MEDICAL COMPLICATIONS

O1 PLACE OF RITUXIMAB IN THE TREATMENT OF RECURRENT PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN THE RENAL TRANSPLANT: A MULTICENTER STUDY WITH PROPENSITY SCORE

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Introduction: The indication of rituximab (RTX) in the treatment of primary focal segmental glomerulosclerosis (FSGS) recurrence after kidney transplantation (KT) remains controversial. The objective of our study was to evaluate the benefit and tolerability of adding RTX to the conventional treatment (CTT) comprising plasmapheresis (PP), corticosteroids, and high-dose anticalcineurins for the treatment of FSGS recurrence after KT.
Methods: This retrospective, multicenter study reports on 147 patients, transplanted between 31 December 2004 and 31 December 2018, aged 38.1 [28.8–49] years, who developed FSGS recurrence at 7 [3–24] days. In all 108 patients received a CTT (Group 1). RTX was introduced in this group after more than 28 days of CTT for failure or for therapeutic intensification (n = 23, Group 1a), or for early discontinuation of PP (n = 8, Group 1b); 39 patients received RTX associated at the outset with CTT (Group 2).
Results: We observed 46.9% complete remission (CR) and 33.33% partial remission (PR). Ten-year graft survival was 65.6% [51.4–76.6] and 13.8% [3.6–30.8] in responders and non-responders respectively. There was no difference in CR + PR rate between G1 (83.3%) and G2 (71.8%), p = 0.07, confirmed by propensity score −3.5% (CI 95% [−18.5%, 11.4%], p = 0.64). Following addition of RTX (Group 1a) we observed a CR rate of 30.4% and a PR rate of 34.8%. In multivariate analysis, the RTX response factor was the absence of treatment of the initial nephropathy by at least two treatments (OR = 0.04, CI 95% [0.003, 0.59], p = 0.01). Patients with and without RTX experienced similar infection rates (71.4% and 80.5%, p = 0.30) and rejection rates (18.6% and 28.6%, p = 0.16).
Conclusion: Rituximab could be used in cases of CTT failure or in remission patients for early weaning of plasmapheresis, without increasing infectious risk.

O2 ASSESSMENT OF PROTEINURIA REPORTED AS ADVERSE EVENTS IN *DE NOVO* RENAL TRANSPLANT RECIPIENTS RECEIVING AN EVEROLIMUS-BASED REGIMEN: 24-MONTH RESULTS FROM TRANSFORM

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Background: mTOR inhibitors (eg, everolimus [EVR]), are thought to increase the risk of post-transplant (Tx) proteinuria (PU). Here, we assess PU onset and outcomes in de novo renal Tx recipients (RTxRs) receiving EVR + reduced CNI (EVR + rCNI) or mycophenolate + standard CNI (MPA + sCNI) from the TRANSFORM study.
Methods: In this 24-month (M), multicenter, open-label study (NCT01950819), RTxRs were randomized to EVR + rCNI (N = 1022) or MPA + sCNI (N = 1015) + induction and steroids. EVR trough level (C0), urine protein:creatinine ratio (UPCR), antihypertensive medication use and onset time in patients with PU adverse events (AEs) were assessed up to M24.
Results: At M24, proportion of patients in both arms was similar across UPCR categories (<500 mg/g: >85% in both; 500-<3000 mg/g: 13.3% [EVR + rCNI] and 8.07% [MPA + sCNI]; and > 3000 mg/g: ~1% in both). Incidence of PU as an AE was 14.1% (EVR + rCNI) and 7.0% (MPA + sCNI). Median time to PU onset was 76 vs 63 days with EVR + rCNI vs MPA + sCNI. Drug discontinuation due to PU AE was noted in 26 vs 0 patients in EVR + rCNI vs MPA + sCNI (Table). Among RTxRs with PU, baseline demographics were mostly balanced, except for higher proportion of RTxRs with cold ischemia time > 20 h in EVR + rCNI vs MPA + sCNI arm (18.9% vs 9.9%). In patients with PU AE, though mean EVR C0 was within target range from M1-M6, it was slightly lower in patients who continued (5.4–6.1 ng/mL) vs those who discontinued (5.9–7.0 ng/mL). Between-arm difference in median UPCR up to M24 was 2.5-fold higher in EVR + rCNI vs MPA + sCNI arm among patients with PU. Median UPCR of patients discontinuing study drug was higher than that of those continuing study drug in both arms. Use of loop diuretics was more frequent in EVR + rCNI vs MPA + sCNI arm.
Conclusions: Although EVR + rCNI regimen was associated with a high incidence of PU AEs, these were not associated with EVR C0 outside target range and rarely led to drug discontinuation.

O3 IMPACT OF WEIGHT CHANGE, 1 YEAR AFTER RENAL TRANSPLANTATION, ON LONG-TERM SURVIVAL

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Background: Post-transplant weight gain is a common phenomenon in USA affecting 50% of the recipients, with an average weight gain between 5 and 10 kg. However, few European data are available. Our objective was to evaluate the long-term effect of one-year post-transplant weight change.
Methods: 997 kidney transplant recipients between January 2007 and November 2017, with a functional graft at one year, were included in this study. 4 groups were formed according to one-year weight change : 1) stable weight ranging less than 5% of initial weight (reference), 2) weight loss >5 %, 3) weight gain between 5 and 10% and 4) weight gain greater than 10%. Our primary outcome was death-uncensored graft survival.
Results: At one-year post-transplantation, we found an average weight gain of 0.86 ± 6.58 kg. The median follow-up time was 4.24 years [2.27–7.52]. 4-year survival was 91.80% [89.80%–93.90%]. At one year, the weight was: stable in 412 recipients (41.30%), increased by 5 to 10% in 180 recipients (18.05%) and greater than 10% in 181 recipients (18.15%). Conversely, there was a weight loss greater than 5% in 224 patients (22.40%). One-year weight loss was significantly associated with a risk of transplant failure (HR 1.55 [1.02 - 2.36]). However, we did not show any influence of weight gain (weight gain between 5 and 10%: HR 0.70 [0.40–1.23], weight gain ≥ 10%: HR 1.43 [0, 87 to 2.35]).
Conclusion: Our study shows that weight loss at one year of transplantation is significantly associated with the risk of transplant failure. This suggests that weight loss may be a simple factor reflecting deleterious events that may have occurred during the first few months of transplantation. It should alert the clinician and require specific management of these at-risk patients, in order to improve their nutritional status with an enhanced monitoring.

O4 IDARUCIZUMAB (PRAXBIND®) FOR DABIGATRAN REVERSAL IN PATIENTS UNDERGOING HEART TRANSPLANTATION: A RETROSPECTIVE COHORT OF 10 PATIENTS

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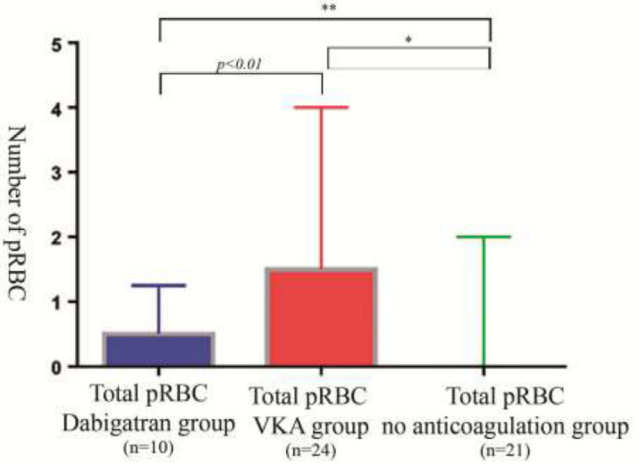
Background: Novel oral anticoagulants are used for the prevention of stroke in atrial fibrillation (AF) and both prevention and treatment of thromboembolic events. The necessity to reverse their activity in case of urgent procedures with unknown timing, like heart transplantation (HTX), is crucial. Idarucizumab has been approved for reversal of dabigatran in situations of life-threatening hemorrhage or emergency surgery.
Objectives: We report a monocenter experience of 10 patients on dabigatran who were given idarucizumab prior to HTX.
Methods: This is a retrospective analysis of a cohort of 10 patients treated with dabigatran for AF and who underwent HTX after having received 5 g idarucizumab. Clinical details and laboratory findings at baseline, during surgery and 24 hours after surgery were assessed.
Results: Patients presented with various characteristics of heart failure including dilated cardiomyopathy, ischemic cardiomyopathy or other common causes like restrictive or valvular cardiomyopathy. The mean plasma concentration of dabigatran prior to reversal was 139 ± 89 ng/ml. Hemoglobin, hematocrit and platelet levels were decreased after surgery, as were activated coagulation and Kaolin clotting times. HTX procedures were successfully

performed with no increased risk in bleeding complications. All patients were alive and well after 90 days.
Conclusions: Dabigatran reversal with idarucizumab in contexts of emergency surgery/urgent procedures is an attractive and safe option to be taken in consideration for patients with end-stage heart disease awaiting transplantation. These results have to be confirmed in clinical trials before the use of idarucizumab in this setting can be recommended whether the dose of plasma dabigatran is documented or not.



O5 ACCURATE ASSESSMENT OF THE GLOMERULAR FILTRATION RATE (GFR) IN KIDNEY TRANSPLANT RECIPIENTS USING BAYESIAN ESTIMATION OF THE IOHEXOL CLEARANCE

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Background: Plasma iohexol clearance ($CL_{iohexol}$) is a reference technique for GFR evaluation. In routine practice, $CL_{iohexol}$ is calculated using one of several formulas, which have never been validated in kidney transplant recipients. We aimed to model iohexol pharmacokinetics in this population, evaluate the predictive performance of three simplified formulas, and evaluate whether a Bayesian estimator (BE) improves $CL_{iohexol}$ estimation.
Methods: After administration of iohexol, six blood samples were drawn from 151 patients at various time-points. The dataset was split into two groups, one being used to develop the population pharmacokinetic model and the other to estimate the predictive performances of the various GFR estimation methods. GFR reference values (GFR_{ref}) in the validation dataset were obtained by non-compartmental analysis. Predictive performances of the three abbreviated formulas and the BE were evaluated in terms of bias (ME), imprecision (RMSE) and number of predictions out of a ± 15% error interval around the GFR_{ref}.
Results: A two-compartment model best fitted the data. The BE with samples drawn at 30, 120, and 270 min allowed accurate prediction of GFR_{ref} (ME = 0.47%, RMSE = 3.42%), as did the Bröchner-Mortensen (BM) formula (ME = −0.0425%, RMSE = 3.40%). With both methods, none of the CL estimates were outside the bounds of acceptance of ± 15%. By contrast, Christensen and Jacobson's formulae failed to provide satisfactory results. The BM formula performed very well in patients with GFR < 30 mL/min/1.73 m^2 but the Bayesian method could not be evaluated in-depth due to the too small number of such patients with appropriate sampling times in the validation group.
Conclusion: GFR can be estimated with acceptable accuracy in kidney transplant patients using the BM formula, but also using the Bayesian algorithm developed herein. Its forthcoming availability as a free online calculation tool will allow its wide use in renal transplant patients.

O6 FEATURES AND OUTCOMES OF NATIVE KIDNEY CANCER IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: The risk of renal cancer in native kidneys among kidney graft recipient is 15-times higher than in the general population. Though the prognosis is usually good, it's the third leading cause of related cancer deaths in transplantation, and there is no recommendation on screening.
Methodology: Our study included all cases of native kidneys cancers of kidney transplant recipients, diagnosed in the University Hospital of Amiens between January 1998 and December 2017. We studied the patients and cancer characteristics, and analyzed them according to the histological type and size of the cancer.
Results: Among 53 patients, 57 cancers were diagnosed, with a mean follow-up of 98.9 ± 60 months. The mean age at diagnosis was 52.7 ± 10.1 years, the mean time between transplantation and diagnosis was 58.9 months. Fifty-one cancers were diagnosed during an annual screening, and 2 as a result of symptom. Clear cell renal cell carcinoma (CCRCC) was diagnosed in 56.1% of the cases, papillary renal cell carcinoma (PRCC) in 43.9%. At diagnosis, 48 cancers were classified T1a according to TNM staging, and 2 were metastatic. During the follow-up, 17 patients (32.1%) died. The main causes of death were infections (29.4%), cardiovascular events (23.5%), and cancer progression (11.8%). The 2 patients with metastatic cancer died within the year of diagnosis. CRCC were diagnosed earlier than PRCC (59.4% before 36 months after kidney transplantation vs 32.0%, p = 0.04). Tumors larger than 2 cm at diagnosis, were associated with a longer dialysis time (more than 36 months : 57.1 vs 26.7%, p = 0.028).
Conclusion: Renal cell carcinoma of native kidney, and more specifically PRCC are more common in kidney transplantation. The diagnosis when established at an early stage leads to favorable patient survival. Life expectancy in case of metastasis is less than one year. The impact of immunosuppressive treatment, and the modality of screening remain to be determined.

O7 EARLY BLOOD TRANSFUSION AFTER KIDNEY TRANSPLANTATION AND INDUCTION WITH ANTI-THYMOCYTE GLOBULIN DOES NOT LEAD TO DNDSA DEVELOPMENT

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The outcomes after kidney transplantation are largely driven by the development of *de novo* donor-specific antibodies (dnDSA), which may be triggered by blood transfusion. In this study, we investigated the link between early blood transfusion (EBT) and dnDSA development in a mainly anti-thymocyte globulin (ATG)-induced kidney transplant cohort.

We retrospectively included all recipients of a kidney transplant performed between 2004 and 2015, provided they had no pre-transplant anti-HLA alloantibodies and a graft survival of >3 months. DSA development was evaluated using Luminex. EBT was defined as the transfusion of at least one red blood cell unit over the first 3 months post-transplantation. Maintenance immunosuppression was based on tacrolimus and mycophenolic acid.

A total of 737 patients transplanted between 2004 and 2015 were included in our center, of which 737 satisfied our inclusion criteria. EBT was required for 207 patients (28%). Most patients received ATG induction (82.4%); the others received basiliximab induction (13.8%). DSA-free survival at 1-year post-transplantation was similar between EBT+ (1.45%) and EBT- patients (1.32%, chi-squared p = 1).Univariate Cox's regression between dnDSA-free survival and EBT was not significant (HR = 0.94, p = 0.83).

In a multivariate Cox's regression, adjusting for potential confounders, hemoglobin level was associated with dnDSA-free survival (HR = 0.76 for each 1 g/dL increase of hemoglobin, p < 0.001), independently of the number of HLA mismatches between donor and recipient (HR = 1.39 for each mismatch, p < 0.001), tacrolimus trough level (HR = 0.85 per 1 μg/L increase, p = 0.035), MPA dose (HR = 1.6 per 1 g/day increase, p = 0.17), recipient's age (HR = 0.98, p = 0.048), and graft rank (HR = 1.33, p = 0.45).

EBT did not induce dnDSAs in our cohort of ATG-induced patients, but later low hemoglobin level was associated with dnDSAs. This suggests a protective effect of ATG induction on preventing dnDSA development at an initial stage.

O8 HYDROCHLOROTHIAZIDE EXPOSURE INCREASES THE RISK OF LONG-TERM SQUAMOUS CELL CARCINOMA AFTER KIDNEY TRANSPLANTATION

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Introduction: Squamous cell carcinomas (SCC) and basal-cell carcinomas (BCC) represent a major concern for solid organ transplant recipient (SOTR). Aside from immunosuppressive status, known risk factors for non-melanoma skin cancer (NMSC) include age, male sex, light skin and - and especially for SCC - sun exposure. Hydrochlorothiazide (HCTZ) is a diuretic widely used to treat hypertension including in SOTR, that has been implicated in skin photosensitivity reaction. Recently a well-conducted observational case-

control study in the general population, found that HCTZ use was associated with an increased risk of NMSC especially SCC.
Methods: In our monocentric cohort of kidney (n = 2244), pancreas (n = 65) and combined kidney pancreas (n = 304) transplant recipients, transplanted between 2000 and 2017 we evaluated the association between HCTZ exposure and NMSC.
Results: Among the 2613 SOTR, 281 (10.8%) were exposed to HCTZ after the transplantation. The mean cumulative dose was 15 118 mg. Overall cumulative incidence rate of NMSC by 10 and 15 years was of 7.2%, 10.2% for SCC and 8.8%, 12.8% for BCC respectively. In a multivariate Cox regression analysis HCTZ exposure was associated with an increased risk of long-term SCC (after 3000 days post-transplantation) with an HR of 2.57 (95% CI: 1.20 - 5.47, p = 0.01). Multivariable logistic regression identified a dose-dependent relationship. We found no association between HCTZ exposure and BCC.
Conclusion: Physicians should be aware of the risk of long-term SCC in patients exposed to HCTZ and consider use of alternative antihypertensive agents, especially in patients with known non-modifiable risk factors.

O9 CHARACTERISTICS OF T/NK-CELL LYMPHOMAS AFTER RENAL TRANSPLANTATION: A FRENCH NATIONAL MULTICENTRIC RETROSPECTIVE STUDY

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Introduction: Post-Transplant Lymphoproliferative Disorders (PTLD) encompass a spectrum of heterogeneous entities ranging from benign lymphocytic proliferations to high-grade malignant lymphomas. Because the vast majority of cases PTLD arise from B cells, available data on T/NK-cell PTLD are scarce, which limits the quality of the management of these patients.
Methods: All adult cases of PTLD diagnosed in the 35 kidney transplant centers in France were prospectively recorded in the national registry between 1998 and 2007. To ensure all cases of PTLD-T/NK were identified, registry data were cross-checked with those of 2 independent databases: K-ViroGref and Tenomic.

