAL FUNCTION IN LIVER TRANSPLANT RECIPIENTS: 36 AND 48 MONTHS RESULTS FROM THE H2304E1 STUDY

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Purpose: Preserving long-term renal function (RF) in liver transplant recipients (LTxRs) remains a major concern. This study evaluates if early introduction of everolimus (EVR) with reduced tacrolimus (rTAC) provides long-term renal benefits in LTxRs.
Methods Patients: Who completed the 24 month (M) randomized H2304 study could continue their assigned treatment regimen during the 12 M extension study: EVR + rTAC (N = 106, EVR C0 3–8 ng/mL; TAC C0 3–5 ng/mL) or TAC standard exposure (TAC-C) (N = 125, C0 6–10 ng/mL). In the extension phase, patients in the EVR + rTAC arm were followed by in additional 12 M follow-up on the same regimen. Key primary endpoint was RF assessed by estimated GFR (eGFR) using MDRD4. Additionally, evolution of RF from M24 to M36 was explored using a mixed-effect model for longitudinal data.
Results: At M36, the EVR + rTAC arm had lower incidence of composite efficacy failure (11.5% vs 14.6% in TAC-C, risk difference −3.2%, 97.5% CI: −10.5, 4.2; $p = 0.334$). Mean eGFR was superior with EVR + rTAC vs TAC-C (78.7 vs 63.5 mL/min/1.73 m^2) with a difference of 15.2 mL/min/1.73 m^2 in favor of the EVR + rTAC arm ($p < 0.001$; all extension patients). Proportion of patients with eGFR <60 mL/min/1.73 m^2 was significantly lower with EVR + rTAC (28.0% vs 42.6% in TAC-C, $p = 0.032$). At M48, mean eGFR in the EVR + rTAC arm was 80.5 mL/min/1.73 m^2 and the number of patients with eGFR <60 mL/min/1.73 m^2 decreased to 15%. From M24 to M36, longitudinal data analysis for eGFR showed no change in RF for the EVR + rTAC arm vs a decrease for TAC-C arm (0.04 vs −0.26 mL/min/1.73 m^2/month). Fewer patients in the EVR + rTAC vs TAC-C arm experienced renal failure (2 vs 10) and renal impairment (1 vs 3) with none vs 2 patients discontinuing study medication due to these AEs. Proteinuria (≥3 g/day) was not reported in either arm.
Conclusion: Early introduction of EVR to reduce TAC exposure preserves long-term RF in LTxRs. The 48M data show that a notable RF was maintained for patients on EVR with rTAC.

O29 IMPACT ON RENAL FUNCTION OF STEPWISE WITHDRAWAL OF TACROLIMUS COMBINED WITH EVEROLIMUS AND EC-MPS VS STANDARD TREATMENT COMBINING TACROLIMUS AND EC-MPS IN DE NOVO LIVER TRANSPLANT RECIPIENTS: RESULTS OF THE SIMCER STUDY

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Introduction: Long-term post-liver transplant (LTx) complications, particularly impaired renal function (RF) and its consequences, remain a concern. Presented here are the results of the SIMCER Study evaluating the efficacy and safety of treatment with everolimus (EVR) combined with enteric-coated mycophenolate sodium (EC-MPS) after the stepwise withdrawal of tacrolimus (TAC) vs standard TAC + EC-MPS treatment.
Methodology: This is a prospective, open-label study conducted in 15 French centers. 188 patients were randomized at 1 month (M1) post-LTx (1:1) to

receive EVR(C0 6–10 ng/ml) + EC-MPS(1440 mg/d) + TAC (stepwise withdrawal over 8 weeks on average) or TAC(C 0 6–10 ng/mL) + EC-MPS (1440 mg/d). All received basiliximab ± corticosteroids. The primary objective was to evaluate whether EVR + EC-MPS leads to better RF (eGFR, abbreviated MDRD) at 6 months(M6) vs standard treatment.
Results: Patient characteristics were comparable between the EVR + EC-MPS (n = 93) and TAC + EC-MPS (n = 95) groups. The analysis of covariance of eGFR progression between randomization and M6 shows a significant difference in favor of the EVR + EC-MPS group (+14.3 mL/min/1.73 m², 95% CI 7.3–21.3; p < 0.0001). The incidence of treatment failures was comparable between EVR + EC-MPS and TAC + EC-MPS (8.9% vs 4.3%; p = 0.210, of which 7 vs 2 treated BPAR, 0 vs 1 graft loss, 1 vs 1 death), and the incidence of adverse events (AEs) was: 90% and 90.4% respectively, p = 0.923. The incidence of serious AEs was significantly higher in the EVR + EC-MPS group than in the TAC + EC-MPS group (46.7% vs 29.8%; p = 0.018).
Conclusion: The SIMCER Study has evaluated for the first time the EVR + EC-MPS combination from M1 post-LTx with stepwise withdrawal of TAC compared with the TAC + EC- MPS combination. A significant benefit in terms of renal function was reported in the EVR + EC-MPS group, with efficacy of immunosuppression comparable to the standard treatment. These results require confirmation over the longer term.

O30 BELATACEPT-TREATED PATIENTS HAD SUPERIOR GRAFT SURVIVAL COMPARED WITH CYCLOSPORINE-TREATED PATIENTS: FINAL RESULTS FROM BENEFIT

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Introduction: No prospective, phase 3, randomized studies of immunosuppressive regimens has shown a survival advantage over cyclosporine (CsA)-based regimens. At 3 year post-transplant in BENEFIT, renal function was improved in belatacept (bela)-treated vs CsA-treated kidney transplant recipients. We report final 7-yr results from BENEFIT.
Methodology: Pts were randomized to more (MI) or less intense (LI) bela-based or CsA-based immunosuppression. Outcomes were assessed for all randomized, transplanted pts at yr 7. In a prospective analysis, time to death or death-censored graft loss was compared between regimens using Cox regression. Presence of donor-specific antibodies (DSAs) was determined centrally. Kaplan–Meier estimates were calculated for the cumulative rate of de novo (DN) DSA development from randomization to yr 7.
Results: In total, 153/219 bela MI-treated, 163/226 bela LI-treated, and 131/221 CsA-treated pts were evaluable for death/graft loss at yr 7. Hazard ratios comparing time to death/graft loss were 0.573 for bela MI vs CsA (p = 0.02) and 0.570 for bela LI vs CsA (p = 0.02), corresponding to a 43% risk reduction in death/graft loss for bela (MI or LI) vs CsA. Mean MDRD estimated GFR (as observed, ANOVA) at mo 84 for bela MI, bela LI, and CsA was 74, 78, and 51 mL/min/1.73 m², respectively. Cumulative event rates for DN DSAs at yrs 3, 5, and 7 were 1.18%, 1.86%, and 1.86% for bela MI; 3.40%, 4.64%, and 4.64% for bela LI; and 8.72%, 16.19%, and 17.81% for CsA, respectively. The rates of serious AEs were similar across regimens (71%, bela MI; 69%, bela LI; 76%, CsA). PTLD occurred in 3 bela MI-treated, 2 bela LI-treated, and 2 CsA-treated pts; all PTLD cases in bela-treated pts occurred before mo 24.
Conclusions: In this analysis of 7-year results from BENEFIT, bela conferred statistically better graft survival and renal function, with a reduced incidence of DN DSAs vs CsA. The bela safety profile was consistent with prior reports.

O31 LONG-TERM SURVIVAL OUTCOMES IN BELATACEPT-TREATED VS CYCLOSPORINE-TREATED PATIENTS: FINAL RESULTS FROM BENEFIT-EXT

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Introduction: At 3 and 5 year post-transplant in BENEFIT-EXT, renal function benefits and similar pt/graft survival were seen in belatacept (bela)-treated vs cyclosporine (CsA)-treated kidney transplant recipients. We report final 7-year results from BENEFIT-EXT.
Methodology: Recipients of extended criteria donor kidneys received more (MI) or less intense (LI) bela-based or CsA-based immunosuppression. All randomized, transplanted pts were analyzed through 7 year. In this prospective analysis, time to death or death-censored graft loss was compared between regimens using Cox regression. Presence of donor-specific antibodies (DSAs) was determined centrally. Kaplan–Meier estimates were calculated for the cumulative rate of de novo (DN) DSA development from randomization to yr 7.
Results: In total, 128/184 bela MI-treated, 138/175 bela LI-treated, and 108/184 CsA-treated pts were evaluable for death/graft loss at yr 7. HRs comparing time to death/graft loss were 0.915 for bela MI vs CsA (p = 0.65) and 0.927 for bela LI vs CsA (p = 0.70). Mean MDRD estimated GFR (eGFR, as observed, ANOVA) at mo 84 for bela MI, bela LI, and CsA was 58, 59, and 45 mL/min/1.73 m^2, respectively. HRs comparing rates of freedom from death, graft loss, or eGFR <20 mL/min/1.73 m^2 were 0.754 for bela MI vs CsA (p = 0.10) and 0.706 for bela LI vs CsA (p = 0.05). Cumulative rates of DN DSAs at yrs 3, 5, and 7 were 2.32%, 6.21%, and 6.21% for bela MI; 1.52%, 2.39%, and 4.48% for bela LI; and 11.25%, 17.07%, and 22.87% for CsA, respectively. Rates of serious AEs (87%, bela MI; 89%, bela LI; 84%, CsA) and exposure-adjusted incidences of serious infections and malignancies were similar across regimens. Nine PTLD cases were observed prior to mo 84 (n = 2, bela MI; n = 6, bela LI; n = 1, CsA).
Conclusions: At 7 years post-transplant, bela was associated with similar death/graft loss, improved renal function, and a reduced incidence of DN DSAs vs CsA. The bela safety profile was consistent with prior reports.

O32 IMPACT OF THE CALCINEURIN INHIBITORS WITHDRAWAL FOR MYCOPHENOLATE MOFETIL MONOTHERAPY GUIDED BY THERAPEUTIC DRUG MONITORING

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Introduction: CNI (calcineurin inhibitor) induces chronic renal dysfunction but their withdrawal for MMF (Mycophenolate mofetil) monotherapy remains controversial due to an increased risk of acute rejection. To avoid this risk MMF may be monitored and targeted into a safe window guided by therapeutic drug monitoring of mycophenolate acid (MPA). The aim is to evaluate efficacy, safety and benefit of MMF monotherapy in liver transplant patients.
Methods: Between 2000 and 2014, liver transplant patients, with CNI severe side effects, were included and followed prospectively to be treated by MMF monotherapy. Before CNI withdrawal, MMF daily doses were adjusted to reach the MPA target of 45 μg.h/mL. Clinical and biological data as AST, ALT, GGT, PAL, bilirubin, leukocytes and renal function (MDRD) were prospectively collected at CNI withdrawal, M1, 1 year and every year until 5 years. End points were: 1) rate of acute rejection and kinetic of liver enzymes, 2) clinical and biological tolerance of MMF, 3) evolution of renal function after CNI withdrawal.
Results: 122 patients were included. The main cause (70%) for LT was alcohol. MMF monotherapy was conducted on average 6.2 ± 3.8 years after liver transplantation (LT). The main reason for CNI withdrawal was chronic renal dysfunction. Mean MPA AUC was 47.3 ± 17 μg.h/mL. 5 recipients presented an acute rejection (4%). One year after CNI withdrawal, there was no significant change for: AST, ALT, bilirubin, GGT, leukocytes. After 1 year, renal function improved significantly and also in patients with a clearance lower than 60 mL/kg/min and 30 mL/kg/min. The benefit was sustained until 5 years. Patients with a metabolic syndrome did not improve their renal function.
Conclusion: A MMF monotherapy regimen after LT is safe when an AUC at 45 μg.h/mL is targeted before CNI withdrawal. The risk of acute rejection is low. Renal function improves during the first year and maintains until 5 years.

O33 CONVERSION TO EVEROLIMUS (EVL) AFTER LIVER TRANSPLANTATION (LT) IN THE REAL LIFE: DATA FROM THE EVEROLIVER MULTICENTER REGISTRY

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Everolimus (EVL) has been approved for use in de novo LT recipients. The aim of this multicenter study is to analyze the current reasons for conversion, modalities of use in terms of dosage, trough levels, efficacy and safety of EVL in the real life practice.
Patients and Methods: From 2006 till 2012, 557 liver transplant patients from 10 centers were switched to EVL. Data were collected every three months the first year then every 6 months.

Results: Adult recipients (74.2% male) had a mean age of 53 ± 10 years. Mean delay between LT and introduction of EVL was 4.5 ± 5.4 years {median: 2.2 (0–26 years)}. The reasons of introduction of EVL were chronic renal failure (34.9%) treatment of recurrent HCC (7.1%) or de novo cancer (19.7%), prevention of HCC recurrence (14.9%) and various other reasons related to CNI side effects. EVL was introduced with a median dose of 2 mg/day. CNI were withdrawn in 39.6% and 62.9% of the patients respectively at M3 and M12. In the group of patients with an eGFR at baseline ≥60 mL/mn/1.73 m^2 (n = 260) median time from transplant to conversion was 15.8 months, mean eGFR at M24 and M36 didn't differ statistically from baseline. In the group of patients with a chronic renal failure stage 3 at baseline (eGFR <60 mL/mn/1.73 m^2; n = 245) median time from transplant to conversion was 34.9 months, mean eGFR improved statistically from 43.3 ± 9.8 at baseline to 48.2 ± 16.8 mL/mn/1.73 m^2 at M24; p = 0.006). Nine patients (1.6%) developed a histologically proven acute rejection with a median delay of 3.8 months (extremes 1.3–30.8). Patient survival rates of the global population at 1 and 2 years were respectively 91% and 83%.
Conclusion: This real life registry showed that late conversion from CNI to EVL allowed a significant weaning of CNI and a significant improvement of GFR in patients with chronic renal failure with a very low risk of rejection.