Medical files of T/NK-cell PTLD were reviewed and data were compared with that of i) the 440 cases of B-cell PTLD from the registry, and of ii) a control cohort of 148 "conventional" T/NK-cell lymphomas.
Results: 58 cases of T/NK-cell PTLD were enrolled in the study. T/NK-cell PTLD occurred significantly later after transplantation and had a worse overall survival than B-cell PTLD ($p < 0.0001$). Depending on the clinical presentation, 2 subtypes of T/NK-cell PTLD could be distinguished: i) cutaneous (n = 16, 28%) and ii) systemic (n = 42, 72%), the latter being associated with a worse prognosis ($p < 0.0001$). Compared with systemic T/NK-cell lymphomas diagnosed in immunocompetent patients, overall survival of T/NK-cell PTLD was worse ($p < 0.0001$). This difference was neither entirely explained by the higher tumor mass at diagnosis, nor the more aggressive histological phenotype of systemic T/NK-cell PTLD, since multivariate analysis identified transplantation as an independent factor associated with death. Interestingly, transplanted patients were less intensively treated and responded less to immunochemotherapy than controls.
Conclusion: Systemic T/NK-cell are rare type of PTLD with bleak prognosis, likely because of suboptimal treatment and/or the detrimental impact of therapeutic immunosuppression.

BASIC TRANSPLANTATION

O10 MONITORING OF BKV-SPECIFIC IMMUNITY AFTER KIDNEY TRANSPLANTATION

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Introduction: BKV-associated complications are frequent following kidney transplantation but there is no specific biomarker to identify the recipients at risk. We evaluated the immunomonitoring of anti-BKV adaptive responses in this context.
Methods: We included kidney transplant recipients between March 1st and July 31st, 2019. IFN_γ secretion by PBMCs was assayed by EliSpot following stimulation by five major BKV antigens (VP1, VP2, VP3, small T and Large T). Genotype-specific BKV-neutralizing antibody (Nabs) titers in serum were assayed by seroneutralization. Patients were tested at Day (D) 0, D7, D30 and D90 post-transplant.
Results: 28 patients were included and followed for 99 ± 45 days after transplantation. BKV replication was detected in urine samples in 6/28 (delay: 16.7 ± 10.2 days). 4/6 developed a viremia (delay: 50 ± 27 days). There were no BKV nephropathy. At transplantation (D0), 25/28 recipients were BKV-seropositive (Nabs > 3 log IC_{50}). Among them, anti-VP1 specific responses were high (median 29.2 SFU/10^6 $CD3^+$, IQR [12.5–76.3]). All 25 patients showed a loss of BKV-specific T cells by D7 (VP1 median 13.3 SFU/10^6 $CD3^+$, IQR [0–30.0], $p < 0.01$). 15 patients completed the study by D90: anti-BKV responses remained inhibited in 5 patients, recovered to D0 levels in 8 (including 2 viremic) and were markedly increased in the 2 other viremic patients. BKV-specific T-cell numbers in patients with or without BKV replication were similar at each time. The 6 patients who developed a BKV replication had low humoral protection (Nabs < 4 log IC_{50}) against the donor's BKV genotype(s) at D0.
Conclusion: The early post-transplant period is associated with a significant impairment of BKV-specific immunity. Hence, the presence of an effective humoral protection may be critical in this period. Clinical and biological follow-up of the patients with BKV replication should be continued to evaluate the potential utility of this immunomonitoring strategy.

O11 MISSING SELF TRIGGERS NK-MEDIATED MICROVASCULAR INJURIES AND CHRONIC REJECTION OF ALLOGENIC KIDNEY TRANSPLANTS

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Introduction: Organ transplantation is the best treatment for terminal organ failure. However, long-term outcome of organ transplantation remains limited by inexorable loss of graft function, which the prevalent dogma links to the microvascular inflammation triggered by the recipient's antibody response against alloantigens (chronic antibody-mediated chronic rejection, cAMR).
Methods & Results: Analysing a cohort of 129 renal transplant patients with microvascular inflammation on graft biopsy, we found that, in half of the cases, histological lesions were not mediated by allo- or auto-antibodies. In these patients, genetic studies revealed a higher prevalence of mismatches between donor HLA-I and inhibitory Killer-cell immunoglobulin receptors (KIR) of recipient's NK cells. We hypothesized that the allogeneic nature of graft endothelium could create a "pseudo-missing self" situation, thereby the recipient's NK cells exposed to inflammatory stimuli would not receive HLA-I-mediated inhibitory signals from donor endothelial cells. In co-culture experiments with human NK cells and endothelial cells, we demonstrated that the lack of self HLA-I on endothelial cells can activate NKs. In return, these NKs can kill endothelial cells. Finally, we confirmed the existence of missing self induced NK-mediated rejection in a murine heart transplantation model.
Conclusion: Our work identifies a new type of chronic rejection, exclusively mediated by innate NK cells, that has the same detrimental impact on graft survival as cAMR.

O12 T-CELL RECONSTITUTION AFTER LYMPHOCYTE DEPLETION FEATURES A DIFFERENT PATTERN OF INHIBITORY RECEPTOR EXPRESSION IN ABO-VERSUS HLA-INCOMPATIBLE KIDNEY TRANSPLANT RECIPIENTS

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Chronic antigen stimulation can lead to a state of reversible T-cell dysfunction, sometimes refer to as immune exhaustion. Several phenotypic signatures of T-cell immune exhaustion have been described in various pathological situations, characterized by aberrant expression of multiple inhibitory receptors. This signature has been barely studied in the context of allogenic organ transplantation. Thus, we undertook a cross-sectional analysis of the expression of inhibitory receptors (CD244, CD279, TIGIT and CD57) and their correlation with cytokine-producing functions in T cells reconstituting after lymphocyte depletion in patients with a high immunological risk, owing to the presence of donor-specific antibodies, transplanted with kidneys from living donors. In the group of patients transplanted across the ABO barrier, T cells progressively acquired a phenotype similar to healthy donors, and the expression of several

inhibitory receptors marked cells with increased functions, with the exception of TIGIT, which was associated to decreased cytokine production. In stark contrast, T-cell reconstitution in patients with anti-HLA antibodies was characterized with an increased co-expression of inhibitory receptors by CD4+ and CD8+ T cells, and specifically by an increased expression of TIGIT. Furthermore, expression of these receptors was no longer directly correlated to cytokine production. These results suggest that T-cell alloreactivity in HLA-incompatible kidney transplantation drives an aberrant T-cell reconstitution with respect to inhibitory receptor profile, which could have an impact on the transplantation outcome.

O13 EVALUATION WITH SINGLE ANTIGEN BEADS ASSAY OF THE DILUTION EFFECT OF THE MFI SIGNAL OF ANTI-HLA ANTIBODIES TARGETING PUBLIC EPITOPES

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Introduction: Anti-HLA antibodies (Abs) can target public epitopes shared by different HLA alleles. These Abs can be detected by several Single Antigen (SAG) beads. The MFI of these Abs can thus be diluted on all the beads sharing the public epitope. In case of specific immunization against the graft, there is a risk of underestimation of the MFI of the specific Ab if it targets a public epitope.
Methods: The public epitopes E2, 2C, Bw4 and 40.G + 47C present respectively on 5, 12, 25 and 6 SAG beads were studied. For each epitope, about ten sera from different patients with specific immunization against a public epitope were selected based on the results of the SAG tests from the Histocompatibility Laboratory at Saint-Louis Hospital. To study the dilution effect, public epitopes were isolated from the routine SAG panel using isolated beads (SAGi) carrying one of the selected public epitopes. The MFI of these SAGi beads was compared alone (SAGi condition) and then mixed into the SAG routine panel (SAGp+i condition). A decrease in the MFI of SAGi beads between the 2 conditions was expected, ranging from 80% to 96% depending on the epitope.
Results: For each epitope in routine SAG testing, the MFI of the beads which didn't carry the epitope was negative (MFI < 500) confirming the specificity of the selected sera. For epitopes E2 and 2C, a non-significant decrease in the MFI of 2% and 1% respectively was observed between the 2 conditions ($p > 0.05$). For epitope Bw4, the MFI of the SAGi bead decreased from 10535 ± 5250 to 9577 ± 4998 ($p < 0.05$) corresponding to a significant decrease of 10% between the 2 conditions, far from the expected decrease of 96%. Concerning the 40.G + 47C epitope, a significant increase of 10% in MFI ($p < 0.05$) was found between the 2 conditions.
Conclusion: The decrease in MFI was less than the inter-series variations of the Luminex technique (15%). No dilution effect related to the public nature of the epitopes has been identified.

O14 CELL THERAPY FROM CIRCULATING ENDOTHELIAL PROGENITORS TO REDUCE ISCHEMIA/REPERFUSION INJURY IN LIVER TRANSPLANTATION: ESTABLISHMENT OF THE PROOF OF CONCEPT *IN VITRO* AND IN A MURINE MODEL OF HEPATIC ISCHEMIA REPERFUSION

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Extended criteria donors are particularly sensitive to ischemia-reperfusion (IR) occurring during transplantation. The aim of this study is to develop a cell therapy strategy using circulating endothelial progenitors (ECFCs) to reduce IR injury during liver transplantation.

In vitro, two models of hypoxia-reoxygenation (HR) have been developed for human hepatocytes (HepG2 cell line) (cold hypoxia, 24 h, UW (HF-R) and warm hypoxia 14 h (HC-R)). Cell survival (LDH release, Cristal Violet, XTT assay) and transcriptomic modifications (RT-qPCR) were evaluated in the presence of medium conditioned by ECFC (CM) or exosomes (from ECFCs) isolated by ultracentrifugation and characterized (electronic microscopy, western blot). *In vivo*, a model of IR has been used on wild type C57 black 6 (10 animal per group) : ischemia 70 minutes, 70% with intra-portal injection (groups sham, IR + vehicle, IR + exosomes) with biochemical follow-up as well as histological analysis at Day 14.

Both HR protocols induce a significant hepatocyte death and the use of CM during reoxygenation significantly reduce this mortality (HF-R). The use of exosomes during reoxygenation impact cell transcriptional profile towards a better cell survival (HC-R). *In vivo*, our first results allow validating both the model of intra-portal injection after murine hepatic IR and the mice follow-up until Day 14; with an observed peak of ALAT/ASAT at Day 1 and LDH at Day 5. Histological lesions are present at Day 14 (necrosis, fibrosis area, inflammatory infiltrate).

Those results bring the *in vitro* proof of concept of the interest to use ECFCs or exosomes in adjuvant cell therapy for liver transplantation. The experimental groups allowing the *in vivo* assessment of exosome impact have just been performed and results will be available after the 14-days period of mice follow-up.

O15 HUMAN CIRCULATING T FOLLICULAR HELPER CELLS ACQUIRE AN ACTIVATED PHENOTYPE AND ROBUST B-CELL HELPER FUNCTION DURING ANTIBODY-MEDIATED REJECTION AFTER KIDNEY TRANSPLANTATION

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Introduction: Antibody-mediated rejection (ABMR) is the leading cause of allograft failure after kidney transplantation. The cellular events that lead to the induction of a deleterious alloantibody response are poorly understood in humans.
Methods: Using high-dimensional flow cytometry, *in vitro* assays and RNA-sequencing, we broadly characterized circulating T follicular helper cells (cT_{FH}) in patients with biopsy-proven ABMR (N = 21), patients with DSA without ABMR (N = 27) and patients without DSA (N = 48) in the first year post kidney transplantation.
Results: At the time of ABMR, cT_{FH} upregulated multiple activation markers and expressed more ICOS, PD-1, c-Maf and Irf4 as compared to patients with DSA without ABMR and those without DSA. Consistently, cT_{FH} transcriptomic profile was highly enriched with costimulatory and germinal center T_{FH} gene signatures in patients with ongoing ABMR. cT_{FH} from these patients were more functionally capable to induce B-cell differentiation into antibody-secreting cells and DSA generation *in vitro*.

Unlike non-rejectors, cT_{FH} cells co-expressing Ki67 and ICOS greatly expanded up to 6 months prior to ABMR and remained elevated at the time of rejection. $Ki67^+ICOS^+$ cT_{FH} correlated with the concomitant expansion of effector B cells and the emergence of high levels DSA. Moreover, high frequencies of $Ki67^+ICOS^+$ cT_{FH} identified patients with a more severe form of ABMR associated with increased IgG3 and complement-binding DSA response, more severe allograft injury and increased rate of allograft loss.
Conclusion: In patients with ongoing ABMR, cT_{FH} cells acquire an activated phenotype and a specific transcriptomic program with enhanced capability to provide robust B-cell help. Monitoring and targeting cT_{FH} response represent valuable strategies to early detect and prevent ABMR occurrence post-transplant.

O16 HUMAN CIRCULATING T FOLLICULAR HELPER CELLS WITH TH17 POLARIZATION ARE HIGHLY FUNCTIONAL AND CORRELATE WITH DONOR-SPECIFIC ANTIBODIES PATHOGENICITY IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: T follicular helper cells (T_{FH}) provide help to B cells that is critical for class-switched antibody generation. How T_{FH} subsets may differently impact the magnitude and the quality of donor-specific antibody (DSA) response is unclear.
Methods: Using multiparametric flow cytometry and *in vitro* assays, we evaluated the heterogeneity of circulating T_{FH} cells (cT_{FH}) subsets, their relationship with B-cell response, DSA pathogenicity (strength, C1q-binding, IgG subclasses) and antibody-mediated rejection (ABMR) in 96 kidney recipients.
Results: At the time of DSA detection, patients who developed DSA (N = 48) had higher frequencies of activated ($Ki67^+ICOS^+$) cT_{FH} ($CD4^+CD45RO^+CXCR5^+$) than patients without DSA. Frequencies of $Ki67^+ICOS^+$ cT_{FH} correlated with the expansion of antibody-secreting cells (ASC) and DSA MFI levels. Four distinct polarized subsets were identified according to CXCR3 and CCR6 expression : Th1, Th1/17, Th2 and Th17.

While frequencies of Th1 and Th1/17 were comparable, Th17 $Ki67^+ICOS^+$ cT_{FH} was significantly increased in patients with $IgG3^+$ and those with $C1q^+$ DSA compared to patients with $IgG3^-$ and $C1q^-$ DSA respectively.

Conversely, frequencies of Th2 $Ki67^+ICOS^+$ cT_{FH} were higher in patients with $IgG1^+$ compared to patients with $IgG1^-$ DSA. There were no differences in subsets distribution according to IgG2 or IgG4 DSA status.

Patients who developed ABMR displayed higher frequencies of Th17 compared to those with DSA without ABMR.

When co-cultured with B cells, all subsets of cT_{FH} could induce ASC formation. However, cT_{FH}-Th17 induced more ASC and IgG3 production while cT_{FH}-Th2 induced greater IgG1 production compared to all other subsets.
Conclusion: Despite heterogeneity in cT_{FH} subsets, we found that cT_{FH}-Th17 was predominantly associated with DSA pathogenicity *in vivo* and had the best helper function *in vitro*. Specific targeting of cT_{FH}-Th17 response may represent a valuable strategy for therapeutic intervention in ABMR.

O17 AN AUTOMATIC SOLUTION FOR THE INTERPRETATION AND MANAGEMENT OF ANTI-HLA ANTIBODIES DETECTED IN "SINGLE ANTIGEN": CONCEPT AND FUNCTIONALITIES

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The interpretation of the single antigen (MFI) fluorescence profiles of the anti-HLA antibodies (Ab) can be complex, because of the subtleties of the polymorphism of the many HLA alleles studied in these tests [nearly 100 in class I (A, B, C) and as many in Class II (DR, DQ, DP)]. Indeed, an Ab recognizes an epitope and not the whole antigen, and the distribution of epitopes does not follow the official antigenic HLA nomenclature, used by the CRISTAL tool of the Biomedicine Agency (ABM). In addition, alleles are present at very different frequencies in the population. Finally, DQ and DP are heterodimers of two polymorphic chains each having its own epitopes and others involving particular combinations of the two chains. In pre-transplantation, organ graft allocation is based on compatibility at the antigen level, but HLA typing often defines the most probable alleles of the recipient and donor without error. By reasoning at a level of information equal to that of the study of Ab, one can thus avoid penalizing a patient by overestimating or misestimating his immunization. In post-transplant, it will be the same for the identification of a donor-specific Ab (DSA). However, in practice, without an automatic analysis tool, taking into account of all the elements mentioned above requires a significant investment of time, with the risk of error inherent in manual interpretation.

We will describe a tool for automatic interpretation of "single antigen" profiles, adaptable to the needs of each team, which integrates the constraints exposed as well as the SFHI criteria of analysis of Ab. This tool makes it possible to precisely define (qualitative: antigenic / allelic and quantitative: level of MFI), 1) in a serum the profile of Ab and DSA, and 2) from all the studied sera of the patient the profile of unacceptable/ grey zone / acceptable antigens for CRISTAL, with update during pre-transplant follow-up. It has been working in the laboratory since august 2nd, 2019.

O18 KIDNEY-CENTERED RADIOTHERAPY ATTENUATES RENAL ISCHEMIA-REPERFUSION INJURY IN MOUSE

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Introduction: Whole-body irradiation has been associated with renal ischemic preconditioning in mice. Here, we investigate the functional and fundamental impact of radiotherapy centered on the kidneys before renal ischemia/reperfusion (I/R).
Methods: Experience 1: Animals (n = 6) were anesthetized and placed in the irradiator. Two beams of X-rays (225 Kv, 13 mA) specifically targeted both kidneys to deliver a dose of 8.56 Gy. Thirty days later, a right nephrectomy was performed, and a left renal ischemia was induced for 30 min. After 48 h of reperfusion, the left kidney was collected, as well as blood. Control group (n = 6) underwent a similar renal I/R, with no prior irradiation.

Experience 2: Unilateral irradiation of left kidneys (8.56 Gy) was performed on mice (N = 11). Thirty days later, the left (irradiated) kidney was removed, as well as (controls) kidneys from non-irradiated mice (N = 5). Total RNAs were extracted from irradiated and control kidneys to perform comparative transcriptomics (BaseSpace Illumina; DAVID program).
Results: Following kidney I/R, blood urea nitrogen (BUN) levels were significantly lower in pre-irradiated mice (148 $\pm$ 93 mg/dl) compared to controls (495.7 $\pm$ 33.3, $p < 0.01$). The number of PCNA-positive proliferating cells was significantly lower in irradiated mice compared to controls (131 $\pm$ 53 vs. 545 $\pm$ 257/mm^2, $p < 0.001$). The renal infiltration by inflammatory CD11b-positive cells (90 $\pm$ 32 vs. 414 $\pm$ 149/mm^2) and F4-80-positive macrophages (81 $\pm$ 23 vs 179 $\pm$ 68/mm^2) was significantly reduced in irradiated animals. Comparative transcriptomics showed a significant up-regulation of signaling pathways of angiogenesis (Hmox1) and stress response (Hspa1a, Hspa1b), and a down-regulation of oxido-reduction (Nox4).
Conclusion: Kidney irradiation induces ischemic preconditioning in mice, with improved renal function and decreased inflammation following renal I/R. The aforementioned signaling pathways may play a role in irradiation-associated kidney resistance to I/R.