O34 ETUDE DE LA VARIABILITÉ INTERINDIVIDUELLE DE LA RÉPONSE PHARMACOCINÉTIQUE AU TACROLIMUS PAR UN SCREENING GÉNÉTIQUE À HAUT DÉBIT

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Introduction: CYP3A4 and CYP3A5 variants explain only a part of the variation in Tacrolimus (Tac) metabolism suggesting the involvement of a wide network of candidate genes. With a high-throughput genetic screening approach, we aimed to identify a set of co-variant germline polymorphisms predictive of the inter-patient Tac pharmacokinetics variability.
Methodology: DNA samples from 280 kidney transplant recipients prospectively followed-up for 3 months were genotyped for 16 561 SNPs using a customized Illumina SNP chip. We used a predictive multivariate approach integrating both a features selection step to reduce the high dimensional feature space (16 561 SNPs) and a regression step (Partial Least Squares) in order to capture the inter-patients variability in log-transformed Tac concentration/dose ratio (C0/Dose) at each time and for all times.
Results: At days 10, 14, 30, 60, 90 and over all days, the predictive models explains 30.5%, 27.5%, 41.5%, 70.2%, 62.9% and 22.9% of total Tac Co/Dose variability with 5, 19, 12, 44, 33 and 16 genes, respectively (p-value <0.003, confirmed by a permutation test). As expected, all the models include CYP3A4 and CYP3A5 variants and highlight that the most enriched pathways in molecular interaction networks are related to oxydoreduction functions and monooxygenase activity. We found an intronic variant of the gene encoding the drug transporter SLC28A3 (C501T, rs10868152) that significantly impacted Tac adjusted doses. Carriers of at least one gene variant (T) displayed significantly higher Tac adjusted dose compared with CC carriers over time, suggesting that SLC28A3 variants might increase Tac biodisponibility. Moreover, we found no linkage disequilibrium for rs10868152.
Conclusion: Our multivariate predictive modelling based on a high-throughput genetic screening approach led us to identify the SLC28A3 polymorphism as a potential candidate gene to explain a part of the Tac pharmacokinetics inter-patients variability.

O35 DONOR AGE, WARM ISCHEMIA TIME AND IMMUNOSUPPRESSIVE DRUGS DIFFERENTLY AFFECT ARTERIAL STIFFNESS IN RENAL TRANSPLANTATION

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Introduction: Some studies suggest that arterial stiffness assessed by pulse wave velocity (PWV) is a risk factor for death in renal transplantation. However, determinants of high PWV are not well known, especially those associated with donor characteristics and immunosuppressive drugs.
Methods: Prospective cohort study in renal transplant recipients included between october 2012 and march 2015. Carotido-femoral PWV was measured using applanation tonometry (SphygmoCor®).
Résultats: 286 patients (age: 52 ± 18, 57.8% men; diabetes: 26.1%, duration of transplantation: 54 ± 73 months; first graft in 88%) were included. Warm ischemia time (WIT) was 52 ± 17 min., cold ischemia time (CIT) was 1013 ± 430 min.; machine perfusion was used in 15.4% of patients. We chose the 75th percentile (i.e. 13.2 m/sec) as the cut-off value for high PWV (PWV was >10 m/sec in half of our population).

In univariate analyses, donor and recipient age at the time of graft, WIT and cardiovascular cause of donor death were associated with high PWV, but not CIT nor the need for machine perfusion use. In multivariate analyses, only donor age (OR: 3.12 [1.23–7.92]; p = 0.0169) and WIT (OR: 1.92 [1.04–3.55], p = 0.0383) were associated with a risk of high PWV.

Among immunosuppressive drugs, calcineurin inhibitors (CNI) were associated with a greater risk (OR: 3.21 [1.42–3.25], p = 0.0048) and mTORi with a lower risk of high PWV (OR: 0.44 [0.21–0.90], p = 0.024), even in multivariate analyses. No significant interaction was noted between CNI and mTORi for the risk of high PWV (OR: 0.66; [0.05–8.06], p = 0.743).
Conclusion: Donor age, warm ischemia time and immunosuppressive drugs affect arterial stiffness in renal transplantation.

O36 IMPROVED BIOAVAILABILITY AND REDUCED DOSE REQUIREMENTS OF ENVARSUS®, NOVEL ONCE-DAILY, MELTDOSE® TACROLIMUS FORMULATION COMPARED TO PROGRAF® (TAC BID, TWICE-DAILY TACROLIMUS), IN DE NOVO KIDNEY TRANSPLANTATION (KTR) PATIENTS: RESULTS OF A PHASE 3 DOUBLE-DUMMY, RANDOMIZED TRIAL

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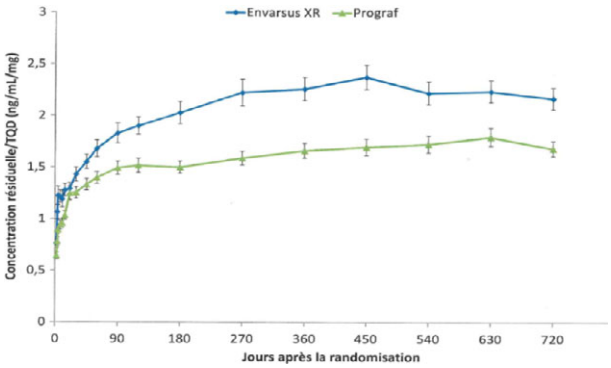
Improved bioavailability and reduced dose requirements of Envarsus®, a novel once-daily, MeltDose® tacrolimus formulation compared to Prograf® (twice-daily tacrolimus), in de novo Kidney Transplant Recipients (KTR): Results of a Phase 3 double-dummy, randomized trial.

Tacrolimus (tac) is an immunosuppressant with a narrow therapeutic range. Adequate trough levels (C0) following kidney transplantation (Tx) (≥6 ng/mL depending on regimen and time post-transplant) are required to prevent rejection while Cmax should not be too high (generally <12 ng/mL) or there is an increased risk for toxicity and adverse events. Contributing to tac dosing challenges are sub-optimal pharmacokinetics (low bioavailability, high fluctuation) of the twice-daily formulation, and differences in tac metabolism among specific patient populations. Envarsus® is an extended-release, once-daily, using MeltDose® drug delivery technology which decreases drug particle size down to a molecular level resulting in improved absorption and once-daily dosing. Randomized trials in de novo and stable KTR have shown increased bioavailability, reduced Cmax with similar efficacy and safety as tac BID, at a 20–30% reduction in total daily dose (TDD).

The purpose of the present analysis was to examine dosing and bioavailability (C0/TDD) of tac over a 2 year period in de novo KTR randomized to Envarsus® (n = 268; initial dosing 0.17 mg/kg/day) or tac BID (n = 275; initial dosing 0.10 mg/kg/day).

Immediately post-Tx, target C0 was more rapidly achieved in the Envarsus® group vs the tac BID group. After dose adjustments (>day 2) TDD were similar between both groups at day 10, but this TDD was 7% lower at day 30, 18% lower at 1 year and 24% lower at 2 years than tac BID with similar C0 throughout the 2-year phase 3 trial (5.5 vs. 5.7 ng/mL at 2 years).

These data show that Envarsus® is associated with continued improved absorption/bioavailability, resulting in the requirement for a lower TDD vs. tac BID, over 2 years.



O37 EFFICACY AND SAFETY OF SOFOSBUVIR-BASED ANTIVIRAL THERAPY TO TREAT HEPATITIS C VIRUS INFECTION AFTER KIDNEY TRANSPLANTATION

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Hepatitis C virus (HCV) infection is responsible in kidney-tranplant recipients for decreased survival of patients and kidney allografts, increased liver fibrosis, increased infection rates, new-onset diabetes mellitus, and cardiovascular disease. There is no approved therapy for HCV infection after kidney transplantation, and no data regarding the use of new-generation direct antiviral agents (DAAs) have been published so far. The aims of this pilot study were to assess the efficacy and safety of an interferon-free sofosbuvir-based regimen to treat chronic HCV infection in kidney-transplant patients.

Twenty-five kidney-transplant patients with chronic HCV infection were given for 12 (n = 19) or 24 weeks (n = 6): sofosbuvir plus ribavirin (n = 3); sofosbuvir plus daclatasvir (n = 4); sofosbuvir plus simeprevir, with (n = 1) or without ribavirin (n = 6); sofosbuvir plus ledipasvir, with (n = 1) or without ribavirin (n = 9); and sofosbuvir plus pegylated-interferon (PegasysÒ, Roche) plus ribavirin (n = 1).

A rapid virological response defined by undetectable viremia at week 4 after starting DAA therapy was observed in 22 of the 25 patients (88%). At the end of therapy, HCV RNA was undetectable in all patients. At 4 and 12 weeks after completing DAA therapy, all had a sustained virological response. The tolerance to anti-HCV therapy was excellent and no adverse event was observed, especially no acute-rejection episode or graft loss was noticed during therapy. However, the monitoring of immunosuppressive drug levels has showed a decrease in tacrolimus trough levels after HCV clearance. Hence, physicians should monitor calcineurin inhibitors and increase their doses if necessary.

This is the first study to assess the efficacy of new-generation DAAs in a large population of HCV-positive RNA-positive kidney-transplant patients. DAA therapy is efficient and safe to treat HCV infection after kidney transplantation.

O38 RENAL DYSFUNCTION IN LIVER TRANSPLANT RECIPENTS TREATED WITH SOFOSBUVIR-BASED THERAPY FOR HCV RECURRENCE: RESULTS FROM THE FRENCH PROSPECTIVE MULTICENTRIC STUDY ANRS CO23 CUPILT

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Introduction: Recent data suggested that renal dysfunction could occur among liver transplant (LT) patients treated with second-generation direct acting antiviral (DAA). The aim of the present study was to evaluate renal function before, during and after DAA treatment.

Patients and Methods: The study population included 204 (156 M/48 W) patients, aged 58.6 ± 8.9 years. Patients received sofosbuvir (SOF) + ribavirin (RBV) in 17.6% or SOF + daclatasvir (49%) or SOF + daclatasvir + RBV (33.3%). Mean duration between LT and initiation of DAA was 72.1 ± 70.5 months. The overall SVR rate at 12 weeks was 97.4%. A renal dysfunction (RD) was defined according to the stage 1 RIFLE criteria: decrease of 25% of the glomerular filtration rate (GFR) estimated from MDRD formula.

Results: Ciclosporine, tacrolimus, everolimus, mycophenolate mofetil was used in 27.9%, 60.3%, 7.4% an 53.9% of the patients, respectively. Combined liver-kidney transplant was performed in 3.4%. High blood pressure was present in 49.5%, type 2 diabetes in 36.3%, a cardio-vascular disease in 20.1%, a renal disease in 27%. A RD was observed in 37.1% of the patients, including 10.9% with a persistent RD after the end of DAA therapy. The presence of a preexisting renal disease (OR = 2.31(1.23–4.37), p = 0.01), a fibrosing cholestatic hepatitis (FCH) (OR = 3.84 (1.53–9.67), p = 0.026) or a combined liver-kidney transplantation (OR = 11.0 (1.3–92.9), p = 0.028) were significant predictive factors of RD. FCH (OR = 10.3 (2.73–39.0), p = 0.0005) and baseline GFR (OR = 1.03 (1.01–1.05), p = 0.003) were independently associated with a persistent RD at the last visit of follow-up. Ribavirin or daclatasvir use, immunosuppressive drugs and metabolic factors had no impact on the occurrence of RD.

Conclusion: In our large cohort, a RD was frequent. A renal disease before DAA treatment and the presence of FCH were the two main risk factors. Intensive renal function monitoring should be done in those patients.

O39 RISK FACTORS OF NOCARDIOSIS AFTER SOLID ORGAN TRANSPLANTATION: RESULTS FROM THE FIRST EUROPEAN RETROSPECTIVE CASE-CONTROL STUDY

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Introduction: Nocardiosis are rare and life-threatening opportunistic bacterial infections occurring after 0.1 to 3.5% of solid organ transplantations (SOT). We aimed to assess the risk factors of nocardiosis after SOT.

Methods: We performed a European (France, Belgium, Switzerland, Netherlands, Spain) retrospective matched case-control study including cases of nocardiosis after SOT diagnosed between 2000 and 2014. Two control subjects were matched per case according to center and transplanted organ. Significant variables (p-value <0.05) identified by univariate analysis were included in a multivariate analysis using conditional logistic regression.

Results: One hundred and seventeen cases and 234 matched controls were included. In the 6 months preceding the diagnosis of nocardiosis, percentages of patients who experienced acute allograft rejection, received high-dose corticotherapy, or had a CMV infection were respectively 21.6% (25/116), 17.2% (20/116) and 14.5% (17/117), respectively. In the month preceding nocardiosis, an elevated calcineurin inhibitors level was observed in 43.6% (51/117) of the cases. At time of diagnosis, mean dose of methylprednisolone was 8.8 ± 6.8 mg, and 18% (21/117) of the cases were receiving cotrimoxazole prophylaxis. After multivariate analysis, variables statistically associated with the occurrence of nocardiosis were elevated calcineurin inhibitors level (OR = 6.11 [2.58–14.51]), use of tacrolimus (OR = 2.65 [1.17–6.00]), the dose of corticosteroids at the time of diagnosis (OR = 1.12 [1.03–1.22]), age (OR = 1.04 [1.02–1.07]), and length of stay in intensive care unit after SOT (OR = 1.04 [1.00–1.09]). After multivariate analysis, cotrimoxazole prophylaxis did not appear to be protective.

Conclusion: We identified 5 risk factors of nocardiosis and observed that low-dose cotrimoxazole did not prevent Nocardia infection. These findings may help to improve the management of SOT recipients.