TRANSPLANT SURGERY

O19 ROBOTIC-ASSISTED KIDNEY TRANSPLANTATION IN OBESE RECIPIENTS COMPARED TO NON-OBESE RECIPIENTS: THE EUROPEAN EXPERIENCE

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Background: The main objective of this present study, from the European Robotic Urological Section (ERUS) group, was to compare postoperative minor (Clavien I-II [1]) and major (Clavien [3]III) complications between obese recipients ([3]30 kg/m^2 BMI), overweight recipients (<30/[3]25 kg/m^2 BMI) and non-overweight recipients (<25 kg/m^2 BMI). The secondary objective was to compare functional results (renal function) between obese, overweight and non-overweight recipients.
Methods: We reviewed the multi-institutional ERUS-RAKT database to select consecutive recipients undergoing RAKT from living donors. Functional outcomes, intra- and postoperative complications were compared between obese, overweight and non-overweight recipients.
Results: 169 RAKTs from living donor were performed from July 2015 to September 2018. 32 (18.9%) recipients were obese, 66 (39.1%) recipients were overweight and 71 (42.0%) recipients were non-overweight. In terms of minor and major postoperative complications, no statistical differences were identified in obese, overweight and non-overweight recipients. There were no major intraoperative complications in the different groups and the surgical conversion rate was similar. In the univariate analysis, age, BMI and the number of graft arteries were significant predictors of suboptimal renal function (eGFR < 45 ml/min/1.73 m^2) on POD 30. Only the number of graft arteries was an independent predictive factor of suboptimal renal function on POD 30 in the multivariate analysis. One-year serum creatinine and eGFR were similar in the different groups.
Conclusions: In obese recipients, RAKT provides excellent graft function and similar complication rates compared to overweight and non-overweight recipients. Robotic surgery would therefore enable obese patients with ESRD to access kidney transplantation.

O20 LAPAROSCOPY FOR LIVING DONOR NEPHRECTOMY: COMPARISON OF THREE-DIMENSIONAL AND TWO-DIMENSIONAL VISION

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Objectives: The objective of this preliminary study was to compare safety and efficacy of three-dimensional laparoscopy versus two-dimensional laparoscopy for living donor nephrectomy.
Methods: All patients who underwent a left laparoscopic living donor nephrectomy were included from January 2015 to April 2018 in a university center. All surgeries were performed by three experimented surgeons.
Results: 73 patients were included: 16 underwent a living donor nephrectomy using 3D laparoscopy (3D group) and 57 using 2D laparoscopy (2D group). The two groups were equivalent for all parameters except the number of patients with medical history of high blood pressure (7 versus 4 in 3D and 2D group respectively, $p = 0.001$). The warm ischemia and operative time were significantly lower in 3D group (warm ischemia: 1.7 $\pm$ 0.6 versus 2.3 $\pm$ 0.9 minutes in 3D group and 2D group respectively, $p = 0.02$), (operative time: 80.9 $\pm$ 10.2 versus 114.1 $\pm$ 32.3 minutes in 3D group and 2D group respectively, $p = 0.0002$). The length of hospital stay was significantly shorter in the 3D group. Postoperative complications rate was similar in both study groups. No transfusion was recorded.
Conclusions: Three-dimensional laparoscopic living donor nephrectomy is a safe procedure. The 3D vision system allows to decrease warm ischemia, operative time and length of hospital stay compared to two-dimensional laparoscopy.

O21 LIVING DONOR KIDNEY TRANSPLANTATION: COMPARISON OF SEQUENTIAL AND SIMULTANEOUS SURGICAL ORGANIZATIONS

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Purpose: The objective was to compare living donor kidney transplantation (LDKT) performed either sequentially, in one operating room, leading to extended cold ischemia time (CIT) or simultaneously, in two different operating room, with shorter CIT.
Methods: We retrospectively included all living donor nephrectomies and kidney transplantations, performed from March 2010 to March 2014, in three French university centers. In the first one (C1), LDKT was performed in sequential manner (Sequential group) and in C2 and C3, LDKT were performed in simultaneous manner (Simultaneous group).
Results: A total of 324 LDKT were performed: 176 LDKT in Sequential group and 148 LDKT in Simultaneous group. Patients characteristics were equivalent in both groups, except for left nephrectomy side, ABO mismatch and previous kidney transplantation rate, that were significantly higher in Sequential group. CIT, rewarming time, transfusion and delayed graft filtration were significantly higher in Sequential group. One- and five-year serum creatinine, 5-years eGFR and graft losses, were similar between groups. In univariate analysis, no predictive factor of suboptimal renal function at 5-years was identified.
Conclusions: Sequential surgical organization presents same functional results than simultaneous surgical organization.DGF was higher for LDKT performed sequentially but at 5-years, graft losses and eGFR were similar between these two types of transplant organizations.

O22 OUTCOMES OF KIDNEY TRANSPLANTATIONS INTO INTESTINAL RECONSTRUCTION OF THE LOWER URINARY TRACT: A BICENTRIC CONTROLLED TRIAL

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Introduction: Chronic asymptomatic bacteriuria and increased risk of pyelonephritis in patients with intestinal reconstruction of the lower urinary tract (LUT) have long dismissed these patients from transplantation despite their young age and potential transplantations benefit. Available studies concerning graft survival, surgical complications, pyelonephritis occurrence in these patients remain old and uncontrolled. The aim of our study was to report the prognosis of transplantations in patients with intestinal reconstruction of the LUT compared to transplantations in patients with normal LUT in the current context of surgical and immunosuppressive therapy.
Methods: We conducted a retrospective study including 23 patients with a LUT reconstruction who received a kidney transplant between 2004 and 2016 at two French transplant centers. Patients were matched by propensity scores to 46 kidney recipients with normal LUT. We compared 1, 5- and 10-years graft survival between the two groups and their overall survival, graft function, surgical complications and pyelonephritis occurrence.
Results: One, 5- and 10-years graft survival was respectively 98%, 88% and 69% in reconstruction group and 96%, 89% and 70% in controlled group ($p = 0.974$). Patients with reconstruction had increased risk of pyelonephritis at 10 years (72% vs 19%; Log-rank < 0.01), had as many surgical complications but more urological complications than controlled group (62% vs 28%; $p < 0.01$). Graft function at 1-,5- and 10 years was similar.
Conclusion: Our study consolidates results concerning safety by transplanting patients with LUT reconstruction with intestine using a strong validated matching method and gives new information about graft function, pyelonephritis and surgical complications occurrence.

O23 SUCCESSFUL REUSE OF A KIDNEY GRAFT IN AN ADULT RECIPIENT EIGHT MONTHS AFTER EARLY RECURRENCE OF IDIOPATHIC FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS

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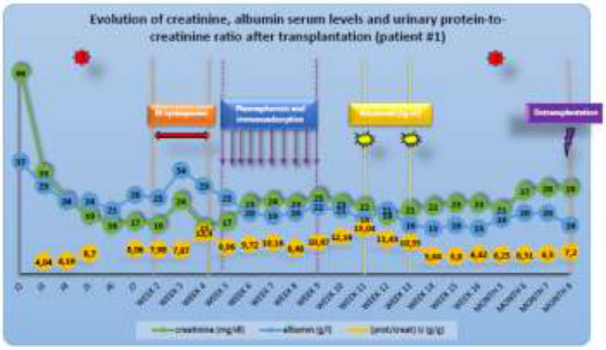
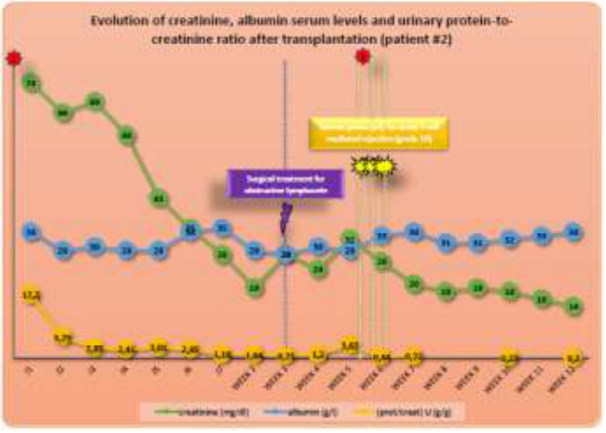
Introduction: Idiopathic focal and segmental glomerulosclerosis (iFSGS) frequently recurs after transplantation (30–40% of cases). Due to the lack of effective therapy able to control the nephrotic syndrome, the question of detransplantation may arise in this situation. To date, only 2 cases have described in this particular situation the reuse of a detransplanted graft for a second recipient, in pediatric patients and very shortly after transplantation (within a month).

We describe hereafter the reuse of a kidney graft in an adult recipient eight months after early iFSGS recurrence resistant to all available therapeutics.
The case: The patient P1, a 23-year-old man, followed for end-stage renal disease secondary to iFSGS, was first transplanted in 2018 with a cadaveric donor graft. We observed an immediate recurrence of biopsy-proven iFSGS (within the first 15 days). After four lines of treatment including IV Ciclosporin, plasma exchanges, immunoadsorption and 2 injections of 1 g-Rituximab, the patient remained nephrotic (proteinuria 7 g/24 h, albuminemia 16 g/L). Serum creatinine levels at M3 and M8 were respectively 19 and 28 mg/L.

At M8, after approval of both Biomedicine Agency and patient P1, the graft was detransplanted and reimplanted in patient P2, a 78-year-old recipient, isogroup, non-immunized, and anephric (binephrectomy 2 years before for bilateral renal carcinoma). We observed an immediate kidney function and a progressive decrease in proteinuria (creatinine serum 14 mg/L, proteinuria 0.2 g/24 h at M3). (See figure) The biopsies performed during and after surgery (red stars on the figure) confirm the persistence of iFSGS-related and segmental podocytic lesions, without any chronic kidney damage.
Conclusion: This is, to our knowledge, the first reported case of successful reuse of a renal graft in an adult recipient, several months after the early recurrence of a corticosteroid-resistant nephrotic syndrome.





O24 EVALUATION OF CT PARAMETERS TO PREDICT COMPLICATIONS IN OBESE RENAL TRANSPLANT PATIENTS

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Purpose: To develop a model for predicting surgical complications and need of postoperative dialysis using scanographic measures of abdominal obesity in renal transplant obese recipient.
Methods: A retrospective monocentric study, from 2012 to 2017, of kidney transplant recipients with body mass index over 25 kg/m^2 was performed. CT measures were done retrospectively on the preoperative CT scan. Multivariate logistic regression was used to create predictive models of surgical complications and the use of postoperative dialysis.

Results: A total of 224 patients were analyzed of whom 155 (67%) had no surgical complication. Stepwise selection retained a model with external anteroposterior diameter, cold ischemia time, residual diuresis and smoking for the occurrence of at least one surgical complication with an area under the curve (AUC) of 0.6347. At least two dialysis was needed in 51 patients (23%). A model with sex, external perimeter and age was selected (AUC 0.6477 versus 0.556 for BMI alone). Parietal complications occurred in 13 patients (6%). The selected model included external perimeter, external/internal perimeter ratio, skin-vessels distance and sub-cutaneous thickness (AUC 0.8443 versus 0.723 for BMI alone). Urinary complications occurred in 14 patients (6%). The selected model included external anteroposterior diameter and smoking (AUC 0.6918 versus 0.503 for BMI alone).
Conclusion: Prediction models of surgical, parietal, urinary complications and also the need for postoperative dialysis using scanographic measures of obesity were created. However, a validation with an external cohort is needed.

O25 RENAL ALLOGRAFT VENOUS THROMBOSIS IN KIDNEY TRANSPLANTATION AND ITS IMPACTS

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Background: Kidney transplantation is the best treatment for end-stage renal disease. Improvement of immunosuppressive therapies has led to better outcomes. Vascular complications, mainly early Renal Vein Thrombosis (RVT) are found in 1 to 5% of the patients and are a major cause of early graft loss despite urgent intervention.
Patients and Methods: We retrospectively reviewed 946 transplant patients between May 2009 and May 2019 in our center to identify the frequency of RVT, its clinical presentation, associated risk factors, their management and outcomes.
Results: 21 patients (2.2%) had RVT, diagnosed in most of the cases during the first 2 days after transplantation (16 patients, 72%). Urgent exploration (Doppler ultrasound, CT scan or MRI) was performed in all cases. Several factors have been identified, relied to the donor (n = 11) (9 patients had a graft from non-heart beating donors, one had small vessels from a very young donor and one had a retro aortal vein), or to the recipient (the mean BMI is 28 kg/m^2 with 9 patients having a BMI above 30, five patients had a medical history of venous thrombosis and three patients had a constitutive hypercoagulation status) or to technical difficulties during the surgery (n = 10).

20 out of the 21 patients lost their graft and had a nephrectomy. Only one graft was salvaged because the diagnosis of RVT was made at the end of the transplantation and an immediate thrombectomy was performed with anticoagulant treatment immediately started following the surgery. RVT patients had a longer stay in the hospital and more post-operatory complications than RVT free patients. 38% became highly sensitized after this 1st complicated transplantation and access for a second transplantation was more complicated.
Conclusions: RVT is an uncommon but serious event. The usual issue is graft loss because the diagnosis is almost always too late.

O26 IS KIDNEY TRANSPLANTATION WITH CONCOMITANT NEPHRECTOMY AN EFFECTIVE STRATEGY IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE?

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Introduction: In autosomal dominant polycystic kidney disease (ADPKD), native kidney nephrectomy can be indicated for complication or in order to receive a kidney transplant. The aim of the study is to evaluate post-operatory results and long-term outcomes of two strategies: nephrectomy with concurrent transplantation or nephrectomy prior to transplantation.
Methods: 76 patients with ADPKD which had a transplantation and an ipsilateral nephrectomy, concurrent or not, between 2007 and 2017 were included, except those who underwent simultaneous liver-kidney transplantation and patients with missing data: 38 with concurrent surgery (Group 1) and 38 with nephrectomy prior to transplantation (Group 2). Donors and recipients characteristics were evaluated retrospectively. Every postoperative and long-term complications were reviewed. Graft survival was monitored comparing renal function with t test.
Results: 76 patients had comparative characteristics beside age (51.6 yo, group 1 vs 55.9 yo, p = 0.024), preemptive transplantation rate (76.3, group 1 vs 2.6%, p < 0.0001). They were 86.5% living donor (LD) in group 1 vs 15.1% in group 2. The average time from nephrectomy to transplantation was 56.5 months. Complication rate, including parietal ones, was similar. Acute and chronic rejection was similar to a comparative pre-transplantation risk. Graft survival wasn't different between the groups (p = 0.1) with a 6.8 years of follow-up.
Conclusion: Transplantation with concomitant nephrectomy is an effective strategy in ADPKD, with selected patient especially with LD. Morbidity and graft survival are similar. It reduces the number of hospital stays and can allow preemptive transplantation without transitory dialysis, particularly with LD.

O27 IS THERE A ROLE FOR ROBOTIC-ASSISTED LAPAROSCOPY IN PYELOURETERAL ANASTOMOSIS AFTER KIDNEY TRANSPLANTATION?

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Introduction: Urinary complication rate after kidney transplantation is about 5%.

Open surgery is still the gold standard for pyeloureteral anastomosis after kidney transplantation, but robotic-assisted laparoscopy could be interesting in those cases.

We evaluated short outcomes after robotic-assisted laparoscopic pyeloureteral anastomosis post kidney transplantation.
Methods: We included 4 patients which had a robotic-assisted pyeloureteral anastomosis after kidney transplantation between 2018 and 2019.

Each patient had an initial Lich Gregoire ureterovesical anastomosis during transplantation.

They all had a robotic-assisted laparoscopy using per operative intracorporeal ultrasound to find the graft pyelon.
Results: The indication was in 3 cases a complicated reflux with iterative pyelonephritis with endoscopic treatment failure, and was a urinary fistula in 1 case.

Four left kidney grafts were transplanted in right iliac position.

The mean operative time was 99 minutes [79–119], blood loss was 80 ml [50–150]. Mean length of stay was 8 days [6–11]. No patient developed any severe complication (Clavien ≥ 3). Mean preoperative creatinine was 130.7 μmol/L and postoperative 121 μmol/L.

In a 5-month follow-up, they were no recurrence or major change in creatinine.
Conclusion: Robotic-assisted laparoscopy for pyeloureteral anastomosis seems an interesting alternative to deal with urinary complication after kidney transplantation, allowing with the use of intracorporeal per operative ultrasound. Our results show a low morbidity, a short length of stay and no recurrence.

IMMUNOSUPPRESSION

O28 INDUCTION THERAPY IN ELDERLY KIDNEY TRANSPLANT RECIPIENTS WITH LOW IMMUNOLOGICAL RISK

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Background: In non-immunized patients, similar rejection rates are observed for patients who have undergone Thymoglobulin (ATG) or Basiliximab (BSX) therapy. Whilst ATG may improve Delayed Graft Function (DGF), it may also be associated with higher infection rates and malignancy risk. We compared survival and clinical outcomes in elderly recipients with low immunological risk according to their induction therapy.
Methods: We conducted a multicentric study on non-immunized ≥65 years of patients receiving a first kidney transplant between 2010 and 2017. The principal outcome was patient and graft survival. Secondary outcomes were cumulative probabilities of infection, first acute rejection episode, malignancy, de novo DSA, Post-Transplant Diabetes (PTD), cardiac complications, eGFR, occurrence of DGF. Cox, logistic or linear statistical models were used depending on the outcome studied, and models were weighted on the propensity scores.
Results: 204 patients were included in the BSX group and 179 in the ATG group, with the average age 71.0 and 70.5 years respectively. Patient and graft survival at 3 years post-transplantation were 74% (95%CI from 65% to 84%) and 68% (95%CI from 60% to 78%) in ATG and BSX group respectively, without significant difference. Occurrence of PTD was significatively higher in BSX group (23% vs 15%, p = 0.04) due to higher trough levels of Tacrolimus on month 3 (9.48 vs 7.30 ng/ml, p = 0.023). There was no difference in other evaluated outcomes.
Conclusion: In elderly recipients, ATG does not lead to poorer outcomes compared to BSX and could permit lower trough levels of Tacrolimus, thus reducing occurrence of PTD.