O40 KINETICS, ANTIBIORESISTANCE AND MOLECULAR EPIDEMIOLOGY OF *ESCHERICHIA COLI* URINARY TRACT INFECTIONS IN KIDNEY TRANSPLANT RECIPIENTS: THE PREDICOLI STUDY

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Introduction: Urinary tract infections (UTI) are very common after kidney transplantation (KT) and frequently involve Escherichia coli strains of digestive origin. In immunocompetent hosts, uropathogenic strains usually belong to specific phylogenetic groups that are different from those of commensal strains. In this work, we compared the molecular epidemiology and antibioresistance of E. coli strains isolated from UTIs and from the feces of the host. We used it to infer the kinetics of UTIs.

Methods: Fecal samples were collected before KT and at each UTI episode during the 1st 6 months after KT in all the patients of our institution in 2013. Samples from patients who presented at least one E. coli UTI and whose samples were all technically acceptable were analyzed. 20 E. coli colonies per stool and 5 colonies per urine were characterized: identification of unique strains and determination of phylogenetic group by PCR, and determination of antibioresistance by antibiogram.
Results: 7 patients presented 1 UTI and 4 presented 2 UTIs (11 patients and 15 UTIs in total). The 11 stool samples collected before KT and the 16 stool samples collected at the time of each UTI were analyzed. In 11 UTIs (73%), the urinary strain was present in the feces at the time of infection, in 6 cases (40%) it was the dominant fecal strain, and in 2 cases only, the urinary strain was present in the feces collected before KT. Urinary strains belonged equally to phylogroups usually associated with commensalism and to phylogroups usually associated with uropathogenicity. Antibioresistance of urinary strains was high: amoxicillin: 95%, ofloxacine: 30% and cotrimoxazole (used as prophylaxis): 100%. The proportion of strains resistant to at least 3 antibiotics increased from 13.8% before KT to 57% after ($p < 0.005$)
Conclusion: UTI strains are usually acquired in the gut after KT and involve resistant strains that frequently belong to phylogroups usually associated with commensalism.

O41 RISK OF BKV VIREMIA IS NOT PREDICTABLE BEFORE KIDNEY TRANSPLANTATION WITH USUAL CLINICAL AND BIOLOGICAL DATA

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Introduction: BKV viremia got ahead of BKV nephropathy which can lead to graft loss. This infection is due to over immunosuppression. Identification of risk factors of BKV viremia could lead to best choice of immunosuppressive strategy.
Patients and methods: All consecutive kidney transplant patients with BKV viremia monitored by quantitative PCR and follow-up >3 months have been included in this single-center retrospective study. We excluded 2 patients: lack of BKV viremia monitoring (n = 1) and one patient in whom viremia preceded the graft. We reviewed the individual files for immunosuppressive treatments, clinical biological and histological data.
Results: We analyzed 314 patients (age = 53 ± 16 years, sex ratio = 1.84, first graft = 86%, anti-HLA before transplantation = 36%). Among them, 39% received anti-thymocytes globulins. Maintenance immunosuppressive regimen based on tacrolimus (79%), cyclosporin (16%) or a mTOR inhibitor. At the first viremia, eGFR was 45.5 ± 19.0 mL/min, while 31 patients received tacrolimus (trough level = 7.8 ± 2.3 μg/mL), 6 cyclosporin (T + 2H = 673 ± 170 μg/mL) and 12 a mTOR inhibitor (T0 = 8.4 ± 2.4 μg/mL). Interestingly, delay between transplantation and viremia was higher in patients treated by mTOR inhibitor than cyclosporin (5.5 ± 3.6 versus 2.8 ± 1.9 months, p = 0.048). However, de novo use of mTOR inhibitors did not prevent risk of viremia (OR = 1.989 [0.784–5.049], p = 0.148). Finally, none pre-transplant parameters was associated with BKV viremia occurrence, even pre-transplant B and T lymphocytes number.
Conclusion: None pre-transplant clinical and biological data can be used to stratify risk of BKV viremia.

O42 FAVORABLE OUTCOME OF LATE-ONSET CMV DISEASE IN D + R- KIDNEY TRANSPLANT RECIPIENTS TREATED WITH UNIVERSAL PROPHYLAXIS

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Introduction: Universal prophylaxis and preemptive strategy are both recommanded for the prevention of cytomegalovirus (CMV) disease after organ transplantation. Universal prophylaxis is used in most of the centers but leads to higher incidence of late-onset CMV disease (LOD), which has been associated with poor patient and graft survival in kidney transplant recipients (KTR). The purpose of this retrospective study was to reappraise the impact of LOD in KTR with the highest risk for CMV infection, seronegative recipients transplanted with a seropositive donor (D + R-). Methods? Early-onset disease (EOD) was defined as the first episode of CMV disease occurring before 3 months and LOD after 3 months post-transplantation. According to the period, either universal prophylaxis or preemptive treatment was used for CMV prevention.
Results: 168 D + R- KTR were included between 2003 and 2011, 36 with LOD, 41 with EOD and 91 without disease. 86% of LOD occurred after universal prophylaxis whereas 83% of EOD occurred after preemptive strategy (χ^2; $p < 0.0001$). Compared to patients with EOD, patients with LOD had shorter treatment to obtain eradication, less mutation, lower peak viral load, less viral (Odd Ratio = 0.09; 95% CI = 0.03–0.25; p = 0.001) and clinical recurrences (Odd Ratio = 0.16; 95% CI = 0.05–0.55; p = 0.01). Furthermore, at three year post-transplantation, LOD, EOD and no disease were not significantly different for acute rejection (33.3%, 26.8% and 24.2%; p = 0.6), graft failure (8.3%, 14.6% and 7.7%; p = 0.29) and patient's death (2.8%, 2.4% and 0%; p = 0.3). In D+R- KTR, universal prophylaxis is associated with more LOD which had a better infection management, and no detrimental effect on graft and patient outcomes, than EOD.
Conclusion: These results support the use of universal prophylaxis over a preemptive strategy and reappraise the outcome of LOD previously associated with a worst prognostic in D+R- KTR.

O43 NON-INVASIVE DIAGNOSIS OF BK VIRUS-ASSOCIATED NEPHROPATHY BY USING THE URINARY PEPTIDOME

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Introduction: Analysis of urinary peptides derived from kidney allografts could allow non-invasive diagnosis of opportunistic infectious complications. The aim of this study is to diagnose BK virus-associated nephropathy (BKvN) by means of the urinary peptidome in a case-control study.
Material and methods: Urine was collected prior to allograft biopsy. BKvN « cases » were defined as having SV40 positive biopsy immunostainings, « controls » were defined by the absence of viremia and viruria. When the status for BKvN was uncertain, samples were excluded from the main analysis (« uncertain diagnosis » group). We used capillary electrophoresis coupled to mass spectrometry (CE-MS) to characterize the naturally occurring (non trypsinized) urinary peptides. A bioinformatic model known as « Support Vector Machine » (SVM) was established with the most discriminative peptide candidates.
Results: 116 urine samples were analyzed, comprising 25 BKvN cases, 52 controls and 39 uncertain diagnoses. Cases and controls were grouped as a training (20 cases, 41 controls) and a validation set (5 cases, 11 controls). In the training set, 34 peptides reached $p < 0.20$ in False Discovery Rate statistics and were considered as peptide biomarker candidates for BKvN. In order to establish a predictive bioinformatic model with these 34 peptides, correlation analyis was performed in the training set to identify and remove peptides associated with both NBKv and confounding factors. The final model consisting of 15 peptides allowed to correctly classify all 5 NBKv and 10 out of 11 controls in an independent validation cohort, yielding an area under the curve of 0.927. T cell-mediated acute rejection cases were well diagnosed in the training and validation cohorts.
Conclusion : 15 urinary peptides allowed to build a multi-peptide biomarker to detect BKvN without biopsy.

O44 INTERLABORATORY COMPARISON OF BK VIRUS DNA LOAD MEASUREMENT: IMPACT OF VIRAL POLYMORPHISM

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Introduction: International guidelines recommend screening of kidney transplant recipients for BK virus (BKV) replication and define BKV viremia ≥4 log 10 copies/mL as presumptive BKV-associated nephropathy (BKVN) and a cutoff for therapeutic intervention. Hence, BKV DNA load (BKVL) assays need to be comparable to ensure appropriate patient care.
Methods: To assess interlaboratory variability in BKV viruria and viremia testing, 27 laboratories were sent 15 (5 urine, 5 whole blood and 5 plasma) and 8 (4 urine, 2 whole blood and 2 plasma) clinical specimens in 2013 and 2014, respectively. Samples harboring single or multiple BKV genotypes, including minor genotypes II and IV, were chosen to represent a wide range of BKV DNA concentrations.
Results: High interlaboratory variability was observed, with a variation ranging from 1.32 to 5.55 log 10 copies/mL (mean = 2.61 log 10 copies/mL). Nevertheless, 68% of the reported results fell within the acceptable range of the expected result ±0.5 log 10. BKV genotype II and IV specific polymorphism, namely the number and position of mutations in amplification target genes, and/or deletion in standards arose as major sources of interlaboratory disagreements. The diversity of DNA purification methods also contributed to the interlaboratory variability, in particular for urine samples. Our data strongly suggest that commercial external quality controls for BKVL assessment should include all major BKV genotypes to allow the correct evaluation of BKV assays. Moreover, the BKV sequence of commercial standards should be provided to

users to verify the absence of mismatches with primers and probes of their BKV assays.
Conclusion: Optimization of primer and probe design and standardization of DNA extraction methods may substantially decrease interlaboratory variability and allow interinstitutional studies to define a universal cutoff for presumptive BKVN and ultimately ensure adequate patient care.

O45 ARE CIRRHOTIC PATIENTS AWAITING LIVER TRANSPLANTATION PROTECTED AGAINST VACCINE PREVENTABLE DISEASES?

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Cirrhotic patients are spontaneously immunocompromised and are at increased risk of infection. Vaccination may reduce the mortality related to infectious complications in those patients. Few data regarding vaccination are available in cirrhotic patients awaiting liver transplantation (LT).

The aim of this study was to prospectively assess the prevalence of hepatitis A, B and varicella viruses (HAV,HBV,VZV) serological markers and to evaluate the immunization status in a cohort of cirrhotic patient awaiting LT to determine the need of vaccination.

All the cirrhotic patients registered on the LT waiting list in a single center were questioned about vaccinations. ELISA method was used to assess HBsAg, anti-HBc, anti-HBs, anti-HAV and anti-VZV antibodies, positivity was defined as: HBsAg ≥1 mUI/mL, anti-HBs ≥10 mUI/L, anti-HBc ≥1 mUI/L, anti-HAV(IgG) ≥1 mUI/mL and anti-VZV(IgG) ≥165 mUI/mL for HBV, HAV and VZV viruses, respectively.

201 patients (age: 54 ± 11 years) have been evaluated. The indication for LT was HCV-related cirrhosis (42.4%), HBV cirrhosis (9%), alcoholic cirrhosis (43.1%), NASH (6.1%) and hepatocellular carcinoma (42%). Forty-five percent were class A, 33.2% B and 18.9% C according to Child-Pugh score; median MELD score was 12 (6–33). Only 2.5% of patients had a vaccination book, 50% were anaware of having or having not a pasthistory of HBV, HAV or VZV infection. Twenty-nine percent, 6.7% and 4.0%, respectively, reported a vaccination against HBV, HAV and VZV. Seroprevalence was 11% for HBsAg, 32.2% for anti-HBc, 34% for anti-HBs, 19.8% for anti-HBc-/anti-HBs+, 79.4% for anti-HAV and 91.7% for anti-VZV.

Despite vaccination recommendations in cirrhotic patients awaiting LT, only few patients are informed and vaccinated while on the LT waiting list in a large Parisian center. Serological protection for VZV and HAV was high (91.7 and 79.4 respectively), but it was low for HBV (34%), demonstrating the urgent need of vaccination management in this population.

O46 IS THERE A PLACE FOR THE ANALYSIS OF DSA ABILITY TO FIX C1Q AFTER KIDNEY TRANSPLANTATION IN 2015?

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The analysis of the ability to fix c1q by the DSA could be a way to better evaluate the potential deleterious impact of a DSA on the allograft. We have evaluated the significance of this test in a cohort of kidney transplant patients with DSA who underwent a graft biopsy.
Patients and methods: In a cross sectional study of 943 patients with a sera tested in 2011 by Luminex assay (Lab. One Lambda), we identified by Single Antigen 127 recipients with at least one DSA for which we analysed the capacity of fixing c1q. Among these DSA+ patients, 89 had an allograft biopsy. In this cohort, we correlated MFI in SA, C1q positivity and histological features.
Results: There was an excellent correlation between MFI in SA and c1q positivity. All DSA with MFI < 5000 were c1q- and all DSA with MFI >10 000 were c1q+. When MFI was between 5000 and 10 000, around 50% of DSA were c1q+. Among patients with MFI <5000 (n = 33), 17 developed an antibody mediated rejection (ABMR) and 16 had no humoral lesions. Among patients with MFI >10 000 (n = 34), 29 patients developed an ABMR and 5 have normal biopsy. When MFI was between 5000 and 10 000 (n = 21), 14 (8 with c1q+DSA) had ABMR and 7 (5 with c1q-DSA) no feature of ABMR. In this latter group (5000–10 000), the c1q analysis should have an interest to better evaluate the DSA toxicity whereas in the 2 other groups (MFI <5000 and MFI >10 000, 77% of the cohort), c1q assay did not give supplementary information compared to MFI in SA.
Conclusion: DSA c1q fixation, evaluated by Luminex assay, is strongly correlated to DSA MFI in SA. For this reason, this expensive test does not seem to have a great interest when MFI are weak (<5000) or strong (>10 000). When MFI are in-between, c1q assay could help to evaluate the potential toxicity of DSA on the allograft.

O47 C3D DSA WITH HIGH MFI IS ASSOCIATED WITH A HIGHER RATE OF GRAFT LOSS IN A PEDIATRIC COHORT OF LT PATIENTS

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The incidence and the clinical impact of DSAs developed after liver transplantation remain controversial and have not been extensively studied, especially in pediatric populations.