O29 EFFECT OF INDUCTION THERAPY ON OUTCOMES OF *DE NOVO* RENAL TRANSPLANT RECIPIENTS RECEIVING EVEROLIMUS WITH REDUCED-DOSE CALCINEURIN INHIBITOR: 24-MONTH RESULTS FROM TRANSFORM STUDY

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Background: To assess the effect of induction therapy on efficacy and safety outcomes of de novo RTx recipients (RTxR) receiving everolimus with reduced calcineurin inhibitor (EVR+rCNI) vs mycophenolate with standard CNI (MPA + sCNI) in the TRANSFORM (NCT01950819) study.
Methods: In this 24-month (M), phase IV, multicenter, open-label study, adult RTxR stratified by induction type (basiliximab [Bax] or rabbit anti- thymocyte globulin [rATG]) were randomized (RND) to receive EVR + rCNI or MPA + sCNI with steroids. Efficacy assessments were incidence of binary composite of tBPAR or eGFR < 50 mL/min/1.73 m2, incidence of tBPAR, graft loss (GL), or death, and evolution of eGFR up to M24; safety assessments were incidence of adverse events (AE) and infections.
Results: Of 2037 RND patients, 1693 received Bax and 342 received rATG. Consistent with overall data, the EVR + rCNI regimen was noninferior ($p < 0.001$) to MPA + sCNI for the binary endpoint at M24 for both induction groups. At M24, incidences of tBPAR, GL, and death were comparable between EVR + rCNI and MPA + sCNI arms regardless of induction type. Compared to Bax group, incidence of tBPAR was lower in both arms of rATG group. Mean eGFR was stable from Week 4 to M24 and comparable between arms at M24 for both induction groups. Though the incidence of AE leading to study drug discontinuation was higher in EVR + rCNI arm, the incidence of AE leading to dose adjustment/interruption was higher in MPA + sCNI arm. Incidence of viral infections was lower in EVR + rCNI vs MPA + sCNI arm in both induction groups. Consistent with overall data, incidence of CMV (Bax:8.4% vs 22.6%; rATG:10.1% vs 20.5%) and BKV (Bax:10.1% vs 14.1%; rATG:10.7% vs 20.5%) infections was lower in EVR + rCNI vs MPA + sCNI arm in both induction groups.
Conclusion: Irrespective of the induction type, EVR + rCNI regimen offers comparable efficacy and safety and stable renal function to that of MPA + sCNI regimen up to M24 post-RTx.

O30 EFFICACY, RENAL FUNCTION AND SAFETY OF EVEROLIMUS [EVR] WITH REDUCED-DOSE CALCINEURIN INHIBITOR [RCNI] IN *DE NOVO* KIDNEY TRANSPLANT RECIPIENTS [KTXR]: M24 RESULTS FROM THE FRENCH PATIENTS IN TRANSFORM STUDY

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Background: TRANSFORM is the largest prospective study in *de novo* kidney transplant recipients comparing efficacy and safety of EVR+ rCNI (tacrolimus [TAC] or cyclosporine [CsA]) to mycophenolic acid [MPA]+standard-dose of calcineurin inhibitors [sCNI] using a composite endpoint: antirejection efficacy and renal function.
Methods: This is a multicenter, open-label, randomized non-inferiority study. 2037 patients in 42 countries including 85 KTxR in 6 French centers received either EVR + rCNI (N = 41) or MPA + sCNI (N = 44). Patients received basiliximab or anti-thymocyte globulin induction with steroids. The primary objective was incidence of binary composite of treated biopsy-proven acute rejection [tBPAR] or estimated glomerular filtration rate [eGFR] < 50 mL/min/1.73 m^2; key secondary objective was incidence of tBPAR, graft loss, or death at M24. Incidences of donor-specific antibodies [DSA], adverse events [AE] and infections were also evaluated.
Results: In the French cohort, 87% of pts completed medication up to M24. The primary endpoint incidence was 57.7% with EVR and 58.6% with MPA (difference −0.9%; 95% CI −22.6 to 20.9). Composite of tBPAR, graft loss, or death at Month 24 occurred in 22% with EVR and 9.6% with MPA (difference 12.4–3.1, 27.9; tBPAR: 10% *vs* 2.3%, graft loss: 4.9% *vs* 4.5%, death: 7.7% *vs* 2.9%).Mean eGFR at M24 was 44.7 mL/min/1.73 m^2 (41.8; 51.3) for EVR and 48.4 mL/min/1.73 m^2 (42.5; 54.9) for MPA. Cytomegalovirus (0% *vs* 9.6%) and BK virus infections (7.1% *vs* 19.6%) were less frequent in the everolimus arm than in the MPA arm. Overall, 34.1% and 6.8% of patients treated with EVR and MPA, respectively, discontinued the study drug due to adverse events.
Conclusion: The results of the TRANSFORM study in France over 24 months reflect the results obtained over the entire study population. These results confirm the non-inferiority of the combination EVR + rCNI *vs* MPA + sCNI for efficacy, renal function, and tolerance with lower incidences of viral infections

O31 SAFETY OF BELATACEPT IN HIV-POSITIVE KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Kidney allograft survival in HIV-infected patients is lower than in the general population. Belatacept (instead of anticalcineurins (CNI)) has been shown to have a benefit in terms of long-term survival of patients and kidney allografts. Its use in transplanted HIV+ patients is currently poorly documented.
Methodology and methodology: All French kidney transplant centres were contacted and all HIV+ patients treated with belatacept were analyzed retrospectively. We studied patient survival, allograft survival, HIV disease progression, incidence of acute rejection and opportunistic infections, and evolution of donor-specific anti-HLA antibodies (DSA).
Results: Twelve patients were included in the study: 2 (16%) received belatacept de novo and 10 (84%) received a CNI-belatacept switch 10 [2–30] months after transplantation. One year after the start of treatment, patients' survival was 91% and kidney allografts survival was 91%. HIV infection remained controlled outside 2 (17%) reactivations (therapeutic non-compliance). Two (17%) acute corticosteroid-resistant cell rejects, 2 months and 2 years after the switch, were identified followed by a loss of the kidney allograft. Two (17%) opportunistic infections, tuberculosis with macrophage activation syndrome and norovirus diarrhea, have been reported in two patients within three months of treatment. DSAs were stable at 12 months of treatment.
Conclusion: After kidney transplantation, in HIV+ patients, belatacept can be used as a replacement for CNI with good survival of patients and kidney allografts and without major side effects within one year of treatment. A study with more patients and longer follow-up is needed to define the place of belatacept in HIV+ renal transplant patients.

O32 BELATACEPT TREATED PATIENTS EXPERIENCE IMPROVED HEALTH-RELATED QUALITY OF LIFE AND LOWER SYMPTOM DISTRESS COMPARED TO CYCLOSPORINE TREATED PATIENTS: AN ANALYSIS OF THE BENEFIT AND BENEFIT-EXT COHORTS

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Purpose: New immunosuppressive agents in transplant should not only be efficacious but also help patients feel better (i.e. lower patient-reported symptoms and improve health-related quality of life (HRQoL). Herein, we analyzed patients in the BENEFIT and BENEFIT-EXT trials longitudinally to determine the relative symptom and HRQoL differences between cyclosporine (CsA) and belatacept.
Methods: Patients were evaluated using the SF-36 (HRQoL) and the MTSOSD-59R (symptom) at baseline, 12, 24, and 36 months post-transplant for SF-36 (n = 831) and MTSODS-59R (n = 394, inclusive of patients who reported SF-36). We examined change from baseline and differences between treatment groups for all 8 subscales of the SF-36. The most distressing symptoms were identified and compared by treatment over time using ridit analysis.
Results: Overall, compared to CsA, belatacept treated patient had better HRQoL scores post-transplant across most SF-36 subscales (Figure A). Between treatment groups, there were a higher number of distressing symptoms ($p < 0.01$) in CsA treated patients at 12, 24, and 36 months post-transplant relative to belatacept treated patients. The symptoms that highly

differentiated cyclosporine from belatacept was trembling hands, feeling of warmth in hands and feet, swollen ankles, change in facial features, increased hair growth, muscle cramps, and swollen gums (Figure B). No symptoms appeared more distressing in patients treated with the belatacept less intense (LI) regimen.

Conclusions: Belatacept treatment (compared to CsA) resulted in improved HRQoL and lower symptom distress. Therefore, in addition to some clinical benefit of belatacept (i.e. lower DSA, improved graft survival), belatacept patients also feel better and have a better quality of life.

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Figure A. Average SF-36 scores at baseline, 12, 24, and 36 months post-transplant by treatment, n=831.

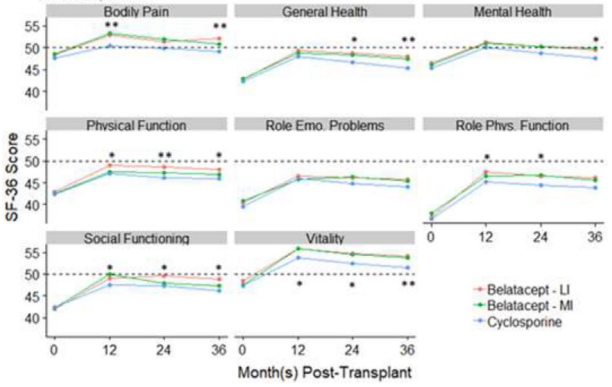

Figure B. Comparison of symptom distress at various time points between Cyclosporine, Belatacept – LI and Belatacept – MI based on ridit analysis, n=394.

Timepoint	Symptom	Mean Ridit			p-value
		Cyclosporine	Belatacept - LI	Belatacept - MI	
Month 12	Trembling hands	0.60	0.46	0.45	3.46E-08
	Feeling of warmth in hands/ feet	0.55	0.48	0.48	1.60E-03
	Swollen gums	0.56	0.47	0.48	8.75E-06
	Swollen ankles	0.55	0.48	0.48	3.01E-03
	Changed facial features	0.55	0.48	0.48	1.30E-03
	Increased hair growth	0.62	0.45	0.43	5.38 E-13
	Muscle cramps	0.54	0.46	0.50	5.10E-03
Month 24	Trembling hands	0.56	0.48	0.47	5.40E-04
	Swollen gums	0.54	0.47	0.49	8.66E-04
	Swollen ankles	0.55	0.49	0.47	4.54E-03
	Increased hair growth	0.58	0.46	0.46	3.36E-07
	Muscle cramps	0.55	0.46	0.49	1.27E-03
Month 36	Sores on lips or in mouth	0.46	0.49	0.54	5.82E-03
	Oily skin	0.56	0.46	0.49	2.31E-04
	Trembling hands	0.55	0.48	0.48	7.62E-03
	Swollen gums	0.55	0.48	0.48	1.49E-04
	Swollen ankles	0.56	0.46	0.48	2.98E-04
	Diarrhea	0.47	0.48	0.55	6.63E-03
	Increased hair growth	0.60	0.45	0.46	1.56E-10
	Muscle weakness	0.54	0.44	0.52	1.05E-03

O33 ONCE-DAILY MORNING IMMUNOSUPPRESSION: A SOLUTION TO LONG-TERM TREATMENT ADHERENCE

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Introduction: Chronic graft rejection, eventually favored by non-observance, is one of the principal cause of graft dysfunction. If calcineurin inhibitor (CNI) may be administered once daily, there is no available prolonged-release formulation of mycophenolic acid (MPA). Preliminary study in our center, reveals identical pharmacokinetics of MPA given once daily compared to twice (n = 9 patients). Our observational prospective study aims to evaluate safety of once-daily administration of MPA in transplanted patients.

Material and Methods: Since 2016, once-daily protocol administration of MPA was proposed i) to patients with kidney or simultaneous pancreas-kidney (SPK) transplantation, ii) in association with once-daily CNI administration. Daily MPA posology was not modified.

Results: 65 patients (including 12 SPK), with a mean age of 49.8 years were included. Mean time from transplantation was 33 months. Mean follow-up was 16.3 months (6–48). 37 % had previous HLA immunization. 40 % received steroids during the protocol. Once-daily tacrolimus was advagraf (81.5%), Envarsus (17%) and Advagraf/Rapamune (1.5%). 88% of patients had 720 mg per day of MPA (dose variation 360 mg to 1440 mg). Clinical and biological tolerance was perfect except in two patients with digestive intolerance requiring MPA interruption. Two patients develops de novo donor-specific antibodies. Three patients suffered each from one episode of cellular graft rejection. Three adverse events were noted (BK virus nephropathy, pneumonia, lymphoma). Observance was improved, with a strong adherence to the patients.

Conclusion: Once-daily administration of MPA is well tolerated and favored observance in transplanted patients. Safety remains to be studied on larger cohorts.

O34 RESULTS OF HLA-INCOMPATIBLE KIDNEY TRANSPLANTATION FROM LIVING OR DECEASED DONORS AFTER DESENSITIZATION

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Introduction: In patients with end-stage renal disease, kidney transplantation is associated with a better quality of life and longer survival as compared to hemodialysis. HLA sensitization in these patients may results in a higher difficulty to access a kidney transplant and a longer time on the waiting list. Recipient's desensitization is a procedure to remove HLA donor-specific antibodies (DSAs). Kidney transplantation of recipients with one or more DSAs is called HLA incompatible (HLAi-KT).

The aim of this study was to assess the results of HLAi-KT from living or deceased donor.

Methods: We included highly sensitized recipients who received a kidney transplant in our hospital after desensitization which consisted in Rituximab and plasmapheresis (double filtration and/or semi-specific immunoadsorption). Immunosuppressive treatments were started prior to transplantation and included Tacrolimus (trough concentration 8–12 ng/ml), Mycophenolic acid (1 g/day) and steroids (0.5 mg/kg/day). Induction therapy consisted of Thymoglobulins (1 mg/kg/day for 5 days).

Results: Since 2015, 32 recipients received an HLA-incompatible KTx after desensitization. Eighteen (56.2%) received a graft from a living donor, 14 from deceased donors. Mean time of follow-up was 20.4 months [0.1–43]. At that time, median serum creatinine level was 127 ± 89 μmol/L and proteinuria was 0.07 ± 0.38 g/l. Biopsy-proven rejection occurred in 13 patients (40%) at 13 month [0.5–36]. Two were cellular rejections, 3 were acute antibody-mediated rejections and 8 were chronic antibody-mediated rejections. BK viremia occurred in 3 patients (9%) and CMV viremia requiring treatment in 5 patients (16%) at a median time of 3.2 and 3.1 months respectively. One patient had terminal renal failure due to rejection. Due to a surgical complication 1 lost his graft and 1 patient died.

Conclusion: In our experience, HLAi-KT allows good results despite a higher rate of complications as compared to HLA compatible kidney transplantation.

O35 IMPROVEMENT OF GRAFT SURVIVAL AFTER BELATACEPT RESCUE THERAPY IN KIDNEY TRANSPLANT RECIPIENTS WITH VASCULAR LESIONS

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Immunosuppression in kidney transplant recipients with decreased graft function and severe histological vascular changes can be particularly challenging. Belatacept could be a valuable option, as a rescue therapy in this context, improving kidney allograft function. Nevertheless, the real impact on kidney graft survival has never been studied.

We report a retrospective case-control study comparing a CNI to belatacept switch in 51 patients with vascular damage (cv ≥ 2, g + cpt ≤ 1, i + t ≤ 1) and low eGFR (≤40 mL/min/1.73 m^2) to a control group of 37 matched patients with CNI continuation.

Belatacept switch was performed on average 41.4 months after kidney transplantation (6–149 months). There was no difference between the two groups regarding eGFR at inclusion (25.1 ± 6.3 vs 25.2 ± 8.3 mL/min/1.73 m^2) and mean age of kidney transplant recipients was similar (60.6 ± 11.1 vs 60.1 ± 12.4 years) . Mean follow-up was similar in the 2 groups (35.5 ± 22.8 vs 39.6 ± 35.6 months). During this follow-up, we observed in the belatacept switch group 4 graft losses (4/51: 7.8%) and 14 in the CNI continuation group (14/378: 37.8%). In the "CNI to belatacept switch

group" death-censored graft survival was significatively higher than in the "CNI continuation group" (p = 0.001). At 3 years, graft survival was 94.4% in the CNI to belatacept switch compared to the control group, in which survival was 66.9%.

In conclusion, the replacement of CNI with belatacept in patients with decreased allograft function and vascular lesions is associated with an improvement in eGFR, sufficient to increase graft survival, in a context of organ shortage.

O36 PHARMACOKINETIC THERAPEUTIC DRUG MONITORING OF MYCOPHENOLATE MOFETIL IN ABOUT 1,000 PEDIATRIC RENAL TRANSPLANT PATIENTS, USING AN EXPERT SYSTEM ONLINE

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Background: The online expert system ISBA is routinely used by many transplantation centres for the dose adjustment of immunosuppressive drugs in transplant patients. This system assesses the AUC of the drug by PK modelling and Bayesian estimation and proposes dose adjustments to reach predefined exposure targets. This retrospective study aims to analyse mycophenolate mofetil (MMF) PK, exposure and dose adjustment in paediatric kidney allograft recipients.
Methods: Between 2010 and 2018, 3506 requests were posted for MMF dose adjustment by 45 centres, for 930 different paediatric patients. Mycophenolic acid AUC was estimated using 3 plasma concentrations measured at approx. 20 min, 1 h and 3 h post-dose.
Results: MMF was mostly prescribed with tacrolimus (73%). Most requests were made > 1 year after transplantation (60%). At the first request: the median patient age and the MMF dose were 12.4 y and 1000 mg/24 h, respectively; as expected, the mean MMF daily dose prescribed increased with patient age and was lower when MMF was combined with tacrolimus; and the mean MMF dose proposed by ISBA to reach $AUC_{0-12\ h}$ = 45 mg.h/L was statistically higher than the mean dose previously prescribed, whatever the patient age and CNI. Dose adjustment was needed for approximately half of patients to reach the consensually recommended 30–60 mg.h/L target range; 28% were underexposed and 20% overexposed. The subsequent AUC was significantly more often in the recommended range (35–67% vs. 20–47%) and the interindividual AUC variability was lower (CV% = 32–66% vs 48–83%, depending on the post-transplantation period) when the dose previously proposed had been applied than not, at all post-transplantation periods.
Conclusion: PK-guided MMF dose adjustment in paediatric kidney allograft patients allows reaching the AUC recommended range more often and reducing inter-patient variability. Whether it improves outcomes will be evaluated in a future study, called REXETRIS.