This cross-sectional study included 100 nonconsecutive patients who underwent a first LT in childhood (<18 years old at LT) and alive one year or more after LT. Anti HLA immunization study was performed using Luminex Single Ag tests (Immucor) with classical anti-IgG conjugate and new anti-C3d conjugate.

Forty five percent of the patients were male with a median age at LT of 4.6 years. The main indication for LT was biliary atresia (52%). The median time after LT for DSA assessment was 7.8 years (range 1 month–21 years). Twenty-four patients (24%) developed de novo DSA after LT with a prevalence for DSA of 8%, 28%, 33%, 50% respectively 0–5, 5–10, 10–15 and >15 years post LT. De novo DSA were mainly class II (23/24) with a mean MFI of 9.731 ± 5.489 and 18 (79.2%) were C3d-binding DSA.

In univariate analysis, combined liver-kidney transplantation and initial immunosuppression (use of FK, MMF, anti IL2R) were associated with a lower rate of DSA, whereas history of fulminant hepatitis and time elapsed since LT were associated with a higher rate of DSA. Multivariate analysis disclosed that time elapsed since LT ($p < 0.001$) and history of fulminant hepatitis ($p = 0.041$) remained statistically significant.

Liver function tests (at time of DSA assessment) were not different in groups with or without DSA. Patient survival and graft survival were similar between groups, however patients with C3d-positive DSA MFI >10 000 had a significant poorer long-term graft survival ($p = 0.027$).

In conclusion, in our pediatric cohort of LT, prevalence of DSA is high and increases regularly with time. C3d positive-DSA with high MFI are associated with a higher rate of graft loss.

O48 LUMINEX SINGLE ANTIGEN ASSAYS CAN MISS CYTOTOXIC ANTIBODIES

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Introduction: The prozone effect, i.e. the underestimation of anti-HLA antibodies (AHA) by Luminex Single Antigen (SA) assays due to complement activation in particular, has been described. This study highlights the risk of missing antibodies by SA, although they are detected by complement-dependent cytotoxicity (CDC).
Methods: We identified AHA in 46 sera from highly sensitized patients in which we suspected a prozone effect by CDC and by SA (One Lambda, CA), either per manufacturer's recommendations (neat serum) or after 1:10 and 1:50 dilutions in the LS-NC negative control (One Lambda) or after EDTA 8.125 mM in PBS treatment. Normalized Median Fluorescence Intensity (MFI) was compared specificity by specificity. The prozone effect was defined as the underestimation of MFI beyond the inherent variability of the method.
Results: The MFI of most of the specificities decreased after serum dilution but prozone effect was revealed for 11.0% of them by dilution. EDTA treatment revealed 20.0% of prozone-prone specificities, but did not affect the MFI of the other specificities significantly. In the 46 tested sera, respectively 21 and 15 AHA that were missed by SA in neat serum were positive after 1:10 and 1:50 dilution and 114 AHA were positive after EDTA treatment, including 38 with MFI above 10 000, inclusive of 19 CDC-identified AHA (0.37% of assessed specificities).
Conclusion: Performing SA on neat sera poses an important risk of false negatives in highly sensitized patients, especially concerning cytotoxic antibodies that are associated with positive cross-matches. Serum treatment by EDTA controlled that risk in all of the studied cases, without decreasing the sensitivity of the method. Therefore we recommend it, especially when transplantation is performed before the results of the cross-match are available.

O49 DESCRIPTIVE ANALYSIS OF ANTI-HLA IMMUNIZATION IN A FRENCH COHORT OF LIVER TRANSPLANT CANDIDATES

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Anti-HLA sensitization is not taken into account before liver transplantation (LT) in France, where no cohort has been described yet. Within SFT-SFHI national working group, we assess the prevalence of preformed anti-HLA antibodies (AHA) in a French cohort of LT candidates.

This study included all patients who had their first or second LT between 2009 and mid-2015 at Hôpital Mondor and had available pre-LT serum and donor/recipient HLA typing. Multi-organ transplantations were excluded. AHA were screened (cut-off = 2) and then identified on single antigen beads (LABScreen, OL) at Hôpital Saint-Louis.

We analyzed 420 sera from 380 patients (sex ratio = 3.2; median age = 56 years) collected 138 days before LT on average. Main indications for transplantation were hepatocellular carcinoma (38%) and alcoholic cirrhosis (15%). Class 1 and 2 AHA were detected in 46% and 28% of patients and were more frequent in female than in male patients ($p < .001$). In class 1 AHA, 87.7% of AHA screenings had a ratio below the cut-off of 88, below which detecting AHA by CDC is unlikely (data not shown). The prevalence of DSA was 15.7% in class 1 and 20.5% in class 2, with median Median Fluorescence Intensities (MFI) of 1470 and 1300, respectively. The frequency of patients with DSA which maximum MFI and MFI sum were over 10 000 (or over 5000) were 3.3% (7.1%), and 4.0% (8.1%), respectively.

Class 1 and 2 DSA were identified in 16% and 20% of French LT candidates but, according to the literature, the prevalence of potentially liver transplant harming DSA was low: 3% and 7% with a MFI cut-off of 10 000 and 5000, respectively. This could explain the challenge of showing a detrimental effect of DSA in LT. We are currently assessing the impact of DSA with the highest MFI.

O50 INFLUENCE OF TEST TECHNIQUE ON DSA DETECTION AND ANTIBODY MEDIATED REJECTION DIAGNOSIS IN KIDNEY TRANSPLANTATION

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Introduction: Donor specific HLA antibody (DSA) is a major element of the diagnosis and treatment of antibody mediated rejection in kidney transplantation.
Materials and methods: We retrospectively studied kidney transplant recipients with a graft biopsy highly suggestive of antibody mediated rejection (g+cpt >3) and compared the results of 2 DSA Luminex detection tests on synchronous sera: One Lambda LABSCREEN single antigen (test 1: DSA + if MFI >500) and Immucor LIFECODES single antigen (test 2; DSA + if at least 2 positive items among BCM >1500, BCR >4, AD-BCR >5).
Results: Fifty patients had a kidney graft biopsy performed 2.8 years ± 2.5 (0.03–9.2) after transplantation, for graft dysfunction in 68% of cases. Mean microvascular inflammation score (g + cpt) was 3.5 ± 0.7 (3–6). Test 1 detected at least one DSA in 44 patients (88%) and test 2 in 37 patients (74%) ($p = 0.001$). Mean number of DSA was 1.90 ± 0.20 with test 1 and 1.32 ± 0.18 with test 2 ($p < 0.05$). Test 1 highlighted 95 DSA (39 class I et 56 class II; mean MFI 5459, 563–21 598) and test 2 66 DSA (21 class I and 45 class II; mean BCM 5207, 213–18 405; mean BCR: 49.3, 3.5–319.2; AD-BCR: 61.0, 3.5–354.2) ($p = 0.001$). Thirty seven DSA were only detected with test 1 exclusively (21 class I and 16 class II) versus 8 with test 2 exclusively (3 class I and 5 class II). The 2 tests showed exactly the same results in only 21 patients (42%).
Conclusion: To our knowlegde, it is the first report comparing the 2 DSA detection tests actually available. In a context highly suggestive of humoral rejection, One Lambda LABSCREEN single antigen test was more efficient for the diagnosis of antibody mediated rejection.

O51 CLASS 2 C3D-FIXING DONOR-SPECIFIC HLA ANTIBODY DETECTION IS CORRELATED TO LUMINEX MFI (MEAN FLUORESCENCE INTENSITY)

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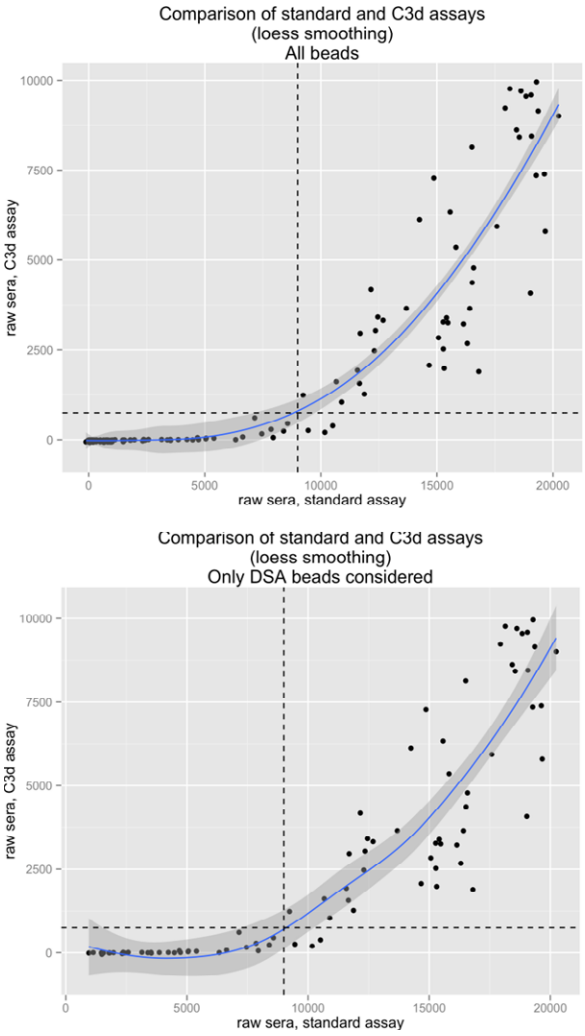
Introduction: Chronic antibody–mediated rejection is one of the main causes of kidney graft loss and therefore early diagnosis is an important part of patient follow-up. Diagnosis is made when donor-specific antibodies (DSA) are found in the graft patient's serum. Single-antigen (SA) Luminex assays are becoming the gold standard to identify specific antibodies. While semi-quantitative, this method provides an estimation of the amount of antibody by mean fluorescence intensity measurement (MFI). Recently, C3d-fixing antibodies were shown to be associated with a worse clinical outcome. It is suggested to use C3d fixing antibody detection kits (C3dDSA) in order to identify more aggressive antibodies.In this work, we compared C3dDSA to standard MFI in a cohort of patients having developed de novo class 2 DSA in order to investigate determinants of C3dDSA positivity.
Methods: We included kidney transplant recipients transplanted between January 2005 and January 2015 in our center, who developed de novo class 2 DSA. Their serum was then tested by standard SA Luminex technique and by C3d-fixing antibody detection system (IMMUCOR®) according to the manufacturer's instructions. A MFI threshold of 1500 was considered for positivity in the case of standard SA Luminex, while a threshold of 750 was used for C3dDSA.
Results: 41 patients were found to have developed class 2 DSA. 65 serum samples were analyzed. Among them, 43 serum samples were negative for C3dDSA (66%). An MFI threshold of 9000 in SA Luminex assay permitted to discern all the negative from the positive C3dDSA. This also holds true when all single bead results are taken into account.
Conclusion: Our results show that C3d fixing antibody detection is highly correlated to SA Luminex MFI. These results could infer that complement activation by class II antibodies depends more on antibody concentration rather than some antibody properties. A correlation study of MFI with clinical patient status is underway.



O52 ROLE OF DONOR SPECIFIC ANTIBODIES IN PROTOCOL LIVER BIOPSIES FOLLOWING PEDIATRIC LIVER TRANSPLANTATION

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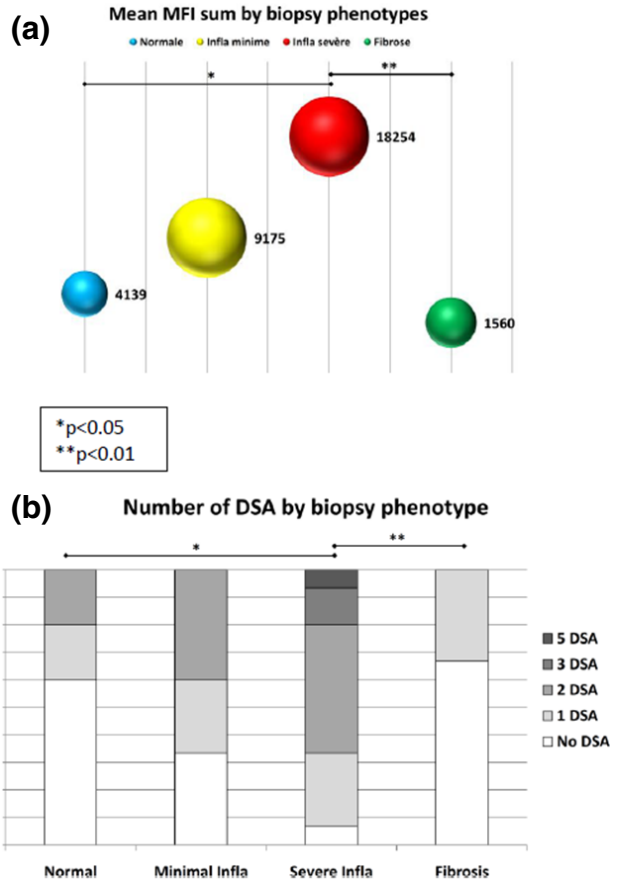
The role of donor specific antibodies (DSA) in the subclinical lesions observed in the liver allograft of long-term pediatric liver transplant (pLT) survivors is unclear.The aim of the study was to analyze the association between DSA and the histological phenotypes of protocol liver biopsies using a retrospective chart review

41 biopsies were classified as normal (n = 5), fibrosis (n = 6), minimal inflammation (n = 15) and severe inflammation (N = 15). Age at pLT or time at biopsy did not differ between histological sub-groups. 68% of patients had DSA Significantly more patients with DSA had severe inflammation on biopsy. Severe inflammatory biopsies had larger number of DSA at biopsy. MFI were also significantly more important in mild-severe inflammation in comparison to normal or fibrotic biopsies (Figure 1A & B).

In our cohort, protocol biopsies were mostly abnormal (88%) with inflammation predominating. Our data suggest a role for DSA in inflammation. Indeed, the presence of DSA, the number of DSA and the MFI were associated with severe inflammation.