INFECTION

O37 PRIMARY EPSTEIN-BARR VIRUS (EBV) INFECTION WITHIN THE FIRST YEAR FOLLOWING RENAL TRANSPLANT AMONG EBV SERO-MISMATCH (D+/R−) ADULT RECIPIENTS: A PROSPECTIVE STUDY IN 13 FRENCH CENTERS OF RENAL TRANSPLANTATION

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Background: Primary EBV infection is a rare but potentially serious complication after renal transplantation in adults. No antiviral prophylaxis strategy has been clearly established. The objective of our study is to measure the incidence of primary EBV infection in the first-year post-transplant in high-risk recipients (EBV D + R− seromissmatch).
Methods: This multicentric prospective study in 13 French transplant centers enrolled all adult recipients of a renal transplant, seronegative for EBV receiving a graft from a EBV seropositive donor (D + R−) from January, 2017 to June 2018. Serology and EBV viral load (PCR) were collected the first year post-transplant.
Results: Among 25 EBV D + R− patients, 17 (68%) developed primary EBV infection at 1 year: 15 with viremia associated seroconversion and 2 with isolated viremia without seroconversion. The incidence of primary EBV infection was lower in patients who received antiviral prophylaxis (9/17, 53%) compared to patients who did not (8/8, 100%; p = 0.053). 3 patients (12%) developed a post-transplant lymphoproliferative disease (PTLD), all of which occurred after primary infection. No association between primary EBV infection and lymphopenia, immunosuppressive regimen and CMV/BK virus infection was found.
Conclusion: Primary EBV infection is a common complication in the EBV D + R− population with an increased risk of PTLD. Our study suggests that antiviral prophylaxis could prevent primary infection.

O38 EFFECT OF MTOR INHIBITORS IN PERSISTENT AND RECURRENT CMV DISEASE

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Introduction: mTOR inhibitors seem to exert a preventive effect on CMV disease in CMV seropositive (R+) kidney transplant recipients, but their impact during curative treatment of CMV disease in high-risk kidney transplant recipients has not been investigated. We aimed to evaluate the efficacy and tolerance from a conversion to mTOR inhibitors in kidney transplant recipients suffering of CMV disease with a persistent or a recurrent CMV DNAemia.
Methods: We conducted a monocentric retrospective study among 63 consecutive kidney transplant recipients, included 78 of D + R−, undergoing CMV disease with persistent or recurrent DNAemia: 16 were converted to mTOR inhibitor and 47 were not.
Results: The Kaplan-Meier curves did not show any significant differences between patients with or without mTOR inhibitor conversion in CMV DNAemia eradication (77% *versus* 88% respectively; HR 1.648 [95% CI: 0.913–2.973]; log-rank test, p = 0.132), DNAemia recurrence (36% *versus* 47%; HR 1.517 [95% CI: 0.574–4.007]; log-rank test, p = 0.448) and clinical recurrence (17% *versus* 27%; HR 1.375 [95% CI: 0.340–5.552]; log-rank test, p = 0.677). Uni- and multivariate time-dependent Cox regressions confirmed that mTOR inhibitor conversion was associated neither with CMV DNAemia eradication, neither with DNAemia recurrence nor with clinical recurrence. Adverse events of mTORi were present in 31.25% of patients.
Conclusion: mTOR inhibitors do not improve accelerate CMV eradication in kidney transplant recipients undergoing CMV disease with persistent or recurrent DNAemia.

O39 γδ T-CELL-BASED IMMUNOTHERAPY AGAINST CMV INFECTION AFTER TRANSPLANTATION: A PRECLINICAL STUDY

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Background: Human Cytomegalovirus (CMV) infection in Solid Organ Transplant Recipients (SOTRs) is associated with increased risks of allograft loss, morbidity and mortality. Current gold standard treatment, based on use of Valganciclovir, fails to prevent late CMV-reactivation or emergence of viral resistance in a significant percentage of SOTRs. Importantly, long-term CMV clearance relies on the establishment of an anti-CMV T-cell response. There is therefore a growing interest in developing anti-CMV cell therapy. Both αβ and γδ T cells are key effectors of the anti-CMV immune response. The goal of this study was to explore a potential γδ T-cell-based immunotherapy.
Methods: Healthy donors (both CMV-positive and CMV-negative) and kidney transplant recipients (KTRs) undergoing refractory CMV infection were enlisted in this preclinical study. γδ T cells were sorted from peripheral blood, then amplified and activated *in vitro,* using a TCR agonist combined to different cytokines, notably IL-4 and IL-15. The reactivity of expanded γδ T cells against CMV-infected target cells was then measured *in vitro*.
Results: The amplification of γδ T cells from healthy donors and KTRs undergoing refractory CMV infection was reproducible and compatible with a human cell-immunotherapy. Amplified cells displayed an activated and differentiated phenotype, but low exhaustion, produced IFNγ in the presence of infected target fibroblasts, epithelial cells and macrophages, and were able to control viral dissemination *in vitro*. Importantly, γδ T-cell expansion and anti-CMV reactivity

were independent of the CMV serotype of the donor, meaning that reactive cells could also be amplified from CMV seronegative transplant recipients
Conclusions: Altogether, these data provide a proof of concept for a future use of amplified γδ T cells, in the prevention and curative treatment of CMV disease in SOTRS. These results pave the way for a future phase I clinical trial.

O40 MENINGITIS IN KIDNEY TRANSPLANT RECIPIENTS: *TRANSMÉNINGES*, A FRENCH MULTICENTRIC RETROSPECTIVE COHORT STUDY

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Introduction: The management of meningitis requires the prompt introduction of high-dose probabilistic anti-infectious therapy. The literature reporting on meningitis in kidney transplant recipients (KTR) is scarce and no recommendation exists for this specific population.
Methods: We retrospectively included all adult KTRs diagnosed with meningitis (cerebro-spinal fluid (CSF) cell count >10/mm^3, positive fungal antigen or positive direct microbial examination) between 2007 and 2018 in 16 French hospitals. Clinical, biological, therapeutic and one-year follow-up data were collected.
Results: Meningitis occurred in 134 KTRs (mean age 57+/11.8 years, 56% male), after a median time of 27 months (IQR 8–65); induction treatment included lymphocyte-depleting antibodies in 63%.

The etiologies included *Cryptococcus neoformans* (35%), Herpesviridae (22%, of which 18% of Varicella-Zoster Virus), idiopathic forms (15%), Gram-negative bacilli (8% of which 20% produced an extended spectrum beta-lactamase), intravenous immunoglobulins (6%), post-transplant lymphoproliferative disorders (6%), Enterovirus (5%), *Aspergillus fumigatus* (1%), *Listeria monocytogenes* (1%), and *Mycobacterium tuberculosis* (1%).

There was one case of *Streptococcus pneumoniae* meningitis occurring as a complication of otitis with mastoiditis. *Neisseria meningitidis* was not isolated in this series.

One-year patient, graft and death-censored graft survival rates were 84%, 76% and 89%, respectively.
Conclusion: Meningitis after kidney transplantation encompasses a wide range of causes, with *C. neoformans* and VZV explaining 50% of the cases. Gram-negative bacilli are the most represented bacteria with a high rate of antimicrobial resistance.

Treatment guidelines should be reconsidered in the specific population of KTRs as the etiology greatly differs from what is observed in the general population.

O41 RIBAVIRIN FOR HEPATITIS E VIRUS INFECTION AFTER ORGAN TRANSPLANTATION: A LARGE EUROPEAN RETROSPECTIVE MULTICENTER STUDY

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Background: Ribavirin is currently recommended for treating chronic hepatitis E virus (HEV) infection. This retrospective European multicenter study aims to assess the sustained virological response (SVR) in a large cohort of solid organ transplant patients with chronic HEV infection treated with ribavirin monotherapy (n = 255), to identify the predictive factors for SVR, and to evaluate the impact of HEV RNA mutations on virological response.
Methods: Data from 255 solid organ transplant patients from 30 European centers were analyzed. Ribavirin was given at the median dose of 600 (29–1200) mg/d (8.6 ± 3.6 mg/kg/d) for a median duration of 3 (0.25–18) months.
Results: After a first course of ribavirin, the SVR rate was 81.2%. It increased to 89.8% when some patients were offered a second course of ribavirin. An increased lymphocyte count at the initiation of therapy was a predictive factor for SVR, while poor hematological tolerance of ribavirin requiring its dose reduction (28%) and blood transfusion (15.7%) were associated with more relapse after ribavirin cessation. Pretreatment HEV polymerase mutations and *de novo* mutations under ribavirin didn't have a negative impact on HEV clearance. Anemia was the main adverse event.
Conclusion: This large-scale retrospective study confirms that ribavirin is highly efficient for treating chronic HEV infection in solid organ transplant patients and shows that the predominant HEV RNA polymerase mutations found in this study do not affect the rate of HEV clearance.

O42 IMPACT OF CMV INFECTIONS ON THE RISK OF ALLOGRAFT REJECTION AFTER HEART TRANSPLANTATION

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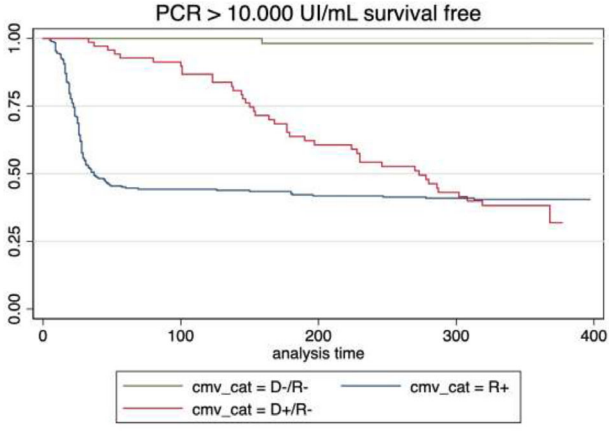
Introduction: The impact of cytomegalovirus (CMV) infections on the risk of allograft rejection after heart transplantation is debated.
Methods: We conducted a single-center retrospective study including patients transplanted between January 2012 and December 2016 who had at least one endomyocardial biopsy (EMB) during follow-up. Patients at high risk (D+/R−) received valganciclovir prophylaxis for 3 months, those at intermediate risk (R +) were treated according to a preemptive strategy (viral replication threshold: 10,000 IU / mL). Protocol monitoring included 13 BEMs per patient in the first year. Allograft rejection was defined as ≥1R1B acute cellular rejection and / or ≥pAMR1 antibody-mediated rejection according to international guidelines. The impact of CMV infection, defined as a viral replication ≥10,000 IU / mL, on the risk of allograft rejection was analyzed using a Cox model, with viral replication accounted for as a time-dependent covariate.
Results: 399 patients met the inclusion criteria, including 60 patients D+/ R−, 256 R+ and 72 D+/R. All patients received an induction therapy and a triple basal immunosuppression. CMV infections were diagnosed in more than half of the patients (Figure). 140 patients (35%) had at least one episode of biopsy-proven ejection. We identified 3 independent risk factors for rejection: the presence of donor-specific anti-HLA antibodies (HR = 1.59, p = 0.007), the number of HLA AB-DR-DQ mismatch (7–8 against ≤6: HR = 1.72, p = 0.002) and type of transplantation (combined vs isolated: HR = 0.27, p = 0.026). CMV infections were not associated with the risk of rejection, both at the time of diagnosis and in the following month (HR = 0.86, p = 0.61, HR = 0.48–1, 53).
Conclusion: CMV infections were common after heart transplantation but were not associated with the risk of allograft rejection.



O43 EFFICIENCY OF INTRAVENOUS IMMUNOGLOBULINS IN PREVENTION OF BK VIRUS REPLICATION IN KIDNEY TRANSPLANT RECIPIENTS

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Background: In kidney transplantation (KT), BKV replication could lead to BKV-associated nephropathy (BKVN) and graft loss. BKV replication post-KT is mostly of donor's origin. There are no BKV-specific therapies. In a previous

work, we demonstrated that BKV genotype-specific neutralizing antibodies (NAb) were protective against BKV replication above the 4 log_{10} threshold and that intravenous immunoglobulins (IVIg) exhibited high anti-BKV-neutralizing activity in vitro and ex vivo. We investigated whether administration of IVIg prevents BKV replication in patient with low Nab titer after KT.
Methods: Adults consecutive kidney transplants recipients in Strasbourg University Hospitals with NAb titer available at the day of transplantation (D0) were enrolled in this retrospective study. Depending on NAb titer at D0, population study was divided in three groups: 1) patients at high risk of BKV replication with an IVIg therapy for secondary immune deficiency, preventive or curative treatment of antibody-mediated rejection during the three first months of KT (n = 44) 2) patients at high risk of BKV replication who did not receive any IVIg therapy during the first year of KT (n = 41) and 3) patients at low risk of BKV replication who did not receive any IVIg therapy during the first year of KT (n = 89). BKV Nab titer, BKV viremia and BKVN were monitored until 1 year after KT (M12).
Results: At M12, the incidence of BKV viremia in the high-risk group treated with IVIg (7%) was reduced to that of the low-risk group (10%) and was lower than that of non-treated high-risk patients (37%) ($p < 0.00001$). Similarly, the incidence of BKVN in the high-risk group treated with IVIg (5%) was reduced to that of the low-risk group (2%) and was lower than that of non-treated high-risk patients (20%) ($p < 0.001$).
Conclusion: IVIg may represent an important strategy to prevent BKV replication after KT. A larger prospective randomized cohort study will start soon to confirm these results.

O44 DEVELOPMENT OF BKV NEPHROPATHY IN RENAL TRANSPLANT PATIENTS: ROLE OF THE SPECIFIC IMMUNE RESPONSE

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Background: In the recent years, BK virus (BKv)-associated nephropathy (BKvAN) emerged as a major complication in renal transplantation, affecting up to 10% of kidney transplant recipients and leading to graft loss in more than 50% of cases. BKv reactivation is favored by therapeutic immunosuppression.
Methods/Materials: To access the immune response against BKv, we prospectively characterized the BKv-specific T-cell functionality in a cohort of 100 kidney transplant recipients with different BKv reactivation levels (without reactivation, viruria, viremia or BKvAN).
Results: Patients with BKvAN had a severe impairment of BKv-specific CD8 T-cell functionality such as a decrease proliferation ($p < 0.05$), TNF-α and/or IFN-γ production ($p < 0.05$) and cytotoxicity capacities ($p < 0.05$) as compared with patients with BKv replication without BKvAN. In contrast, patients with BKvAN had a similar response to other viral antigen (antiviral global stimulation – $p>0.05$). We observed a gradual loss of functional BKv-specific T cells according to BKv reactivation levels ($p < 0.0001$), associated with an inverse correlation between BKv-specific T-cell functionality and plasmatic BKv viral load. This functional impairment suggested an exhaustion of BKv-specific T cells according to BKv reactivation levels.
Conclusion: In conclusion, we observed a reduction of the specific anti-BKv response in patients with BKvAN. The BKv-specific T-cell functionality was negatively correlated with plasmatic BKv viral load. This functional impairment suggested an exhaustion of BKv-specific T cells, leading to a defective BKv-specific CD8 T-cell response, unable to provide a protective immune response against BKvAN.

O45 CHRONIC LYMPHOPENIA, IMMUNOSUPPRESSION MARKER AND RISK FACTOR FOR LATE-ONSET PNEUMOCYSTIS

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In the era of prophylaxis, pneumocystis has become a late-onset opportunistic infection requiring the indications for prolonged prophylaxis. The objective of our study was therefore to evaluate the risk factors including marker of chronic immunosuppression such as CD4 lymphopenia. The secondary objective was to assess the impact on patient survival and graft survival.

We conducted a French bicentric case-control study between 2004 and 2015 in Toulouse and between 2007 and 2018 in Bordeaux by matching 1 case of pneumocystis to 2 controls from the same center on the transplant date and the induction treatment (anti-lymphocyte or anti-IL2R antibody).

Seventy cases of pneumocystis were included and 140 controls. On average, pneumocystis occurred 5 years after transplantation. The CD4 lymphocyte values were significantly lower in cases compared to their controls on the day of pneumocystis (and matched-date for controls) and annually up to 4 years earlier.

The variables independently associated with the risk of pneumocystis by multivariate logistic regression analysis were CD4 lymphopenia one year before pneumocystis, maintenance immunosuppressive regimen with mTOR inhibitors and administration of corticosteroid boli. Pneumocystis occurring with a median of 16.5 months following corticosteroid boli (1st-3rd quartiles 11.5–26). On the contrary, corticosteroids as immunosuppressive regimen, rituximab or plasma exchanges were not associated.

In multivariate Cox analysis, pneumocystis was, independently of acute rejection, significantly associated with graft loss (HR, 4.49; 95% CI 1.813–11.164; $p = 0.001$); and was also associated with the risk of death (HR 4.56, 95% CI 1.13–18.3; $p = 0.03$).

Late-onset pneumocystis has a major impact on the patient and graft survival. A better knowledge of its risk factors, long-term lymphopenia, corticosteroid boli, would allow the introduction of prolonged prophylaxis.

ISLET AND PANCREAS

O46 *EX-SITU* HYPOTHERMIC PERFUSION OF NON-HUMAN PRIMATE PANCREAS: A FEASIBILITY STUDY

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Background: The objective was to evaluate feasibility of hypothermic perfusion (HP) of non-human primate pancreases for potential organ transplantation.
Methods: Seven baboon pancreases were tested, animals were included in a study approved by the French Research Ministry of Health. Two groups were compared: the control group (n = 2) was preserved using conventional static cold storage (SCS) for 24-h and the perfusion group (n = 5) used HP for 24-h, with 3 different perfusion pressures (PP): 15 (n = 3), 20 (n = 1) and 25 mmHg (n = 1).
Results: In control group, focal congestion of islets was observed after 6-h. At 24-h, ischemic necrosis and multifocal congestion occurred. In HP group, at 15 mmHg PP, multifocal congestion of islets was present at 24-h. At 20 mmHg PP, no ischemic necrosis was found after 6-h. At 12-h and 24-h, focal congestion of islets was seen. At 25 mmHg PP, focal congestion of islets appeared after 12-h. Immunostaining for insulin, glucagon and somatostatin was normal and similar in controls and perfused pancreas transplants even after 24-h.
Conclusions: HP of non-human primate pancreas is feasible and not deleterious as far as 24-h compared to SCS. Systolic perfusion pressure between 15–25 mmHg did not cause any pathological injury of the tested organs.

O47 TOTAL PANCREATECTOMY AND PANCREATIC ALLOTRANSPLANTATION IN PORCINE EXPERIMENTAL MODEL

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Background: A model of insulin-deficient diabetes and pancreatic transplantation in large animals are a keys prerequisite in preclinical research, in particular concerning ischemic reperfusion lesions. Porcine model is especially eligible due to the similarity of the vascularisation and the morphology of the pancreas.
Materials and Methods: The study protocol was approved by the French Minister of Research (APAFiS# 18 169). We performed a diabetes induction by total pancreatectomy in 1 male *Sus scrofa* pig and a pancreatic allotransplantation after total pancreatectomy in 6 male *Sus scrofa* pigs (3 donors and 3 recipients). Under general anesthesia, total pancreatectomy was performed, with meticulous dissection of the portal vein and the splenic vein allowed to keep the spleen. Concerning pancreas procurement, extensive pancreas preparation during the 'warm phase', before the cannulation and cold perfusion was performed.
Results: Concerning diabetes induction, glycemic control without hypoglycemic events was obtained using long-acting insulin (Lantus ©) once a day. No rapid-acting insulin has been used. After total pancreatectomy, C-peptide values decreased to zero, in 3-h. Concerning pancreatic

allotransplantation, after enteral feeding was started on, glycemic control without hypoglycemic events, without insulin, were obtained in 2 animals.
Conclusions: In an experimental porcine model, diabetes induction by total pancreatectomy and pancreatic allotransplantation after total pancreatectomy are feasible and effective. The development of these models offers the potential for new investigations in the study of ischemic reperfusion lesions, improvement of pancreas procurement and preservation.

O48 LATE CONVERSION FROM CALCINEURIN INHIBITORS TO BELATACEPT IN KIDNEY TRANSPLANT RECIPIENTS HAS A SIGNIFICANT BENEFICIAL IMPACT ON GLYCEMIC PARAMETERS

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Background: Calcineurin inhibitors (CNIs) and steroids are strongly associated with new-onset diabetes after transplantation (NODAT), worsening of pre-existing diabetes, and cardiovascular events. We assessed the benefit of conversion from CNI-based to belatacept-based immunosuppression in diabetic kidney transplant recipients (KTx) on glucose control and cardiovascular risk factors.
Methods: In this retrospective, non-controlled single-study conducted between May 2016 and October 26, 2018, we recruited KTx converted from CNIs to belatacept. The primary endpoint was the evolution of HbA1c between baseline and after 6 months of treatment. Secondary endpoints included modifications to antidiabetic drugs, other cardiovascular risk factors, and renal function.
Results: One hundred and twelve KTx were included. Of these, 28 (25%) had type-2 diabetes. The patients were either receiving oral antidiabetic drugs (n = 21; 75%) or insulin-therapy (n = 14; 50%). Overall HbA1c decreased significantly from 6.2 $\pm$ 1 to 5.7 $\pm$ 1%, $p < 0.0001$. In diabetic patients, HbA1c decreased from 7.2 $\pm$ 1 to 6.4 $\pm$ 1%, $p < 0.0003$. HbA1c significantly decreased in the subgroup of patients with new-onset diabetes at post-transplantation and whether diabetes was controlled at inclusion or not (i.e., HbA1c $\leq$7% or >7%). Moreover, 46.6% patients with controlled diabetes at inclusion had decreased or stopped antidiabetic drugs. During follow-up, the renal function of the 112 patients remained stable, two patients presented acute cellular rejection and no patient suffered from graft loss.
Conclusions: A late switch from CNI to belatacept was a valuable therapeutic option for diabetic kidney recipients and substantially improved glycemic parameters.

O49 EFFECT OF DULAGLUTIDE ON ENDOTHELIAL TO MESENCHYMAL TRANSITION OF MURINE PANCREATIC INTRA-INSULAR ENDOTHELIAL CELLS INDUCED BY CYTOKINE STRESS AT THE INITIAL PHASE OF PANCREATIC ISLET TRANSPLANTATION

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Introduction: The vascularization of transplanted islets encounters an inflammatory reaction, the IBMIR (Instant Blood Mediated Inflammatory Reaction). The cytokines released are likely to cause the endothelial to mesenchymal (EndMT) transition of pancreatic intra-insular endothelial cells (ECs) leading to islet dysfunction. Dulaglutide, in addition to the preservation of pancreatic islets, exerts vascular protection in type 2 diabetes.
Objective: To evaluate the cytokines mimicking the IBMIR (IL-1β and TNF-α) on EndMT of intra-insular endothelial cells and their modulation by Dulaglutide.
Material and methods: ECs are stimulated for 48 and 72 hours by IL-1β (5, 10, 20 and 25 ng / mL) or TNF-α (20, 50, 100 and 130 ng / mL) to induce EndMT. The ECs are then treated with Dulaglutide at 1 μM 2 h before cytokine application. Expression of mesenchymal (α-SMA / Vimentin) and endothelial (VE-Cadherin / CD31) proteins is measured by Western Blot.
Results: After 72 hours of stimulation, the morphology of the ECs changes in a fusiform aspect. The expression of CD31 and VE-cadherin decreased by 40 $\pm$ 21% ($p = 0.0001$) and 53 $\pm$ 14% ($p = 0.0178$) in the presence of IL-1β (20 ng/mL), 55 $\pm$ 10% ($p = 0.0052$) and 54 $\pm$ 6% ($p = 0.001$) with TNF-α (100 ng/mL). The expression of α-SMA and Vimentin increases by 82 $\pm$ 17% ($p = 0.0085$) and 86 $\pm$ 22% ($p = 0.0162$) in the presence of IL-1β (20 ng/mL), 115 $\pm$ 4% ($p < 0.0001$) and 137 $\pm$ 20% ($p = 0.0026$) with TNF-α (100 ng/ml). In the presence of Dulaglutide, the appearance of ECs is heterogeneous with more rounded cells. Compared with IL-1β and TNF-α treated cells, Dulaglutide increased CD31 expression by 77 $\pm$ 3% ($p = 0.012$) and 91 $\pm$ 1% ($p = 0.0099$) respectively and VE-cadherin of 94 $\pm$ 1% ($p = 0.0261$) and 93% $\pm$ 3% ($p = 0.0021$) whereas there was no difference for α-SMA and Vimentin.
Conclusion: The cytokines of the IBMIR induce the EndMT of pancreatic intra-insular endothelial cells. Dulaglutide restores endothelial markers without altering mesenchymal markers.

O50 PRE-CLINICAL STUDY OF HYPOTHERMIC PULSATILE PERFUSION OF PANCREATIC TRANSPLANTS IN A PORCINE MODEL

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Objectives: The main objective was to compare the different preservation techniques (static cold storage and hypothermic pulsatile perfusion) in a model of porcine pancreatic allotransplantation on insulin-dependent diabetic pigs.
Materials and Methods: We have developed an experimental model of insulin-dependent diabetic pigs by total pancreatectomy. We compared static cold storage (SCS) and hypothermic pulsatile perfusion (HPP) of pancreatic transplants by histological and immunohistochemical analysis and by analysis of pancreatic pain markers. We have developed an experimental model of pancreatic allotransplantation after SCS or HPP on insulin-dependent diabetic pigs.
Results: The experimental model of insulin-dependent diabetic pigs was performed in an animal. After total pancreatectomy, the animal was diabetic. We preserved for 24 hours, 3 transplants with SCS and 3 transplants with HPP. After 6 hours of preservation, the rate of histological lesions was equivalent after SCS and HPP. After 12 hours, the rate of histological lesions was higher after HPP. Levels of markers of pancreatic suffering were lower after HPP. The experimental model of pancreatic allotransplantation after SCS or HPP on diabetic pigs was performed in fourteen animals (six after SCS and eight after HPP). A total of eight immediate postoperative deaths occurred, related to surgical or anesthetic complications. No vascular thrombosis occurred.
Conclusions: To our knowledge, these studies report the first experimental pancreatic transplants on a diabetic pig model after preservation by hypothermic pulsatile perfusion, without early transplant thrombosis. Hypothermic pulsatile perfusion improves preservation conditions when it is less than 12 hours.

O51 PERFORMANCE OF PANCREAS GRAFT BIOPSIES IN THE MANAGEMENT OF PANCREAS TRANSPLANT RECIPIENTS

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Introduction: Pancreas transplant recipients are usually followed with markers of pancreatic exocrine (lipase) and endocrine function and markers of auto and alloimmunity. However, the role of histology is poorly defined. The aim of this study was to assess the contribution of pancreas graft biopsies in the management of pancreas transplant recipients.
Methods: All pancreas transplant recipients followed in our center, who had a pancreas graft biopsy for cause since 2011 were included. Biopsies were performed under ultrasound or computer tomographic guidance. They were analyzed according to Banff grading schema. Indications, results, prognosis, concordance with kidney graft biopsies and complications were analyzed.
Results: 70 pancreas graft biopsies were performed in 53 patients. There were 4 (5.7%) minor complications. 10 (14.3%) biopsies were non adequate.

80% of biopsies performed for lipase increase showed a rejection. There was no association between the value of lipasemia and the result of the biopsy. Only 1 out of 12 biopsies performed for de novo DSA showed an acute T-cell-mediated rejection (TCMR).

While all patients with grade 1 TCMR (n = 11) evolved favorably after treatment, 7 out of 13 (54%) patients with grade 2 TCMR lost their graft within 6 months. The 11 patients whose biopsy was classified in category 2 (indeterminate) of the Banff grading schema evolved favorably without any specific treatment.

Results of simultaneous pancreas and kidney biopsies were discordant for 10 out of 30 patients.

10 biopsies were performed because of an abnormal oral glucose tolerance test (OGTT): none showed rejection or insulitis.
Conclusion: Pancreas graft biopsies are safe and mandatory in case of lipase increase since cellular rejection is diagnosed in 80% of cases. Banff grading schema has a useful prognosis value. Pancreas graft biopsies do not seem useful in patients with an abnormal OGTT.

O52 IMPACT OF PANCREAS TRANSPLANTATION ON BILE ACIDS AND GLUCOSE METABOLISM

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Background: Simultaneous pancreas-kidney transplantation (SPKT) in type 1 diabetes patients (T1D) restores endogenous insulin secretion and normal fasting glucose. However, defects of B-cell function could persist with unclear underlying mechanisms. Enteric drainage of exocrine pancreas (in the ileum) could change gut flora and impact incretins secretion (gut-derived metabolic factors) and the enterohepatic cycle of bile acids (BA : mediators of glucose metabolism).
Methods: We prospectively measured total BA concentration and composition in 15 SPKT subjects before and one year after transplantation, compared to 16 kidney transplant (KT) patients and 10 controls. Oral glucose tolerance test (OGTT) was performed one year post-transplant : glucose, insulin, c-peptide, incretins (FGF-19 and GLP-1).
Results: At one year post-transplant SPKT subjects showed significantly higher insulin levels than the KT and controls. Glucose excursion after OGTT was similar, but late plasma glucose remained significantly elevated in SPKT group and plasma insulin increased less markedly in SPKT subjects and remained elevated. HOMA-IR was significantly higher in SPKT group suggesting a state of insulin resistance and decreased insulin secretion. FGF19 concentration was similar at baseline and increased during OGTT in the SPKT group. GLP-1 was higher at baseline in the transplant groups and remained higher during OGTT. Total BA concentrations and proportion were not different between groups but lithocholic acid concentration decreased after SPKT ($p < 0.01$) and was lower than the KT group ($p < 0.01$); no difference compared to control group.
Conclusion: SPKT patients exhibit an impaired glucose and insulin response after glucose challenge despite a normal fasting glucose and HbA1c. We report a different BA profile of T1D before transplantation that is modified after SPKT. This may be related to a preserved and even higher incretin secretion that may compensate the defect in insulin secretion.

O53 FEASIBILITY AND EFFICACY OF COMBINED PANCREATIC ISLET-LUNG TRANSPLANTATION IN CYSTIC FIBROSIS-RELATED DIABETES: A PILOT STUDY

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Objectives: Diabetes is a factor of mortality in lung transplantation (LT) for patients with cystic fibrosis (CF). The objectives of the study were to evaluate the feasibility and metabolic efficacy of combined pancreatic islet-lung transplantation from the same donor in patients with cystic fibrosis related diabetes (CFRD).
Methods: CF patients with terminal respiratory failure and poorly controlled diabetes were included in a multicenter, prospective phase 1-2 trial. Both lungs and pancreas were taken from the same donor. One week after LT, islets were injected in the liver via portal vein under local anesthesia by percutaneous puncture. Success of the transplantation was defined 1 year post-transplant if 3/4 following parameters were reached: increase in weight >5%, fasting glucose <110 mg/dl, decrease in HbA1c ≥0.5%, decrease in daily insulin requirements ≥30%.
Results: On 1st November 2018, 10 patients (2M/8F, age: 24 years [16–41], diabetes duration: 8 years [4–26]) received a combined lung-islet transplant with 3075 IEQ/kg [1551–10931]. At 1 year post-transplant, fasting plasma C-peptide increased from 0.90 μg/l [0.27–1.83] to 1.30 μg/l [0.63–3.0], HbA1c decreased from 7.6% [6.1–9.1] to 6.2% [5.2–8.5] with a nearly 50% decrease in daily insulin doses. BMI and FEV1 increased from 18.6 kg/m2 [14.5–20.8] to 20.3 kg/m^2 [17–24] and from 26% [13–29] to 68% [45–91] respectively. Assessed by composite score, success was achieved in 8 of the 10 patients (80%). For 2 patients, metabolic control at 1 year post-transplant was insufficient. This was due to therapeutic non-compliance. No complications related to the islet injection procedure were reported.
Conclusion: In our study combined pancreatic islet-lung transplantation restores satisfactory metabolic control and pulmonary function in patients with CF with good therapeutic compliance. Intra-portal injection graft does not increase the morbidity of lung transplantation.

O54 CONTRIBUTION OF EARLY SYSTEMATIC CT-ANGIOGRAPHY AFTER PANCREATIC ALLOGRAFT TRANSPLANTATION

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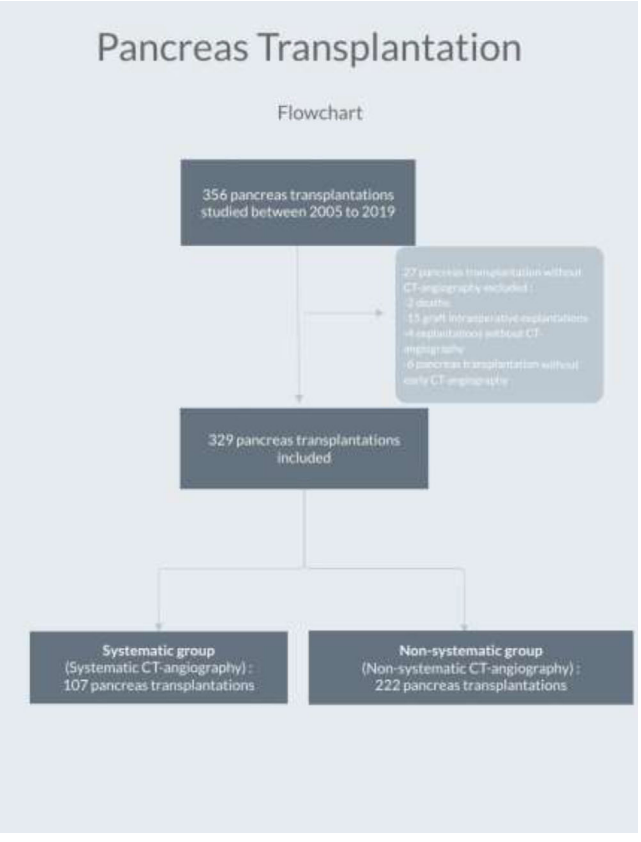
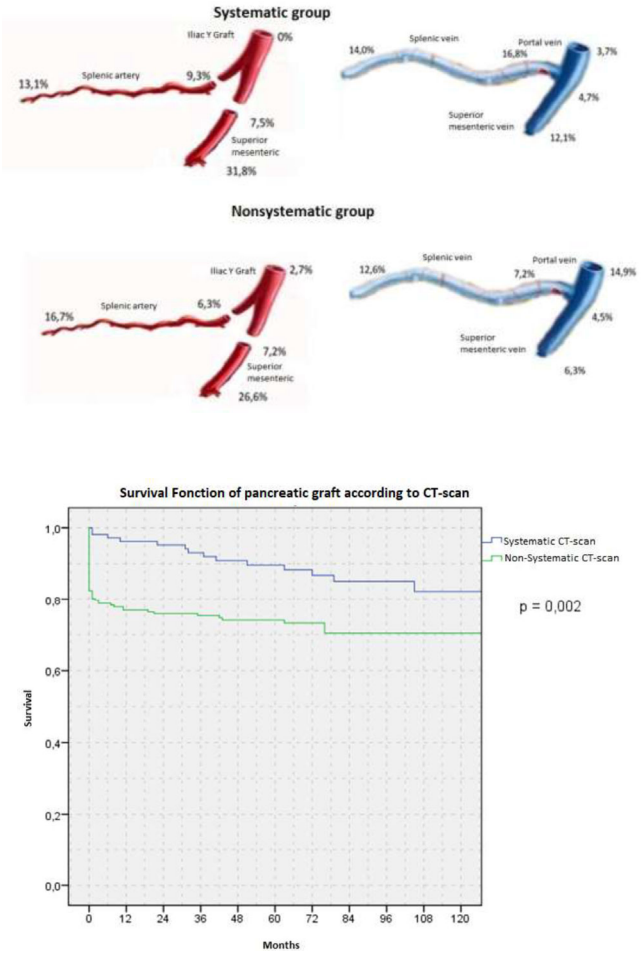
Introduction: Vascular thrombosis is the first cause of early loss of the pancreatic allograft. Performing an early angioscan could help manage pancreatic thrombosis before it is totalized. The objective was to study the incidence and risk factors of these thromboses during the CT scan done systematically.
Material and Methods: It is a monocentric, retrospective, observational, descriptive and analytical study, including all patients who had pancreas transplantation with or without a kidney transplant between 2005 and 2019 as part of the treatment of diabetes. Pancreatic thromboses were classified according to the Cambridge pancreatic thrombosis grading system. The primary endpoint was the incidence of thrombosis on the CT scan.
Results: Three hundred and twenty-nine pancreas transplants were included. In the systematic CT group, 71 (66.4%) vascular thromboses were diagnosed. 53 (49.5%) arterial thromboses were grade 1 or 2. 42 (39.3%) venous thromboses were grade 1 or 2. 1 vein thrombosis was grade 3. In the nonsystematic CT group, 142 (64.0%) vascular thromboses were diagnosed with significantly more grade 3 thromboses ($n = 29$, 13.1%, $p = 0.001$) and fewer grade 2 thromboses ($n = 44$, 19.8%, $p = 0.001$). There was 23.9% revision surgery for suspected thrombosis in the first month. The survival of pancreatic grafts was better in those who underwent systematic computed tomography with 95% survival at 1 year 88% at 5 years and 82% at 10 years.
Conclusion: The occurrence of thrombosis is the main early cause of pancreatic graft loss. The practice of an early systematic CT allows a better management of thromboses.