Image 1A & B::



O53 IMPACT OF BLOOD TRANSFUSION AFTER KIDNEY TRANSPLANTATION ON THE INCIDENCE OF DONOR SPECIFIC ANTI-HLA ANTIBODIES

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Little is known about the impact of post-transplant blood transfusion on the sensitization of anti-HLA antibodies and the formation of donor-specific antibodies (DSAs). The aims of our study were to determine the 1-year incidence of DSAs (assessed using the highly sensitive Luminex SA assay) and antibody-mediated rejection (AMR) in a large population of kidney-transplant patients that had needed a blood transfusion during the first year post-transplantation.

Included were 397 pre-transplant non-HLA sensitized patients who had received an ABO-compatible kidney transplant, had not previously or simultaneously received a non-kidney transplant, and had a functioning graft at month 1 post-transplant.

Sixty-five percent of patients received a red blood-cell transfusion within the first year post-transplantation, mostly within the first month. The overall 1-year incidence of DSAs was significantly higher in patients that had undergone transfusion (8.2% vs. 0.7% in patients with no transfusion). Blood transfusion was an independent predictive factor for de novo DSA formation but not for AMR. Patients who had a transfusion and developed DSAs were more often treated with cyclosporin A rather than tacrolimus.

In conclusion, post-transplant blood transfusion may increase the immunological risk.

O54 ALLOGRAFT NEPHRECTOMY IS RESPONSIBLE FOR A DELAYED SENSITIZATION AGAINST DONOR UNRELATED TO HLA ANTIBODIES GRAFT ADSORPTION

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Background: The mechanism leading to the appearance of anti-HLA antibodies and donor-specific antibodies (DSAs) after an allograft nephrectomy (NTx) is not fully understood. Two mechanisms have been advocated: (i) at graft loss, DSAs are not detected in the serum because they are fixed on the non-functional transplant, and appeared after NTx; (ii) NTx itself is responsible for de novo anti-HLA immunization against residual donor tissue. The aims of our study were to compare anti-HLA antibodies present in the serum and graft at the time of an allograft nephrectomy, and to assess the timing and kinetics of their appearance after an allograft nephrectomy.

Methods: Seventeen patients have undergone NTx, 4 (3–33) months after graft loss. Immunosuppression had been stopped in all patients at least three months before NTx. Anti-HLA antibodies were assessed in the serum before, and 1, 5, 30, and 90 days after NTx. In addition, fragments of the removed kidney allograft were eluted to characterized intra-graft anti-HLA Abs. Anti-HLA antibodies were analyzed using the Luminex Single antigen assay.

Results: On 14 patients with anti-HLA antibodies in the serum at NTx, 11 patients had anti-HLA antibodies fixed in the kidney allograft. No anti-HLA antibodies were detected in the graft if they were also not detected in the serum. Eleven of the 12 patients who had DSAs detected in their sera also had DSAs detected in the grafts. A positive C4d staining was positive in 9 of the 11 patients. Epitopic analysis revealed that most anti-HLA antibodies detected in removed grafts were directed against the donor. All de novo Anti-HLA antibodies and DSAs were detected ≥1 month after NTx. None of the de novo anti-HLA antibodies had been previously detected in the graft.

Conclusion: Our data suggest that anti-HLA sensitization after NTx is related to the NTx itself rather than an anti-HLA antibodies adsorption from the failed kidney.

O55 TORQUETENOVIRUS (TTV) LOAD IN BLOOD AS A MARKER OF IMMUNOSUPPRESSION IN KIDNEY TRANSPLANT RECIPIENTS

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Torquetenovirus (TTV) is a DNA virus belonging to the Anelloviridae family, highly prevalent in the general population. The potential pathogenicity of TTV remains to be clearly established. However, no pathological role has been demonstrated so far. This study aimed at investigating whether TTV viral load (VL) in blood could reflect the level of immunosuppression of kidney transplant recipients and constitute a virological marker for the occurrence of opportunistic viral reactivations during the posttransplantation period.

TTV DNA was quantified retrospectively by real-time PCR in whole blood specimens from 63 consecutive kidney transplant recipients at 0, 3, 6, 9, and 12 months posttransplantation.

Four [3–5] blood specimens per patient were analyzed. TTV was detected in 96.4% of all 254 blood samples tested (median load = 6.85 log copies/mL). TTV VL was not influenced by gender or age of patients but increased significantly (>3 log) up to 3 months posttransplantation, and plateaued thereafter. Immunosuppressive induction therapy (anti-lymphocyte immune globulin or basiliximab) had no influence on the peak of TTV VL. TTV VL varied according to concentrations of tacrolimus (maintenance treatment), lymphocyte and neutrophil counts, creatinine concentration, and valganciclovir treatments. Among all patients, 19 and 39 experienced BK virus (BKV) and cytomegalovirus (CMV) infections. TTV VL was significantly higher when CMV and BKV VL were over 500 IU/mL and 500 copies/mL. TTV was subtyped among 59 patients: genogroups 3 and 4 were the most prevalent, and 81% of patients were coinfected by at leats 2 different genogroups. TTV VL was significantly higher among patients carrying 4 or 5 different genogroups.

These results provide evidence that the monitoring of TTV load in blood may constitute a useful tool to guide immunosuppressive therapy in kidney transplant recipients and to identify patients at risk for viral infections during the posttransplantation period.

O56 EFFECT OF HUMAN LEUCOCYTE MICROPARTICULES IN THE EPITHELIAL-MESENCHYMAL TRANSITION OF BRONCHIAL CELLS. INTEREST IN LUNG TRANSPLANTATION

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Introduction: After lung transplantation, bronchial epithelium is subjected to infectious and immunological agresions leading to Epithelial-mesenchymal transition (EMT) responsible of Bronchiolitis obliterans. Microparticles (MPs), membrane fragments produced by cells in response to stress could contribute to the EMT.

Material and methods: Human CEM T-cells and TPH-1 monocytes derived microparticules produced by inflammatory (TNF-α) and infectious (LPS of P.Aeruginosa) stress were applied on bronchial human cells BEAS-2B for 24 h. Morphology, apoptosis expressed in % of hypodiploïde DNA (flow cytometry), membrane permeability (Evans Blue test, AU: arbitrary unit) and membrane proteins expression from eptihelial phenotype (E-cadhérin and γ-caténin) and mesenchymal phenotype (Vimentin) have been studied using Western Blot (tubulin ratio).

Results: Human CEM T-cells derived MPs produced with TNF-α decreased the expression of E-cadherin (0.55 vs 0.78) and γ-caténin (0.29 ± 0.11 vs 0.38 ± 0.03, n = 3) and increased the expression of Vimentin (0.29 ± 0.05 vs 0.17 ± 0.06, n = 3) of the epithélial cells. Monocytes derived MPs produced with LPS decreased the expression of E-cadhérin (0.48 vs 0.78) and γ-caténin (n = 3) (0.20 ± 0.01 vs 0.38 ± 0.03; $p < 0.05$) and increased the expression of Vimentin (n = 3) (0.52 ± 0.09 vs 0.17 ± 0.06; $p < 0.05$) significantly. Human CEM T-cells derived MPs lead to a significant decrease of apoptosis after 24 h (n = 3) (0.89 ± 0.16% vs 2.68 ± 0.57%; $p < 0.01$), and permeability after 5 h (n = 3) (0.087 ± 0.007 AU vs 0.179 ± 0.02 AU; p: 0.018) of the BEAS-2B without any morphological modifications.

Conclusion: MPs from leukocytes could contribute to EMT of bronchial epithélial cells in inflammatory environment characteristic of the lung transplantation.

O57 TNFα: A NEW IMMUNOSUPPRESSIVE MOLECULE?

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Introduction: CD4+ Foxp3+ regulatory T cells (Tregs) are suppressive immune cells involved in the control of inflammatory and auto-immune disorders. Cell therapy using Tregs can efficiently control graft-versus-host disease (GVHD) in murine models. The different mechanisms used by Tregs to suppress conventional T cells (Tconv) are now well described. However, little is known about the potential effects of Tconv on Tregs. It has recently been shown in an experimental model of auto-immune diabetes that Tconv can boost the proliferation and suppressive capacities of Tregs through the secretion of TNF-alpha (TNFa). Therefore, we sought to investigate the role of TNFa on Treg function and activation in the alloreactive setting of GVHD.

Methods: We used a semi-allogeneic model of bone marrow transplantation and GVHD (B6àB6C3F1) and antigen-specific Tregs, as previously described.

We used three different approaches to block TNFa fixation on the TNFR2 receptor preferentially expressed by Tregs: induction of GVHD by TNFa-KO T cells; injection of a TNFR2 blocking mAB to recipient mice; infusion of Tregs from TNFR2-KO donor mice.

Results: In each of these 3 models, blockade of TNFa signaling resulted in loss of Tregs efficacy, as shown by restored clinical GVHD lesions, weight loss and GVHD lethality.

Immunophenotyping performed on splenocytes harvested at D13 post-transplantation showed that Treg proportion was diminished in the absence of TNFa and that they expressed lower levels of activation markers (CD25, ICOS, CTLA4 and CD44). On the other hand, Tconv showed a more activated phenotype in this setting (upregulation of CD25 and GITR).

Conclusion: In the absence of TNFa fixation on their TNFR2 receptor, Tregs are less activated in vivo and lose their ability to control GVHD. These results open new therapeutic perspectives through stimulation of Tregs by TNFR2 engagement.

O58 PRO-SENESCENT EFFECT OF LEUKOCYTE DERIVED-MICROPARTICLES ON ENDOTHELIAL CELLS: A NEW MECHANISM POSSIBLY CONTRIBUTING TO IBMIR IN ISLET TRANSPLANTAION

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Introduction: Microparticles (MPs) have emerged as a surrogate marker of vascular endothelial cell injury during transplantation and act as noxious mediators in immune response. Tissue Factor (TF) is expressed by inflamed endothelium and is also expressed by the leukocytes recruited at the vicinity of transplanted islets leading to instant blood mediated inflammatory reaction (IBMIR), systemic activation of coagulation and graft loss. We aimed at deciphering the impact of MPs from inflamed rat splenocytes (SR) on endothelial inflammatory response and cell fate.

Methods: Primary endothelial coronary cells (ECs) were incubated with MPs (1–30 nM) isolated from rat splenocytes stimulated by 5 mg/mL LPS or 25 ng/mL PMA-1 mM A23187 ionophore. Senescence-Associated β-galactosidase activity (SA-b-GAL) was assessed by C12FDG probe, senescence markers, oxidative stress, local angiotensin system proteins and TF by western blot. Apoptosis was detected by double propidium iodide/Annexine-V labeling and caspase-3 expression.

Results: MPs induced a significant raise in SA-b-GAL activity in young ECs (from 18 MFI A.U. up to 58 A.U.) after 48 h. Senescence was confirmed by the up-expression of p53, p21, p16 (up to 3-fold). The 2-fold up-expression of NADPH oxidase subunits (gp91, P47 and P22) and 3-fold down-expression of eNOS indicated MP-mediated oxidative stress. MPs prompted thrombogenicity in ECs through TF up-expression (up to 3-fold) and a secondary generation of endothelial MPs. Expression of AT1 and ACE was increased (up to 1.5-fold). Interestingly, no significant variation in apoptosis nor caspase-3 activation could be detected in MP-treated ECs (8% vs 13%), indicating a specific pro-senescent property of MPs.

Conclusion: MPs from splenocytes induce premature senescence and thrombogenicity in young primary ECs. Our in vitro data suggest a new paracrine MP-driven pathway possibly contributing to poor islets survival during IBMIR through endothelial damage.

O59 THE ENVIRONMENT INFLUENCES THE METABOLIC EFFECT OF SIROLIMUS ON HUMAN ISLETS TRANSPLANTED IN VIVO IN IMMUNODEFICIENT MICE

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Introduction: Cell therapy of type 1 diabetes leads to 50% insulin independence at 5 years and 75% of grafts are functional at 10 years under immunosuppression including anti-interleukine 2 receptor, tacrolimus, and sirolimus. Sirolimus, an inhibitor of mTOR, prevents adipogenesis, but its metabolic effects are debated (Lamming, 2012, Fraenkel 2008). Sirolimus may have a dual role on beta cells,according to the metabolic environment.. We tested this hypothesis on a mouse model engrafted with human islets, treated or not with sirolimus and fed a normal or high fat diet.
Methods: Ten mice RAG2KO were transplanted with 400-human islet equivalents under the kidney capsule (Gargani, 2013) and were fed for 6 weeks on a normal (N; n = 4) or high fat diet (HFD; n = 6). Mice received 0.2 mg/kg/day of sirolimus (S) or a vehicle solution (C) intraperitoneally with repeated measures of: weight, blood glucose, human C-peptide, and analysis of the volume of islet grafts after mice sacrifice.
Results: The weight of mice treated with sirolimus were lower than the non-treated mice whathever the N or HFD diet. Mice treated with sirolimus on N diet were more glucose sensitive (OGTT: AUC mouse N/S: 166 ± 2 *vs.* mouse N/C: 236 ± 45). Also HFD/S mice showed lower glucose sensitivity (AUC mice HFD/S: 315 ± 39 *vs.* Mice HFD/C: 269 ± 28). Beta cells of mice treated with sirolimus on C diet were more functional than beta cells of non-treated mice (HOMA2 BS: mice N/S 86 ± 22 *vs.* mice N/C 50 ± 6). The islet volume of human grafts in mice on sirolimus N/S (0.147 ± 0.012 mm^2) was higher than mice N/C (0.097 ± 0.044). The opposite for mice HFD/S (0.117 ± 0.048) and HFD/C (0.167 ± 0.086) was observed.
Conclusion: Sirolimus causes weight loss or less weight gain. Its metabolic effects depend on the metabolic environment: it improves the function of human beta cells under normal diet but is deleterious if given with high fat diet. This observation could explain the controversy in literature.