REJECTION

O55 PROTEOMIC ANALYSIS OF GLOMERULAR LESIONS IN ANTIBODY-MEDIATED REJECTION: THE "GLOMPROT" STUDY

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Introduction: Antibody-mediated rejection (ABMR) remains a major issue in kidney transplantation, accounting for more than half of allograft losses. Its pathophysiology is still incompletely elucidated, while the current diagnosis criteria still lack inter-observer reproducibility and struggle to depict its full dynamic range. The development of molecular functional tools, like the *omics*, from fixed renal samples, is an unmet need.
Methodology: The "GlomProt" study is the first descriptive study focused on the glomerular proteome during ABMR in kidney transplantation. It was performed from formalin-fixed and paraffin-embedded graft biopsies, analyzed by laser microdissection coupled with mass spectrometry. Three groups of patients were defined: active ABMR (n = 11), chronic active ABMR (n = 10) and stable graft controls (n = 8).
Results: 1335 glomerular proteins were quantified per case. A profile of 50 proteins reflecting the activity of antibody-mediated glomerular lesions was identified. These proteins were mainly involved in the integrated cellular stress response, induced by interferon gamma, but also in leukocyte activation, adhesion and migration. Moreover we defined a profile of 90 effectors reflecting the chronicity of antibody-mediated glomerular lesions. These proteins were mainly involved in the glomerular extracellular matrix remodeling, but also in the complement system and its regulation.
Conclusion: Compared to a transcriptomic approach, this study, focused on the glomerular proteome, has several advantages: (i) it concerns translated and biologically active molecules, (ii) it brings new pathophysiological elements of ABMR, notably the major involvement of interferon gamma and leukocyte activation, (iii) it can be transferred to immunohistochemistry (validation currently in progress), which is easier to use in routine diagnosis.

O56 IMPACT OF FCGR3A POLYMORPHISMS ON AMR OUTCOME IN KIDNEY TRANSPLANTATION

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Introduction: Antibody-mediated rejection (AMR) is widely recognized as the first cause of allograft failure. AMR outcome is however heterogeneous at the individual level, making difficult the assessment of the risk of graft loss at the time of diagnosis.

During AMR, the binding of donor-specific antibodies (DSA) on graft endothelial cells is responsible for the recruitment of innate immune cells (in particular NK cells). These cells can damage graft endothelial cells by antibody-dependent cell-mediated cytotoxicity (ADCC). NKs interact with Fc Fragment of DSA by a unique receptor: FcγR3A (CD16A). A SNP (Fcγ RIIIa*559A > C, rs396991) modulates FcγR3A binding capacity to Fc of IgG but its impact in AMR has never been assessed.
Method and results: Among the renal transplanted patients followed in Lyon University Hospital that had a graft biopsy between 2004 and 2015, 118 presented an AMR as defined by Banff: i) presence of microvascular inflammation on biopsy, and ii) circulating DSA. The 15.9 % of patients that were homozygous for the "high-binding" FcγR3A allele had an inferior allograft survival as compared with patients with a "low-binding" FcγR3A (p = 0.03).

An in vitro model of ADCC, in which purified human NKs were co-cultured with endothelial cells coated with DSA, confirmed that NKs with a high-binding FcγR3A displayed stronger activation and promoted more endothelial damages.
Conclusion: Our work demonstrates that FcγR3A polymorphisms impact AMR outcome and suggest that this genetic biomarker could be useful to stratify the risk of graft loss at diagnosis of AMR.

O57 TREATMENT OF NK-MEDIATED REJECTIONS BY MTOR INHIBITORS: A TRANSLATIONAL STUDY

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Introduction: In a previous work, our group showed that some innate immune effectors: Natural Killer (NK) lymphocytes, could perceive the absence of expression of self HLA class (HLA-I) I molecules ("missing self") by graft endothelial cells and cause antibody-independent microvascular inflammation, which has the same detrimental prognosis as chronic humoral rejection.

In this translational study, we aimed at identifying a possible molecular therapeutic target to treat this new type of rejection.
Methods and Results: Purified human NK were co-cultured with K562 cells, which do not express HLA-I. Imaging flow cytometry analyses showed that the mTORC1 pathway was critical during missing self-induced NK activation. The use of a mouse model of missing self-induced NK-mediated rejection revealed that rapamycin (but not cyclosporin) was effective in blocking the mTORC1 pathway in NK and suppressing the development of microvascular lesions in cardiac graft. Based on these experimental results, we tested mTOR inhibitors in 2 transplant patients (1 heart and 1 kidney) diagnosed with missing self-induced NK-mediated rejection. At 6 months both patients showed a significant decrease in the intensity of the rejection lesions on biopsy.
Conclusions: Our work demonstrates that the mTORC1 pathway is critical for missing self-induced NK activation and suggests that mTOR inhibitors may be a valid therapeutic option in this new type of rejection.

O58 CHARACTERIZATION OF *DE NOVO* DONOR-SPECIFIC ANTIBODY SUBCLASSES BY MASS SPECTROMETRY: THE IGG3 PROPORTION PREDICTS ANTIBODY-MEDIATED REJECTION OCCURRENCE AND SEVERITY

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Background: Donor-specific antibodies (DSA) are the main risk factor for antibody-mediated rejection (ABMR) and graft loss; however, not all DSA have the same pathogenicity. We investigated the distribution and role of the different *de novo* immunodominant DSA (iDSA) IgG subclasses in ABMR development and severity.
Methods: Between 2011 and 2018, we enrolled 69 patients who developed *de novo* DSA (n = 29 without ABMR, and n = 40 with ABMR) in two transplant centers. After iDSA isolation with specific single antigen beads, we assessed their IgG composition using an innovative mass spectrometry-based test.
Results: Mass spectrometry analysis of all iDSA showed that overall, 62.7% were IgG1, 26.6% IgG2, 6.6% IgG3, and 4.2% IgG4. The four subclasses were detected for all iDSA. The proportion of IgG3 was significantly higher in the ABMR than no ABMR group (8.4% vs 5.6%, p = 0.003). Higher IgG3 level was correlated with ABMR histological severity (C4d deposition and microvascular inflammation), and with the risk of estimated glomerular filtration rate (eGFR) decline >25%. IgG3 proportion was not correlated with iDSA MFI. Multivariate analysis showed that proteinuria and high level of IgG3 DSA were the only factors independently associated with biopsy-proven ABMR, and predictive of renal function impairment.
Conclusions: This study shows that *de novo* DSA are always composed of the four IgG subclasses, but in different proportions. High IgG3 subclass proportion is associated with ABMR occurrence and severity and poorer outcome, independently of DSA MFI.

O59 BLOOD CD27$^+$CD21$^-$ MEMORY B-CELL EXPANSION IS ASSOCIATED WITH THE DEVELOPMENT OF ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: The role of alloreactive memory B cells in the pathogenesis of antibody-mediated rejection (ABMR) is increasingly recognized. However, a comprehensive characterization of memory B-cell heterogeneity during ongoing donor-specific alloantibody (DSA) responses is lacking.
Methods: Using 22-color flow cytometry and *in vitro* assays, we characterized the phenotype and function of blood subsets of memory B cells in patients who developed DSA (N = 48) and those without DSA (N = 48) in the first year post-transplant.
Results: We identified three distinct subsets of memory B cells in kidney recipients : resting memory (RM, CD27$^+$CD21$^+$), activated memory (AM, CD27$^+$CD21$^-$) and tissue-like memory (TLM, CD27$^-$CD21$^-$) B cells.

At the time of DSA detection, frequencies of AM and TLM B cells were significantly increased compared to patients without DSA. Unlike RM and TLM, frequencies of AM B cells highly correlated with plasmablast emergence, DSA MFI levels and DSA C1q-binding capacity. In DSA+ patients who further developed ABMR (N = 21), unlike those who remained free of ABMR, AM significantly expanded, while RM and TLM B-cell frequencies remained similar. AM B-cell expansion was detectable up to 6 months prior to ABMR and remained significantly elevated at the time of rejection. Phenotypically, AM expressed higher Ki67, CD86, Blimp and Irf4 while TLM upregulated more B-cell exhaustion markers Tbet, PD-1 and CD32 compared to RM B cells. Consistently, when co-cultured with T follicular helper cells, TLM was uncapable of plasmablast differentiation, while AM B cells had potent capacity to differentiate into plasmablast and produce DSA *in vitro*.
Conclusion: We identified a novel subset of AM B cells associated with the development of ABMR, with a highly activated phenotype and prone to differentiation into DSA-secreting B cells. Early detection and therapeutic targeting of AM B-cell response represent valuable strategies to prevent ABMR occurrence post-transplant.

O60 C3D-FIXING DSAS AND INFRA-CLINICAL REJECTION IN KIDNEY TRANSPLANTATION

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Introduction: Donor-specific anti-HLA antibodies (DSAs) have been associated with allograft rejection. It has also been pointed out that not all DSAs have the same degree of pathogenicity. The ability of DSAs to fix the complement (C3d) has been suggested as one of the options to stratify their pathogenicity. If their ability to fix the C3d shows significant clinical relevance, this test could be used as a non-invasive biomarker to help identify patients at higher risk of allograft rejection. This study focuses on infra-clinical patients. The first objective is to determine if identifying C3d-fixing DSAs is helpful for early infra-clinical allograft rejection diagnosis. The second goal is to assess if an early positivity of the C3d test is a predictive marker of lower allograft survival.
Methods: 112 adult patients from multiple centers in France were enrolled. All patients received a kidney transplant and had no pre-formed DSAs. All patients developed at least one de novo DSA. Allograft biopsies were performed at DSA appearance before any clinical sign of rejection. The C3d test (Immucor) was performed on serum collected on the day of the biopsy. Results with a p-value under 0.05 were considered positive.
Results: No significant difference (p = 0.373) in the proportion of C3d+ and C3d− patients in the infra-clinical humoral rejection group. 5 years after the first biopsy, among patients with a renal function decrease above 30%, most of the patients were C3d+ (p = 0.09). At 100 months post-biopsy, the probability of non-dialysis is 83% in the C3d− group, and 75% in the C3d+ group (p = 0.58%). C3d-positivity is significantly correlated with the MFI of the DSAs (p = 0.0001).
Conclusion: The C3d test is not helpful in the diagnosis of infra-clinical rejection. However an early positivity of the C3d test could be a predictive marker of lower allograft survival. But C3d positivity does not show any added value compared to MFI.

O61 COMPARISON OF TWO LUMINEX SINGLE-ANTIGEN BEAD FLOW CYTOMETRY ASSAYS FOR DETECTION OF DE NOVO DONOR-SPECIFIC ANTIBODIES FOR THE DIAGNOSIS OF SUBCLINICAL ABMR AFTER RENAL TRANSPLANTATION

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De novo donor-specific antibodies (DSA) are associated with antibody-mediated rejection (ABMR) and allograft loss. Whether monitoring of de novo DSA paired with systematic kidney biopsy should become routine remains to be established. The aim of this study was to assess if the intensity of de novo DSA determined by 2 Luminex Single-antigen assays (Immucor*; One Lambda*) were similar to help for the diagnosis of subclinical ABMR.

This retrospective multicentric study (9 French kidney transplant units of the Spiesser Group) included 123 patients without graft dysfunction biopsied because of the presence of de novo DSA (One Lambda, MFI > 1000). For 112 patients, sera of the day of the biopsy were tested with Immucor single antigen test.

For 17 patients (17/112: 15.2%), no DSA was detected using Immucor test. Corresponding mean MFI (One Lambda) in this group was 3527 ± 3308 (1017–11858) for the immunodominant DSA (iDSA) and 3527 ± 3308 (1017–11858) for the MFI of the sum of the DSA (sDSA). In this subgroup, systematic biopsies showed active ABMR in 2 patients (11.7%) and chronic active ABMR in 2 other patients (11.7%). For 95 patients, at least one DSA was determined with Immucor: in 79 cases (83.5%) iDSA was similar and different in 17 cases (17.9%). In this cohort, diagnosis of active ABMR was made in 29 cases (30.5%), chronic active ABMR in 17 cases (17.69%) and no ABMR in 45 cases (51.6%). In multivariate analysis, the intensity MFI of One Lambda test of iDSA and sDSA was significatively associated with the diagnosis of active ABMR but intensity criteria of Immucor test (BCM, BCR et AD-BCR) were not.

In conclusion, identification of de novo DSA seems to be more sensitive with One Lambda single antigen in the setting of DSA monitoring post-transplant and this study suggests that performing protocol biopsy for dnDSA could be guided by the MFI of the DSA (One lambda). The 2 tests were not similar in this context.

O62 ^{18}F-FDG-PET/CT IMAGING AT 3 MONTHS *POST*-TRANSPLANTATION DISPROVES SUBCLINICAL REJECTION IN KIDNEY TRANSPLANT RECIPIENTS

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Introduction: Subclinical kidney allograft acute rejection (SCR) corresponds to "the histological documentation of unexpected evidence of acute rejection (AR) in a stable patient". SCR detection relies on surveillance biopsy. Still, non-invasive approaches may help avoid biopsy-associated complications and limitations. Positron emission tomography (PET) after injection of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) may be an option.
Methods: From 11/2015 to 01/2018, we prospectively performed ^{18}F-FDG-PET/CT in adult kidney transplant recipients (KTR) who underwent surveillance transplant biopsy at ~3 months post-transplantation. Banff-2017 classification was used. The ratio of the mean standard uptake value (mSUVR) between kidney cortex and psoas muscle was measured. Statistics were done via Python library SciPy. Our 95-patient cohort was categorized into 3 groups upon Banff-based histology: normal (n = 70); borderline (n = 16); AR (n = 6). Three cases were excluded for PCR-proven BK nephropathy (n = 2) or uninterpretable histology (n = 1).
Results: No clinical or biological difference was observed between groups. mSUVR reached 1.87 ± 0.55, 1.94 ± 0.35 and 2.41 ± 0.54 in normal, borderline and AR groups, respectively. A significant difference of mSUVR was found among groups (F-score = 3, p-value = 0.05). Furthermore, mSUVR was significantly higher in AR versus normal (t-score = 2.3, p-value = 0.02) or borderline (t-score = 2.4, p-value = 0.02) groups. The area under the ROC curve (AUC) was 0.79, with 83% sensitivity using mSUVR threshold at 2.4. mSUVR correlated with total inflammation (r^2 = 0.05; p-value = 0.02) and acute composite Banff scores (r^2 = 0.04; p-value = 0.05).
Conclusion: Our pilot study suggests that ^{18}F-FDG-PET helps non-invasively detect SCR, with a negative predictive value of 96% using 1.6 as mSUV threshold.

O63 ROLE OF DSA GLYCOSYLATION IN ANTIBODY-MEDIATED REJECTION OCCURRENCE

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Background: Immunoglobulins are glycoproteins that perform their effector functions through the Fc fragments. IgG effector function is affected by the composition of the N-glycan attached to asparagine 297 in Fc fragment. We studied the role of the glycosylation of donor-specific antibodies (DSA) in the development and severity of antibody-mediated rejection (ABMR).
Methods: Between 2011 and 2018, we recruited 69 patients who developed a de novo DSA (29 patients without ABMR and 40 patients with ABMR) in two transplant centers. After isolating iDSA with Luminex single antigen beads (One Lambda), we have studied, by a mass spectrometry technique, the glycosylation profile of DSA, more specifically the IgG1 and IgG3 subclasses of DSA.
Results: DSA from patients with ABMR shown a proinflammatory profile (see Figure 1). For IgG1 DSA, galactosylation was significantly lower in ABMR+ patients (50.9% vs. 57.3%, p = 0.023). Regarding IgG3 DSA, in the ABMR + group, we found a significantly lower sialylation (7.5% vs 10.5%, p = 0.0004), a higher proportion of GlcNAc (20.6% vs 17.3%, p = 0.0035) and a trend to lower galactosylation (46.2% vs 49.2%, p = 0.06). The glycosylation profile was not influenced by the DSA MFI. The composition of the N-glycan, however, did not significantly influence the decline of graft function (more than 50% decrease in GFR) or graft loss in this study.