O60 SHORT TERM RAPAMYCIN TREATMENT IN HEPATIC ALLOGRAFT MODEL: IMPLICATION OF IMMUNOREGULATORY CELLS IN INDUCTION OF TOLERANCE

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Introduction: Rapamycin is an immunosuppressive drug frequently used in organ transplant. It has been shown that its protective effect on graft rejection was due to its preferential action on effector T cells without affecting regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC). However, rapamycin is little used in a long treatment in liver transplantation because of the deleterious side effects. We wanted to study the effect of a short treatment with rapamycin on liver rejection in rats.
Methodology: The allogeneic liver transplantation was performed by using Dark Agouti (donor) to Lewis (recipient). Two control groups are based on untreated allogeneic tranplant (group A, n = 4) and allogeneic tranplant treated with rapamycin (group B, n = 4). Rapamycin was administered by gavage at 1 mg/kg / day from day 4 to day 11 post-transplant. Groups A and B were sacrificed at day 11.
Results: We showed that an 8 day treatment of rapamycin started on day 4 resulted in the survival of grafted rats for more than 100 days. On the other hand, untreated rats died of liver failure on day 13. In view of this important result, we wanted to know what mechanism was based on this protective effect. An analysis of splenocytes on day 11 shows that rapamycin promotes increased monocytes-MDSC (94% ± 2.2% vs 73.3 ± 4.01). We did not observe any increase in Treg / Teff ratio in the treated group. In contrast, the fluorescence intensity of CD25 among Treg significantly is higher ($p \leq 0.05$) suggesting that rapamycin could increase the activation of Tregs.
Conclusion: Our study suggests that a short and early treatment with rapamycin could control the liver rejection by increasing monocytes-MDSC and enhancing the activity of Tregs.

O61 DE NOVO PERSISTENT POST-TRANSPLANT HLA DONOR-SPECIFIC ANTIBODIES (DSA) BUT NOT PREFORMED DSA ARE ASSOCIATED WITH WORSE SURVIVAL AND AN INCREASED RISK OF CHRONIC LUNG ALLOGRAFT DYSFUNCTION (CLAD)

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Introduction: The introduction of highly sensitive solid-phase immunoassay technology permitted better detection and characterization of donor-specific HLA antibodies (DSA) in pre- and post-transplant period; however their impact on clinical outcome after lung transplantation (LTx) remains controversial.
Methods and Materials: We performed a post-hoc analysis on a cohort of 138 LTx. Detection of HLA antibodies before LTx (Day 0), and at Month1, 3, 12 and 24 post-LTx was investigated using a Luminex screening assay (LABScreen) and DSA were detected performing Single Antigen kits (Gen Probe) on all positive serum samples.
Results: De novo DSA were frequent (41%), appeared mostly earlier in the post-LTx period (80% M1), and were mostly directed against both HLA class II antigens and putative non classical HLA antigens such as HLA-Cw and –DQA (57% of DSA). Presence of de novo post-LTx DSA at M3 and M12 significantly affected survival ($p < 0.001$ and $p = 0.03$, respectively) and only HLA class I DSA were also associated with CLAD ($p = 0.008$) compared to DSA negative LT recipients (R). De novo DSA which persisted from M1 to M3 (16%) were associated with CLAD ($p = 0.02$) compared with LTR in whom DSA disappeared. Cox proportional hazard regression showed a worse prognosis in LTR who had persistent de novo class II DSA (OR = 2.8, 95% CI 1.2 to 6.7, $p = 0.02$)
Conclusion: Our data suggest that DSA monitoring at M1, M3 and M12 post-LTx, could be recommended to check for persistent DSA in order to discuss earlier, from the 3rd month alternative immunosupressive strategies.

O62 SUCCESSFUL TRANSPLANTATION IN ABO- AND HLA-INCOMPATIBLE KIDNEY-TRANSPLANT PATIENTS

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Introduction: ABO-incompatible (ABOi) and HLA-incompatible (HLAi) kidney transplantation using living donors is common place; however, few data have reported on the outcomes of ABOi/HLAi living-kidney transplantation.
Methodology: Herein, we report on a single-center experience of 12 ABOi/HLAi living-kidney patients (seven females), of which 9 were from group A into O. There were 27 donor-specific alloantibodies (DSAs) (1–6 per patient) with fluorescence intensities ranging from 1500 to 15 000. The desensitization protocol was based on IV-Ig (1 g/kg on day-40 pretransplant), rituximab 375 mg/m^2 (days 30 and 15 pretransplant), tacrolimus (0.2 mg/kg)-based immunosuppression, started on day-10 pretransplant, and apheresis sessions (plasmapheresis, specific or semi-specific immunoadsorption). Patients had a mean of 11 (6–27) pretransplant sessions.
Results: On day 0, 17 of the 27 DSAs were no longer detectable; DSAs >3000 were observed in only three patients. After 19 (3–51) months, patient- and graft-survival rates were 100% and 91.6%, respectively. One graft was lost due to renal-vein thrombosis. No patient had an acute cellular or humoral rejection, whereas three presented with chronic antibody-mediated rejection. At the last follow-up, kidney biopsies were nearly normal in seven cases (58.3%) and renal function was excellent except for two cases of chronic antibody-mediated rejection. One patient developed cytomegalovirus disease, four had BKV infection, and five had pyelonephritis.
Conclusion: We conclude that ABOi/HLAi living kidney transplantation is a reasonable option for highly sensitized patients who have limited access to kidney transplantation.

O63 CLINICAL OUTCOMES ASSOCIATED WITH ANTIBODY MEDIATED REJECTION IN LUNG TRANSPLANTATION

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Background: Graft failure in both kidney and heart transplantation are mainly driven by antibody mediated rejection (AMR). In the context of lung transplant (LT), because of diagnostic difficulties, this clinical entity remains a matter of debate.
Methods and Materials: In order to validate the current AMR diagnostic criteria in LT and demonstrate the impact of AMR on LT prognosis, we conducted a retrospective analysis of our LT cohort (January 2010-December 2013). AMR was defined by association of clinical symptoms, DSA presence (sum MFI >1000), and either C4d+staining and/or histological pattern consistent with AMR. Patients (pts) were categorized in four groups by their DSA:(1) with DSA and AMR (DSA+AMR+), (2) with DSA and no AMR (DSA+AMR-), (3) with non significant DSA (DSAns = one specificity, with an MFI = 500–1000 once), and (4) without DSA (DSA-) The three latter were grouped as AMR- pts. Pre-LT and peri-operative clinical data, cumulative number of acute cellular rejection(ACR) episodes by month 12, freedom from Chronic Lung Allograft Dysfunction (CLAD),and graft survival were reported.
Results: Among 206 transplanted patients, 11% were DSA+AMR+ (n = 22), 41% were DSA+AMR-(n = 84), 6% were DSAns (n = 13), and 42%were DSA- (n = 87).Every AMR+ patient had clinical abnormalities associated, and only 3/22 had histological abnormalities with C4d-staining. Every AMR+ pts were treated with combination of plasmapheresis, rituximab and intravenous immunoglobuline. Comparison showed higher cumulative numbers (mean ± SD) of ACR at month 12 in the DSA+AMR+ group (2.1 ± 1.7) vs DSA+AMR- (1 ± 1.2), DSAns (0.75 ± 1), DSA-(0.7 ± 1.23) groups. AMR+ pts had higher frequencies of CLAD and worse graft survival than AMR- patients (HR = 53.24 $p < 0.0001$ and HR = 5.4, $p < 0.006$ respectively).
Conclusion: Our results show a negative impact of AMR on LT clinical course, and advocate for an early active diagnostic approach and evaluation of therapeutic strategies to improve prognosis.

O64 PROGNOSIS VALUE OF C1Q BINDING ANTI-HLA ANTIBODIES IN ACUTE ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

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Introduction: Antibody-mediated alloimmune response remains nowadays a major cause of graft rejection and failure in organ transplantation. Donor specific anti-HLA antibodies mechanisms explaining their differential pathogenicity are not yet well understood. Complement activation is thought to be a strong participant in antibody-mediated tissue graft destruction.
Methods: We longitudinally analysed C1q complement fraction binding capacity of donor specific anti-HLA antibodies as a renal and histological prognostic marker in acute antibody-mediated rejection. We included patients from the RITUX ERAH study, a multicenter prospective randomized double-blind, placebo-controlled trial. Renal transplant recipients diagnosed with acute antibody-mediated rejection during the first year of transplantation were treated by rituximab or placebo and conventional treatment. Histological evolution was evaluated at 1 and 6 months. Sera samples at the time of transplantation, the time of rejection, at 3 and 6 months after rejection were collected for a centralized analysis. Donor specific anti-HLA antibodies specificities and C1q binding capacity were assessed.
Results: Among the 25 patients included, 17 patients (68%) had C1q binding donor specific anti-HLA antibodies at the time of rejection. The presence of C1q binding donor specific anti-HLA antibodies was significantly associated with more severe evolution of chronic glomerulopathy at 6 months ($p = 0.036$). The persistence of C1q binding donor specific anti-HLA antibodies at 3 months and/or 6 months after rejection was associated with worse chronic glomerulopathy ($p = 0.006$), and more severe C4d score deposition at 6 months after rejection ($p = 0.008$). Proteinuria at 12 months after rejection was worse ($p = 0.022$). C1q binding capacity was associated with the MFI of donor specific anti-HLA antibodies at the time of rejection, at 3 and at 6 months after rejection. After retransplantation, patients had more C1q binding donor specific anti-HLA antibodies ($p = 0.026$).
Conclusion: We showed the prognostic value of the presence and the persistence of C1q binding donor specific anti-HLA antibodies as a pejorative marker leading to chronic histological lesions after antibody-mediated rejection.

O65 TREATMENT OF ACUTE ANTIBODY-MEDIATED REJECTION IN ABO-COMPATIBLE LIVER TRANSPLANTATION

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Background: Recent studies have confirmed inferior clinical outcomes concerning patients with preformed or de novo anti-HLA Donor-Specific Antibodies (DSAs). The diagnostic of aAMR is based on the presence of serum detectable DSA, an H&E (hematoxil and eosin) staining compatible, a C4d staining compatible, and the exclusion of other causes of a similar type of injury. However, the treatment of aAMR is poorly defined.
Patients and Method: Since 01/08, all liver transplant recipients followed in our center with a suspicion of graft rejection were tested for anti-HLA DSAs and received a liver biopsy. C4d stainning was performed in DSA positive recipients if the H&E staining was consistent with the diagnosis of aAMR. Anti-HLA screening was performed with the Luminex single-Antigen® (cut-off MFI >1000). Liver biopsies of patients with a suspicion of aAMR were re-examinated blindly by a transplant pathologist.
Results: 16 patients with an aAMR were found. 3 patients were excluded, due to the absence of liver sample for reexamination. Thus, 13 patients were included (8 with de novo DSAs and 5 with preformed DSAs). 2 patients had anti-class I DSAs, 5 patients had anti-class II DSAs, and 6 recipients had anti-class I and II DSAs. The median-time between the transplantation and the aAMR was 14 [1–84] months. All patients received steroid pulses. 4 patients received a rituximab therapy only. 7 patients received a rituximab therapy, with 6 plasma exchanges and intraveinous immunoglobulins. 2 recipients were treated by polyclonal antibodies. A reevaluation biopsy was performed after a median follow-up of 11 [1–48] months. C4d became negative in 8 recipients. DSAs were still detectable in 8 patients. Clinical and histological findings were favorable for 8 patients, 3 patients died with a liver graft failure, and 2 patients progressed to chronic rejection.
Conclusion: aAMR is a rare complication, but with dramatic consequences. Adding a B-depleting agent seems to be useful.

O66 DSA CHARACTERISTICS ASSOCIATED WITH ANTIBODY MEDIATED REJECTION IN LUNG TRANSPLANTATION

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Background: DSA are frequently observed after LT and represent a pivotal role in AMR associated with clinical symptoms and histological abnormalities. DSA characteristics are not yet fully defined in case of AMR compare to absence of AMR.
Methods and Materials: We retrospectively analyzed DSA characteristics and MFI values of 105 patients (pts) transplanted at our center (2010–2013). They were categorized into 2 groups: pts with DSA and AMR (AMR+), those with DSA without AMR (DSA+AMR-). We considered either immunodominant DSA MFI or global MFI (sum of DSA) determined for the following categories: all DSA, class I or II, preformed, or de novo. The 'peak' time point was defined as the time of AMR, and the time of highest global MFI for AMR- patients.
Results: All AMR+ pts had DQ DSA (95%), except for one (no DQ mismatch). This frequency was significantly lower in DSA+AMR- (60%) groups, $p = 0.0028$. Compared to DSA+AMR-, AMR+ patients had significantly

increased DSA specificities (mean ± SD; 3.4 ± 2.28 vs 1.8 ± 1.2, p = 0.0015), immunodominant DSA MFI (med [IQR 25–75]; 7332 (3382–10 585) vs.1972 (1121–3468), global peak MFI (med[IQR 25–75]; 11563 [6867–16 239] vs 2593[1485–5357], p < 0.0001), de novo peak MFI (8487 [3847–12 296] vs 1305 [0–2722], p < 0.0001),and class II peak MFI (10004 [4399–13 346] vs 1695[681–3365], p < 0.0001). Furthermore, ROC analysis revealed Immunodominant DSA MFI (AUC = 0.8472, 95%IC = 0.76–0.93, p < 0.0001) and global peak MFI (AUC = 0.87, 95% CI (0.8–0.94), p < 0.0001) had great diagnosis performance for AMR. At least we showed that sum MFI demonstrate less overlap between AMR+ and DSA+AMR- pts compare to Immunodominant DSA.
Conclusion: DSA of AMR+ pts have clearly different profiles compared to DSA of DSA+AMR– pts. The strong value of using global peak MFI for AMR diagnosis needs to be prospectively evaluated and validated.

O67 PERIOPERATIVE AND EARLY POSTOPERATIVE COMPLICATIONS AFTER LIVER TRANSPLANTATIONS (LT) FROM TYPE 2-DONATION AFTER CARDIAC DEATH IN FRANCE (TYPE2-DCD): A CASE-CONTROL STUDY

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Background: Assess perioperative and early postoperative complications after LT with grafts from type 2-DCD compared to LT with grafts from brain dead donors. Retrospective, observational, case-control study in 2 accredited centres in Ile-de-France between January 2010 and May 2015.
Methods: Patients undergoing LT from type 2-DCD were included. A control group of patients undergoing LT from brain dead donors were paired with a 1:1 ratio. Pairing criteria were donor and recipient's age, cold ischemia time, MELD score, cirrhosis aetiology and centre. Liver function data, perioperative and early postoperative complications were assessed.
Results: Fourteen LT from type 2-DCD were realized. The incidence of primary graft dysfunction was not higher in the type 2-DCD group (7 (50%) vs. 3 (21%), p = 0.5). Peri- and early postoperative fresh frozen plasma transfusion was more important in the type 2-DCD group (respectively 5 vs. 1, p = 0.008 and 6 vs. 0, p = 0.007). Severity scores on ICU admission, SAPSII and SOFA, were higher in the type 2-DCD group (respectively 42 vs. 30, p = 0.006 and 10 vs. 6, p = 0.011). The incidence of acute renal failure (11 vs. 2, p = 0.008) was higher is the LT from type 2-DCD group. Infectious complications (15 vs. 9, p = 0.219) was not higher in the LT from type 2-DCD group.
Conclusion: LT from type 2-DCD are characterized by an increase in peri- and early postoperative haemorrhagic complications and an increased incidence of early postoperative organ failures.

O68 PREOPERATIVE RISK FACTORS FOR INTRA-OPERATIVE BLEEDING IN PEDIATRIC LIVER TRANSPLANTATION

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Introduction: Intra-operative bleeding is a cause of significant morbidity and mortality in children undergoing liver transplantation (LT). This study analyses the pre-operative risk factors for intra-operative bleeding in our recent series of pediatric LTs.
Methods: Between November 2009 and November 2014, 84 consecutive isolated pediatric LTs were performed in 81 children. LTs combined with other organs (kidney, bowel, multivisceral) were excluded from analysis. Potential pre-operative risk factors for bleeding, amount of intra-operative transfusions, post-operative course and outcome were recorded. Cut-off for severe bleeding was defined as intra-operative red blood cell transfusions ≥1 total blood volume.
Results: Twenty-six patients (31%) had severe intra-operative bleeding. One year patient survival was 68% in this group of patients versus 85% in the others (p = 0.054). Among 13 potential pre-operative risk factors, 3 were identified by uni- and multivariate analysis as independent predictors of severe intra-operative bleeding: abdominal surgical procedure(s) prior to LT (including Kasai operation in most Biliary Atresia patients), factor V level ≤30% before LT, and ex situ parenchymal trans-section of the liver graft (reduced graft and ex situ split graft, whose cut surface has no biological haemostasis before revascularization, as opposed to whole liver, living donor and in situ split grafts). Based on these findings, a model to predict the risk of intra-operative bleeding was established.
Conclusion: Three main risk factors for intra-operative bleeding during pediatric LT were indentified in this series: previous abdominal surgery, factor V level ≤30%, and ex situ trans-section of the liver graft. The model predicting the hemorrhagic risk is expected to allow better anticipation of surgical and anesthesiological management. This model needs validation in other series of patients.

O69 FIRST PURE ROBOTIC-ASSISTED SEQUENCE LIVING DONOR «NEPHRECTOMY – KIDNEY TRANSPLANTATION» WITH TRANSVAGINAL EXTRACTION AND INTRODUCTION OF THE GRAFT

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Introduction: From 2010 robotic-assisted kidney transplantation, introducing the graft through an abdominal incision, has shown real benefit in very selected patients. Transvaginal approach for kidney extraction in living donor has shown advantages in quick recovery and cosmesis without impact on graft function outcome.
Méthodology: We report the case of a 44-year-old female éligible to donate her left kidney to her 43-year-old sister for a second kidney transplantation in left iliac fossa (Wegener disease, creatinine 410 mmol/l). After informed consent we performed, in a pure robotic-assisted sequence, a donor left nephrectomy with graft transvaginal extraction followed by transplantation with graft transvaginal introduction in the recipient.
Results: No per-operatory complications occured. Warm ischémia time for nephrectomy was 1 min 50 sec. Opérative time for donor was 185 min and 180 min for the récipient. Vascular anastomosis time: 45 min. A Lich-Gregoir ureterovesical anastomosis with double J stent was performed. Surgical blood loss was 100 cc. In both procédures vaginal access was performed by pure robotic-assisted procedure. The graft transfer through the vagina was facilitaded utilising an Alexis® (Applied Medical) retractor. A température probe monitorized graft cooling during transplantation (24.0 ± 2.9°C). Graft function recovery occurred 2 h after reperfusion. Creatinine at 1 d was 183 mmol/l and 96 mmol/l at 4 d. Postoperative course was uneventful. Hospital discharge on 2 d for the donor and 4 d for the récipient.
Conclusion: A prospective study is in progress to confirm the promising results of this new mini-invasive approach for living donor kidney transplantation.

O70 BILIARY COMPLICATIONS AFTER "EN BLOC" LIVER BOWEL OR MULTIVISCERAL TRANSPLANTATION IN CHILDREN

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Introduction: « En bloc » liver intestinal transplantation is performed without any biliary anastomosis, however biliary complication (BC) may occur. We analyse this BC in our pediatric series.
Method: Between November 1994 and November 2014, 110 bowel transplantations were performed in 101 children: 61 without liver (IT), and 49 «en bloc» liver intestinal transplantation (LIT) including liver, duodenum, pancreas, small bowel, +/- right colon +/- estomac. Pancréas was reduced to the head till 2009 (36 graft, group A), not reduced since 2009 (13 graft, group B).
Résults: Patients survival (graft) at 5, 10 and 15 years was 73%, 56% et 43% (43%, 23%, 23%) for IT and 58%, 46%, 43% (46%, 43%, 38%) for LIT (NS). BC occured in 8/49 LIT (16.3%): 7 in group A and 1 in group B (NS). In group A, BC were leak or extra +/- intra hepatic stenosis, with associated duodenal necrosis in 2 cases. In group B, the only BC was a delayed stenosis of the intra pancreatic bile duct. The treatment included an interventional radiology in 6 cases, and surgery in 7 cases. One patient died of biliary cirrhosis, an other of septic shock probably secondary to cholangitis; 4 patients with chronic biliary disease, associating chronic cholestasis, bile duct dilatation, reccurent stenosis or cholangitis; Two are alive and well, without sign of biliary disease.
Conclusion: Biliary complications occured after 16.3% of « en bloc » transplantation, and cause severe mortality and morbidity. Pancreas reduction might increase the risk of ischemic bile duct damage. Intrahepatic bile duct compression (possibly due to pancreatic rejection), and Oddi's sphincter dysfunction (possibly due to denervation) are specific complications to "en bloc" liver and intestinal grafts.

O71 EARLY AND MIDTERM RESULTS OF INFRARENAL AORTIC ALLOGRAFTS USED IN VASCULAR INFECTIONS

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Introduction: The treatment of infected aorta (primary or graft infection) bears high rates of morbidity and mortality, as well as a high risk of recurrence,

especially during the perioperative period. Their replacement by a bacteria-resistant substitute is therefore compulsory, such as arterial allografts which are more effective than synthetic substitutes in this context. Accordingly, we studied the results of the placement of allografts in these indications.
Methodology: Early and midterm results (6 months) of cryopreserved allografts implanted for infrarenal aortic infections were retrospectively analized in a monocentric study.
Results: 196 patients, with a mean age of 64.2 years, received an allograft from January 1997 to December 2013. Infection causes were primary or secondary enteric fistulae (27.6%, 54 patients), mycotic aneurysms (2.5%, 5 patients), or secondary prosthetic graft infections (51.5% blood-borne with 101 patients, 18.4% direct contamination with 36 patients). The most frequent infectious organisms were Staphylococcus aureus (31.2%) and Escherichia coli (22.4%). No germ was identified in 16.3% cases. 19 patients (9.7%) required emergency surgery. All synthetic material was removed in 96.4% (189 patients) of prosthetic graft infections. In-hospital mortality was 11.7% (23 patients) and 9.9% if there was no fistula. Two deaths were attributed to an allograft rupture or fistula. At 6 months, 16 patients (8.2%) had presented with an infectious recurrence with one or more of the following complications: 4 enteric fistulae, one urinary fistula, 6 pseudoaneurysms and 14 allograft ruptures. Secondary patency rate at 6 months was 99.3% (5 thromboses).
Conclusion: The low rate of early complications of aortic allografts confirm their resistance in an infected environment and therefore should justify their use as a first choice strategy for aortic infections.

O72 EARLY POSTTRANSPLANT COMPLICATIONS FOLLOWING ABO-INCOMPATIBLE KIDNEY TRANSPLANTATION

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Introduction: Many studies or registries particularly in Japan, but also in Western Europe, have shown that long-term results from ABO-incompatible (ABOi) living-kidney transplantation are as good as those observed for ABO-compatible (ABOc) living-kidney transplantation.

However, it has been reported more posttransplant complications in ABOi patients, such as bleedings or infections.
Methodology: In our single-center retrospective study we assessed all relevant complications occurring within the first 6 months posttransplantation in 44 ABOi and in 44 matched ABOc patients. All patients were comparable at baseline except that ABOi patients had greater immunological risks.
Results: During the 6-month posttransplant period, more ABOi patients presented with postoperative bleeds, thus requiring significantly more blood transfusions. Bleeds were associated with significantly lower values of fibrinogen, platelets, prothrombin time, and hemoglobin levels in the immediate pretransplant period.

Significantly more BK-virus infections occurred in the ABOi group.

Surgical complications, patient- and graft-survival rates, and kidney-function statuses were similar between both groups at 6 months posttransplantation.
Conclusion: We conclude that impairment of hemostatic factors in ABOi patients at pretransplant explained the increased risk of a bleeding episode at posttransplant.

O73 TIME-VARYING EFFECT OF PREEMPTIVE SECOND KIDNEY TRANSPLANTATION ON GRAFT SURVIVAL

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Introduction: Previous studies showed a poorer graft survival in case of second kidney transplantation (SKT). Definitive evidence regarding the impact of preemptive SKT (PSKT) on graft survival is lacking.
Methods: This is a monocentric study (study period from 01/01/1985 to 30/04/2015). We studied graft survival (allograft failure from any cause including death) between patients with or without PSKT (PSKT or NPSKT) using the Kaplan Meier method. Association between PSKT and graft survival was assessed using the Cox proportional hazards model, with PSKT being considered as a time-dependent variable. Proportionality was assessed using an interaction term between PSKT and log-transformed time. As we identified a significant interaction with time ($p = 0.05$), we fitted separate cox models for <5 years and >5 years after transplantation.
Results: During the study period, 2061 patients received a kidney transplant, with 244 NPSKT and 22 PSKT. Age at SKT did not significantly differ between PSKT and NPSKT (47.3 ± 11.5 vs 44.6 ± 12.9, $p = 0.34$), as well as the proportion of living donors (10% vs 8%, $p = 0.67$). Delayed graft function was less frequent in the PSKT group (5% vs 45.5%, $p < 0.001$), even after exclusion of SKT with living donors (5.6% vs 49.0%, $p < 0.001$). During follow-up, 116 events were recorded (72 returns to dialysis et 44 deaths before return to dialysis). KM curves diverged upto 5 years (survival PSKT 94.1 ± 5.7% vs. NPSKT 76.8 ± 2.9% at 5 years) and tended to converge after 5 years (survival PSKT 50.9 ± 15.2% vs. NPSKT 55.5 ± 3.9% at 12 years). Before 5 years post SKT, PSKT was associated with better graft survival (HR = 0.18 (0.02–1.28), $p = 0.08$), but after 5 years, the risk of all-cause graft failure including death was higher (HR = 2.12 (0.90–5.04), $p = 0.08$).
Conclusion: The effect of PSKT on graft survival varies through time. The beneficiary effect observed during the first 5 years appears to fade over time, resulting in similar 12 years kidney graft survival.

O74 LONG TERM EFFECT OF THE HEART DONOR SCORE ON PATIENT SURVIVAL

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Background: We previously developed a heart donor score in order to standardize heart donor quality, based on the factors age, cause of death, compromised history (drug, abuse, sepsis, meningitis, malignancy, HbsAg+ or Anti-HCV+), hypertension, cardiac arrest, echocardiography, coronary angiography, serum sodium and noradrenaline and dopamine/dobutamine dosages. (J Heart Lung Transplant. 2012 Apr;31(4):387–97)
Methods: The heart donor score (HDS) was calculated for donors used for transplantation in Eurotransplant from January 1, 2005 to December 31, 2009 [N = 2705]. HDS ≥17 identified high risk donors (HRD), all others were labelled low risk donors (LRD). Kaplan-Meier survival rates and Cox' regression models were applied in order to study the long term effect of the donor heart score on patient survival.

Results Compared to recipients from HRD [N = 1452], recipients from LRD donors [N = 1252] were younger (under 45 year: 36% vs. 29%, $p < 0.0001$), more often on VAD support (22% vs. 17%, $p = 0.014$) and more often transplanted from high urgency status (65% vs. 52%, $p < 0.0001$). Survival rates 1, 5, and 9 years after transplantation were 83% vs. 77%,77% vs. 63% and 73% vs.54% for LRD vs. HRD, respectively ($p = 0.048$). Multivariate analysis show that both recipient age ($p < 0.0001$) and the heart donor score ($p = 0.001$) remain significant predictors of survival at 9 years after transplantation.
Conclusions: The heart donor score is a strong predictor of long term survival after heart transplantation. Its application at time of donor reporting may allow more appropriate matching of extended criteria donor hearts.

O75 PREEMPTIVE TRANSPLANTATION IS ASSOCIATED WITH IMPROVED GRAFT SURVIVAL: RESULTS FROM THE FRENCH TRANSPLANT DATABASE

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Background: Kidney transplantation (KT) is the treatment of choice for end-stage renal disease. In France, preemptive kidney transplantation (PKT) should be considered when glomerular filtration rate is under 20 mL/min/1.73 m² but European reports on the results of PKT are scarce. Our objective was to evaluate the impact of PKT on the risk of graft failure.
Methods: We included all first kidney-only transplants performed in adults in France between 2002 and 2012. A Cox multivariable model was used to study the impact of PKT on the hazard of graft failure defined as death, return to dialysis, or retransplant, whichever occurred first.
Results: Between 2002 and 2012, 22 288 patients received a first KT, including 3112 (14%) who had a PKT. Mean recipient age at KT was 50.5 ± 13.4 years, 61.9% were men. Median time of follow-up was 4.7 years. In multivariable analysis, after adjustment for age at transplantation and sex of recipients, primary kidney disease, donor type (living or deceased donor, expanded criteria donor or standard), HLA mismatches, center and year of transplantation, PKT was associated with a 43% reduction in the hazard of graft failure when compared with patients who were treated by dialysis before KT (Hazard ratio (HR) 0.57; 95% confidence interval (CI) 0.51–0.63). This reduction in the hazard of graft failure was greater after the first year of transplant (HR within the first year 0.69; 95%CI 0.57–0.83; HR after the first year 0.49; 95%CI 0.45–0.59) and the impact of PKT was also greater in living

than in deceased donor recipients (HR in living donor 0.32; 95%CI 0.19–0.55; HR in deceased donor 0.59; 95%CI 0.53–0.64). Among the subgroup of patients registered on the waiting list before the initiation of dialysis, PKT was associated with a 30% reduction in the hazard of graft failure (HR 0.70; 95%CI 0.57–0.86). Conclusion

In France, PKT is associated with a lower risk of graft failure than KT performed after the initiation of dialysis.

O76 EARLY URINARY CXCL10 IS PREDICTIVE OF SUBSEQUENT ACUTE REJECTION IN CLINICALLY AND HISTOLOGICALLY STABLE KIDNEY RECIPIENTS

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Introduction: Urinary chemokines CXCL9 and CXCL10 are useful non invasive biomarkers for the diagnosis of clinical and subclinical allograft kidney rejection. We hypothetised that longitudinal follow up of these 2 chemokines during the first year post transplant could help predict subsequent acute rejection during the first year.
Methods: We monitored urinary CXCL9 and CXCL10 levels in 1719 urine samples from 300 consecutive kidney transplant recipients, collected during the first post-transplant year and assessed their predictive value for subsequent acute rejection (AR) using 773 biopsies (479 protocol and 294 for cause).
Results: The trajectories of urinary CXCL10 during the first 400 days post-transplantation showed an early increase ($p = 0.0005$ and $p = 0.0009$ at 1 month and 3 months post-transplantation, respectively) in patients who subsequently developed AR. 400 days post-transplantation, the AR-free allograft survival rates were 90% and 54% in patients with urinary CXCL10: creatinine (CXCL10:Cr) levels <2.79 ng/mmoL and >2.79 ng/mmoL at 1 month, respectively ($p < 0.0001$), and 88% and 56% in patients with urinary CXCL10:Cr levels <5.32 ng/mmoL and >5.32 ng/mmoL at 3 months ($p < 0.0001$), respectively. In 220 clinically and histologically stable patients, multivariate Cox proportional hazard analysis confirmed that CXCL10:Cr at 3 months predicted AR, independent of concomitant protocol biopsy results ($p = 0.009$). Finally, early CXCL10:Cr levels independently predicted histological lesions at one year.
Conclusion: Early urinary CXCL10:Cr levels strongly predict the risk of clinical and subclinical AR in the first post-transplant year with high negative predictive value, even in clinically and histologically stable patients.

O77 ADCC OF NK CELLS IN KIDNEY TRANSPLANTATION: A NEW COMPLEMENT-INDEPENDENT TOOL OF DSA MONITORING

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Introduction: Natural Killer antibody-dependent cellular cytotoxicity (NK-ADCC) remains poorly explored in transplantation. We have evaluated the link between NK-ADCC of kidney transplant recipients (KTR) and their graft prognosis. We also have designed an in vitro test evaluating NK-ADCC as a mechanism of anti-HLA donor specific antibodies (DSA) toxicity, independently of complement.
Methods: NK-ADCC response was evaluated by flow-cytometry (CD3- CD56+ CD16+ CD107a+ labelling) in presence of Rituximab and B-cell targets ex vivo in a cohort of 148 KTR. Our in vitro test evaluated DSA binding to CD16, which is a Fc receptor of NK cells. It reveals NK degranulation against allogeneic cells in presence of DSA+ ($n = 50$) or DSA- ($n = 50$) sera. It was also compared to results of 40 transplant biopsies for clinical indication.
Results: Rituximab induced NK-ADCC response was overall inhibited in KTR compared with healthy controls and exhibit a high inter-individual variability. An increased NK-ADCC response was associated with a GFR <60 mL/min ($p = 0.008$). By multivariate analysis, a 2.8 fold increased degranulation level was also significantly associated with a further 10% decreased GFR one year after inclusion (Odds Ratio = 10.3, $p = 0.003$). Our in vitro test revealed a 5.7 fold higher CD16 engagement with DSA+ than DSA- serum samples ($p < 0.0001$). Finally, CD16 engagement was associated with histological lesions of humoral rejection.
Conclusion: Our study suggests an independent and negative impact of a high NK-ADCC response on renal function evolution. This finding is in line with our in vitro test showing a strong ability of DSA to activate NK cells via CD16. The interaction between NK cells and DSA opens a new field in pathophysiology of humoral rejections. The impact of CD16 binding DSA on graft survival remains however to investigate.

O78 EPITOPE LOAD IS PREDECTIVE OF DE NOVO CLASS II DSA OCCURRENCE IN RENAL TRANSPLANT RECIPIENTS AFTER CONVERSION FROM CYCLOSPORINE TO EVEROLIMUS

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Introduction: The identification of patients at risk of developing de novo DSA after transplantation is an important issue. The degree of HLA compatibility between donor and recipient is an important factor misjudged by the sole number of HLA incompatibilities. The HLAMatchmaker software compares the HLA molecules of the recipient and the donor, as a succession of eplets corresponding to amino acid residues accessible to antibodies. The epitope load is the number of eplets incompatible, that are expressed by the donor and absent in the recipient.
Methodology: 93 patients were switched at three months post renal transplantation from cyclosporine to everolimus in the CERTITEM study. The most likely allelic typing (donors and recipients) were determined from the generic typing using HAPLOSTAT software. The epitope load (HLA class II) between donor and recipient was determined by the HLAMatchmaker software.
Results: During follow-up, 26 patients developed Class II DSA (20 DQ, 2 DR and 4DQ + DR). The epitope load was significantly higher in patients who developed DSA DQ: 14.3 ± 4.8 versus 7.4 ± 6.6 eplets DQ ($p < 0.0001$). In patients with more than 10 incompatible DQ eplets, frequency of de novo DSA was 47.6% versus 7.8% ($RR = 6.1$, $p < 0.0001$). In the subgroup of DQ7-negative recipients who received a DQ7-positive graft ($n = 22$), the number of incompatible eplets expressed by DQ7 was significantly higher in patients who developed DQ7 DSA: 12.6 ± 3.6 versus $6\ 7 \pm 3.3$, $p = 0.002$. In those patients who developed a DSA DQ7, some eplets were expressed by DQ7 with a significantly higher frequency (66ER, 67VT, 70RT, 74EL, 77T, 37YA, 52PL3; $p < 0.05$) than in patients who did not.
Conclusion: The study of the epitope load and the eplets expressed by the donor can identify patients at risk of developing de novo DSA after conversion from cyclosporin to everolimus.

O79 EFFICACY AND SAFETY STUDY AFTER A 4-MONTH POST-RENAL TRANSPLANT DOSE REDUCTION OF TACROLIMUS (ADEQUATE STUDY)

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Introduction: The aim of the study was to determine efficacy of Advagraf® minimization between 4 and 12 months post-transplantation.
Methods: This prospective, interventional, open label, randomized, multicenter study was designed to determine the risk/benefit ratio of a 50% reduction of Advagraf® daily dose 4 months after transplantation in non-immunized stable patients previously treated with basiliximab, tacrolimus, mycophenolate acid and steroids. Based on Month-3 eligibility assessments, patients will be randomized in two groups (1:1): patients with 50% reduction of the daily dose of Advagraf® 4 months after transplantation and with targeted tacrolimus trough level higher than 3 μg/L (group A), and patients kept on their usual dose with targeted tacrolimus trough level between 7 and 12 μg/L (group B). Primary

Outcome was renal function at one year post transplantation estimated by the GFR using MDRD 4. Secondary end points included the assessment of 1-year efficacy (including one-year histological lesions) and safety data (metabolic and infectious diseases).
Preliminary Results: Among 300 patients included between September 2012 and June 2014, 188 were randomized (group A: 89, group B: 99). Renal function was similar in both groups. More acute rejections were reported in group A. In agreement, inflammatory lesions were more frequent. Incidence if impaired glucose tolerance was higher in group B.
Conclusion: Minimization during the first year post-transplantation impaired efficacy of immunosuppressive regimen based on Advagraf® in low immunologic risk kidney transplant patients.

O80 EARLY INTRODUCTION OF SUBCUTANEOUS (S.C.) HEPATITIS B IMMUNOGLOBULIN (HBIG) PROVIDES EFFECTIVE PROPHYLAXIS FOR HEPATITIS B VIRUS (HBV) REINFECTION AFTER LIVER TRANSPLANTATION (TX)

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Background and Aims: Subcutaneous HBIg (Zutectra®) in maintenance liver transplant patients assures hepatitis B surface antibody (anti-HBs) serum trough level >100 IU/L. Data regarding early s.c. therapy are lacking.
Methods: Prospective open-label single-arm study, patients undergoing liver tx for HBV infection who were HBV DNA-negative at tx were switched at 8–18 days post-tx from i.v. to s.c. HBIg (500 or 1000 IU once weekly or fortnightly) if they were HBsAg negative at time of switch, and were monitored to month 6 post-tx. Self-injection (or by carer) could be started after week 4 if anti-HBs trough level was >100 IU/L and if patients complied with the injection technique. Primary endpoint was failure rate during 6 months, defined as serum anti-HBs ≤100 IU/L or HBV reinfection with serum anti-HBs >100 IU/L.
Results: 49 patients were recruited (20 weekly dosing, 29 fortnightly dosing); 47 (95.9%) continued treatment until month 6. By week 14, 47 patients (97.9%) patients were completely self-administering or being injected by carers. No treatment failures occurred during the 6-month study treatment period i.e. all patients maintained serum HBs antibody concentrations ≥100 IU/L and remained HBsAg-negative. Mean anti-HBs declined successively to month 6 (Figure). No clinical symptoms consistent with HBV reinfection were observed. Only one non-serious adverse event (mild injection site hematoma) was assessed as treatment-related. No serious drug-related adverse events occurred. All 44 patients who completed an end-of-study questionnaire reported that s.c. injection was convenient and were satisfied with HBIg.
Conclusions: Early switch to s.c. HBIg after liver tx maintained serum anti-HBs at a level which effectively prevented HBV reinfection in all patients. Treatment was well-tolerated. Self-administration of s.c.HBIG as part of the combination treatment with HBV virostatic therapy appears a successful and convenient strategy for preventing HBV reinfection.

O81 B CELLS LOADED WITH SYNTHETIC PARTICULATE ANTIGENS: AN ALTERNATIVE PLATFORM TO GENERATE ANTIGEN-SPECIFIC REGULATORY T CELLS FOR ADOPTIVE CELL THERAPY

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Introduction: Allograft tolerance has been obtained in experimental models with adoptive transfer of ex vivo-expanded regulatory T cells (Treg) specific for donor antigens. Preclinical data have shown that Treg specific for indirectly presented alloantigens (indirect Treg) are mandatory for long-term tolerance. However, the ex vivo expansion of indirect Treg faces limitations, related essentially to the source of autologous antigen-presenting cells (APCs) used to stimulate T cells in vitro. B cells are (i) potent regulatory cells and (ii) APCs able to establish a privileged crosstalk with CD4+ T cells. However, the use of B cells as APCs is made problematic due to their inability to internalize and present non-cognate antigens. We have developed a novel nanobiotechnology-based approach to turn autologous polyclonal B cells into potent stimulators of antigen-specific T reg.
Methods: Synthetic particulate antigens (SPAg) were generated by immobilizing (i) monoclonal antibodies directed against a framework region of B cell receptor (BCR) kappa-light chains and (ii) model antigens on fluorescent nanospheres of 400 nm in diameter.
Results: SPAg behaved like genuine particulate antigens when incubated in vitro with polyclonal murine B cells. SPAg bound to surface BCR of any kappa-positive B cells, triggered activation signal and were internalized in late endosomal compartment of B cells. SPAg-loaded B cells induced activation and proliferation of antigen-specific T cells. This approach was transposable to humans' cells. Importantly, regulatory properties could be conferred to SPAg-loaded B cells by CpG stimulation. SPAg-loaded regulatory B cells prevented proliferation of effector CD4+ T cells and induced proliferation of antigen-specific Treg in vitro.
Conclusion: Autologous polyclonal B cells loaded with SPAg appear as an innovative platform to expand Treg ex vivo. This approach may improve the efficiency and costs of current procedures.