We conclude that a proinflammatory glycosylation profile of DSA is associated with the occurrence of humoral mediated rejection. The role of the DSA glycosylation profile on renal function degradation and graft loss will need to be studied in a larger cohort.

PROGNOSIS

O64 EVOLUTION OF CPRA IN PATIENTS WITH GRAFT DYSFUNCTION RETURNING TO DIALYSIS, ACCORDING TO MAINTENANCE OR NOT OF IMMUNOSUPPRESSION, AND IMPACT ON ACCESS TO A NEW TRANSPLANT

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Introduction: Anti-HLA immunization, following first kidney transplantation, may restrict access to a new transplant. The objective of our study was to determine if pursuit of immunosuppression after returning to dialysis reduced HLA immunization and the waiting time for kidney retransplantation.
Method: Patients registered on the waiting-list for retransplantation between 01/01/2010 and 25/09/2017 were included, excluding patients who had new preemptive transplantation. The primary endpoint was evolution of cPRA between return to dialysis and 6–12 months after. The waiting time, immunosuppression-related complications and allograft survival in case of retransplantation were studied.
Results: 72 patients stopped immunosuppression before 6 months after returning to dialysis, 66 stopped after 6 months and 30 didn't stop. Independent risk factors for immunization were immunosuppression weaning whether it was early or late (respectively OR 9.35, 95% CI [2.33–37.5]; p = 0.002 et OR 6.32, 95% CI [1.55–25.69]; p = 0.01) and an initial cPRA below 50% (OR 13.64, 95% CI [5.83–32.10]; p < 0.001). In multivariate analysis, early and late immunosuppression withdrawal was associated with a more difficult access to a new transplantation (respectively HR 0.37, (95% CI [0.21–0.66]; p = 0.001) et HR 0.31 (95% CI [0.17–0.55]; p < 0.01)). Immunosuppression-related complications during the dialysis wait period were not significantly different between the three groups.
Conclusion: In patients with kidney graft failure returning to dialysis, continued immunosuppression can limit alloimmunization with easier access to retransplantation without increasing the number of serious adverse events.

O65 PREEMPTIVE KIDNEY TRANSPLANTATION IMPROVES TRANSPLANTATION OUTCOMES AMONG CHILDREN WITH END-STAGE RENAL DISEASE: RESULTS FROM THE FRENCH TRANSPLANT DATABASE

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Background: Kidney transplantation (KTX) is the optimal treatment for children with end-stage renal disease (ESRD), with improved survival, morbidity and quality of life compared to dialysis. The benefits of paediatric preemptive kidney transplantation (PKT) remain unclear, with a number of studies failing to prove better graft survival among PKT patients, contrary to what is found in the adult population. The aim of this study was to evaluate the impact of PKT and of pre-transplant dialysis duration on graft survival among French paediatric kidney transplant recipients.
Methods: We analysed all first paediatric kidney-only transplants performed in France between 1993 and 2012. A Cox multivariable model was used to investigate the association of PKT and of pre-transplant dialysis time with the hazard of graft failure defined as death, return to dialysis or re-transplant, whichever occurred first.
Results: 1911 patients were included, of which 380 (19.8%) received a PKT and 1531 (80.2%) who were transplanted after starting dialysis. Median time of follow-up was 7.0 years. Graft failure occurred in 572 patients. After adjustment for recipient sex and age, primary kidney disease, donor age and type (living or deceased donor), number of HLA mismatches and cold ischaemia time, PKT was associated with a 54% reduction of the hazard of graft failure at any time after KT compared to patients transplanted after RRT (HR 0.46%; 95%CI: 0.33–0.63). This reduction of the hazard of graft failure was found whatever the duration of dialysis, even for those who received less 6 months dialysis.
Conclusions: In France, PKT among paediatric patients provides significant benefits in terms of graft survival when compared to KTX after dialysis, including patients who spend only a short period of time on dialysis. Based on these findings, we suggest that PKT should be considered the treatment of choice for children with ESRD.

O66 PROFILING ADHERENCE IN KIDNEY TRANSPLANT PATIENTS: WHEN AND WHY?

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Introduction: Adherence is a critical determinant of transplant patients' outcome. Longitudinal studies are the best way to study this dynamic phenomenon, which varies over time. Our objective was to explore adherence over time in kidney transplant patients followed up for up to three years after transplantation.
Methods: Adherence was repeatedly estimated with the 4-Item Morisky-Green-Levine Medication Adherence Scale in two cohorts of 345 and 367 kidney transplant recipients (EPIGREN and EPHEGREN). Adherence time profiles were explored by mixed effect modeling with latent process and latent classes. Time to rejection was evaluated using Kaplan-Meier analysis and comparison between groups using the log-rank test. The relationship between non-adherence and rejection was explored using a time-dependent Cox proportional hazard model.
Results: Two profiles of adherence over time were characterized: the first subgroup of patients (85%) displayed a good and stable adherence, while patients of the second subgroup (15%) displayed poorer adherence at one month post-transplantation ($p < 10^{-3}$) and a non-adherence behavior worsening over time. Non-adherent patients were younger (<50 years) and declared more depression episodes (13% *vs.* 5%, $p = 0.001$) and a lower mental quality of life (41 ± 13 *vs.* 47 ± 11, $p = 0.015$). Survival without acute rejection episodes was longer in the adherent class ($p = 0.004$).
Conclusion: The risk for a renal transplant patient of being poorly adherent over time could be detected before 6 months post-transplantation, using appropriate and easy-to-use tools, adapted to routine monitoring. Psychological determinants such as depression or quality of life are amenable to change, contrary to age. The early screening of vulnerable patients could allow setting-up targeted actions such as psychological and behavioral interventions, involving multi-disciplinary teams, in order to reduce the risk of poor outcomes related to poor adherence.

O67 A SYSTEMATIC MONTH-3 KIDNEY TRANSPLANT BIOPSY IS ASSOCIATED WITH A BETTER LONG-TERM DEATH-CENSORED GRAFT SURVIVAL – ACCOUNTING FOR PROPENSITY SCORE OF BIOPSY

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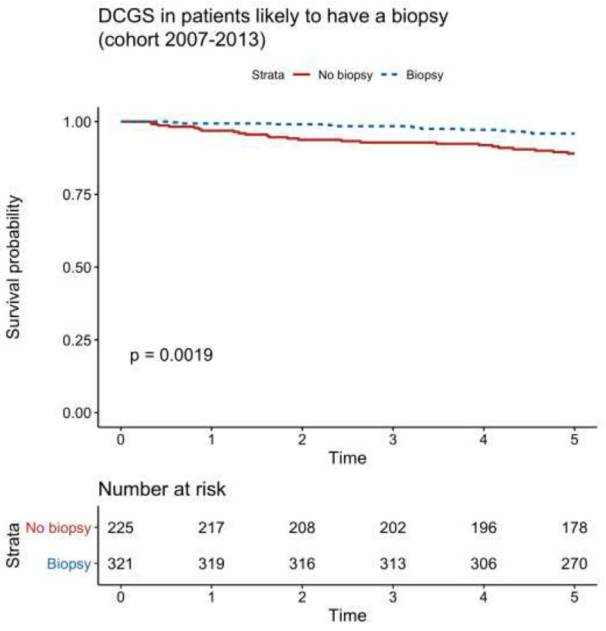
In many centers, a systematic kidney biopsy is performed 3 months after transplantation (M3). Whether this results in improvements of death-censored graft survival (DCGS) over the long term depends on the obvious bias of biopsy contra-indication in patients at higher risk of graft loss. In this study, we compared DGCS between patients undergoing a systematic M3 biopsy and patients without available M3 biopsy, accounting for the previous bias.

We enrolled all kidney recipients transplanted between 2007 and 2013. At our center, a systematic kidney allograft biopsy was introduced in 2009. We therefore defined 3 groups: C2007 for patients transplanted without systematic kidney biopsy in 2008 or 2009, C2009/B- for patients transplanted between 2009 and 2013 but a contra-indication to biopsy and C2009/B+ for patients transplanted between 2009 and 2013 who underwent a kidney biopsy. We built a propensity score to account for biopsy indication bias (adjusting for potential confounders such as donor's and recipient's age, early blood transfusion, medical history…).

Between 2007 and 2013, a total of 660 kidney transplantations were performed at Grenoble University Hospital. Full data were available for 619 patients: 175 patients in group C2007, 111 in group C2009/B- and 333 in group C2009/B+. Overall, there were 110 death-censored graft losses. In a Cox multivariate survival model, we show that undergoing a M3 systematic biopsy is associated with a lower risk of graft loss (HR = 0.29, $p < 0.001$), independently of the propensity score (HR = 0.18, $p < 0.001$) and the transplant era (2007–2008 VS 2009–2013, HR = 0.29, $p < 0.001$). When focusing on the group of patients with a probability of biopsy >0.5, we see a difference between biopsy and non-biopsy patients (log-rank $p = 0.0019$) over the first 5 years (figure 1).

A systematic kidney biopsy at month-3 post-transplantation is associated with a clear survival benefit over the first 5 years post-transplantation.



O68 AN AUTOMATIC SOLUTION FOR THE INTERPRETATION AND MANAGEMENT OF ANTI-HLA ANTIBODIES DETECTED IN "SINGLE ANTIGEN": APPLICATION TO PATIENTS

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We have studied the performance of an algorithm developed to interpret and manage the anti-HLA (class I and II) anti-HLA antibody (Ab) profiles generated by the "single antigen" analyses, which is included into Lymhoe's LymFIP software. This tool allows:

1. the study of the Ab profile of a serum,
2. the identification of donor-specific Ab (DSA) in a serum,
3. the generation as well as the updating of the CRISTAL profile of a patient.

In all 3 cases, we compared the result report with the manual interpretation made with the reasoning supposedly applied by the algorithm, and with the result rendered when applying the rule of the allele with the strongest MFI for each antigen (and without taking into account the alpha chains of DQ and DP). We analyzed 200, 100, and 100 class I and class II sera for applications 1, 2, and 3, respectively, for routine, DSA, and waiting list patients, respectively. The comparison shows that the performance of the tool is perfectly in line with expectations. No errors were detected for Ab analysis of sera (item 1). For the DSA search (item 2), no error was detected, the algorithm allowing in addition to deduce the presence of DSA for the DRB3/4/5 loci according to the knowledge of DRB1 typing, when the typing is incomplete, but the accuracy of the DSA search is obviously limited by the level of accuracy of the typing of the recipient and the donor (resolution, known loci). For the CRISTAL side, the tool perfectly interprets the profiles generated over time to arrive at a final summary exported in CRISTAL, and correctly applies the thresholds of MFI determining the categories acceptable/ grey zone/ unacceptable zone. We will illustrate the performance of the tool with selected informative profiles among those included in this study, and will describe current and future developments.

O69 ECHRONIC/ENEPHRO : CLINICAL EVALUATION OF A TELEMONITORING SYSTEM FOR THE MEDICAL CARE OF THE KIDNEY TRANSPLANT PATIENTS

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Introduction: the aim of the study was to evaluate the efficiency of telemonitoring (TM) in 3 groups of patients with chronic kidney disease, before and after renal replacement therapy. We report here on the clinical results obtained for kidney transplant patients.
Methods: A pragmatic, controlled, randomized study was carried out in 3 transplant centers, including patients transplanted for more than 3 months. In the TM group, patients used a digital tablet with a secured access to the eNephro software, combined with a expert system that analyzed clinical and biological parameters. In the control group, patients had the traditional care.

The primary judgment criterion of the study was the cumulative duration of unplanned hospitalizations during the 1-year follow-up period. Statistical analysis used a ZINB (zero inflated negative binomial) adjusted for the exact duration of each patient's follow-up.
Results: 248 patients were included, 4.7 $\pm$ 2.4 months after transplantation, 126 in the control group, 122 in the TM group. 235 patients completed 1-year study. Mean age was 48.9 $\pm$ 13.8 years, male/female ration was 2.1 and 42.7% had an education level above A-levels. 30 (12.1%) patients were diabetic and 70 (28.2%) had a previous cardiovascular history.

In the control group, 78 p (61.9%) had at least 1 unplanned hospitalization vs 62 (50.8%) in the TM group. During the FU, the number of un planned hospital days was 4.5 $\pm$ 8.9 in the control group vs 4.2 $\pm$ 8.0 in the TM ($p = 0.133$). However, the number of consultations in the transplant center is reduced by 18% in the TS group ($p = 0.03$).
Conclusion: The results of the analysis show a lower frequency of unscheduled hospitalizations and a tendency to decrease their duration over one year in kidney transplant patients receiving TS (NS). Nevertheless TS significantly reduces the number of visits to the transplant center.

O70 EVOLUTION OF THE SENSITIZATION OF HIGHLY SENSITIZED PATIENTS WAITING FOR KIDNEY TRANSPLANTATION: IS A QUARTERLY FOLLOW-UP ESSENTIAL?

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Background: Anti-HLA highly sensitized (HS) patients awaiting kidney transplantation benefit from national priority through the "HAP" program (HS with authorized antigens). Maintaining this priority requires that these patients have a serum tested every 105 days in order to detect potential anti-HLA antibodies emergence and then prevent unexpected positive cross-matches. However, it seems that there is an imbalance between this high surveillance rate and the apparent stability of patient sensitization profiles. Some laboratories use screening assays instead of Single Antigen Flow Beads (SAFB) assays in order to reduce the costs. We aimed to assess the relevance of the quarterly biological follow-up of HS patients.
Methods: We included 168 HS patients displaying at least 2 sera tested at 3-month intervals (M, the most recent, and M-3) during their waiting period, with a median of 3 sera per patient. Anti-HLA antibodies were measured by SAFB assay. We performed screening assays on 15 serum pairs (M and M-3) for which SAFB assay evolution was known.
Results: From the 360 serum pairs studied, only 0.8% of class I beads and 0.5% of class II beads crossed the unacceptable antigen threshold at the M serum [mean fluorescence intensity (MFI) $\geq$ 2000] with a median MFI of 3113 and 2605, respectively. Among them, 78% were already above the threshold of the authorized antigens (500 $<$ MFI $<$ 2000) at M-3. A median of 2 antigens had to be switched to unacceptable in only 18% of serum pairs. This led to an increase of calculated panel reactive antibodies of 4% on average. Otherwise, data provided by screening tests were not able to predict satisfactorily the SAFB profile variations.
Conclusion: Given that changes in HS patient profiles are marginal, spacing of monitoring may be considered. In order to offer the best monitoring strategy, a more detailed study of SAFB profiles is undergoing determining which clinical events cause profile changes.

O71 EVALUATION OF A COHORT OF HEART TRANSPLANT CHILDREN: FUTURE AT ADULT AGE, 20 YEARS EXPERIENCE IN SINGLE CENTER

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Introduction: Nowadays, pediatric heart transplantation is usually performed as a last resort treatment for an advanced heart failure. This study evaluates the future at adult age of a cohort of heart transplant children in Marseille.
Methods: Retrospective study of heart transplant infants (<18) at La Timone children hospital (Marseille) between January 1999 and December 2018. Donor and recipient demographic data, etiology, status in waiting list, hemodynamic data, post-transplantation complications and global mortality were analysed.
Results: 49 transplantations in 48 infants were registered. Median age and weight at transplantation were respectively 8.3 years old [2.9–13.5] and 20.5 kg (5 to 75). The most common diagnosis was cardiomyopathies (CM) in 86% cases (dilated cases in 57% CM), congenital heart diseases 8% and myocarditis 6%. Median waiting time was 46 days [19–132]. 26 patients were transplanted in great emergency. Post-transplantation median follow-up was 3.8 years old [1.5–8]. 9 patients (18%) died, 5 (56%) for graft rejection, 2 (22%) for septic shock, 1 (11%) for post-extracorporeal circulation brain hypoxia and 1 (11%) for primary graft dysfunction. 10 patients (20%) had a symptomatic graft rejection, that appeared after a 12 months median [6–27]. 1 patient had a lymphoma. Median age at the last pediatric follow-up was 14.3 years old [8.7–17.9]. 21 children (43%) were treated for arterial hypertension. No infant needed chronic dialysis. 36% children could attend school on a regular basis, 7 (14%) attended a special school, 1 was in Educational Medical Institute, 1 was out of school.
Conclusion: The analysis of this cohort of heart transplant children shows a good global survival rate and a normal social insertion in 75% cases. Further analyses will be necessary to study their quality of life.

O72 TRANSFORM STUDY (NCT01950819): APPLICATION OF THE IBOX CLINICAL TRIAL SIMULATION TOOL TO PROJECT LONG-TERM KIDNEY ALLOGRAFT OUTCOME

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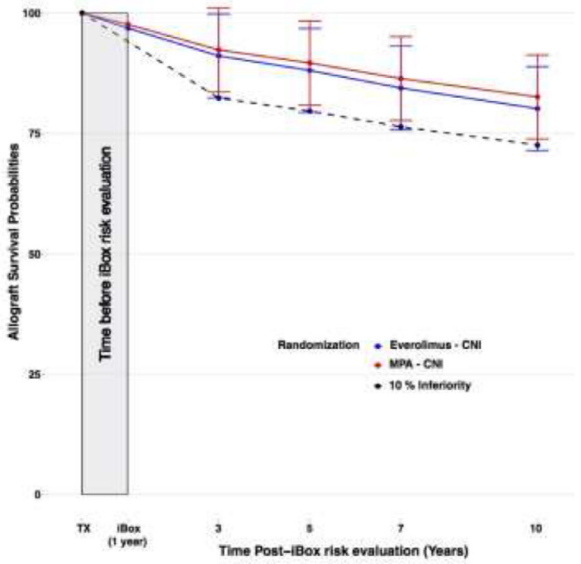
The development of pharmaceutical agents in transplantation is currently limited by long waits for hard endpoints. We sought to use a risk stratification system in a large randomized control trial (RCT) and determine individual patient long-term graft survival.

We used validated data from the TRANSFORM trial (NCT01950819), a RCT that compares kidney transplant recipient to receive everolimus with reduced-exposure calcineurin inhibitor (CNI) or mycophenolic acid (MPA) with standard-exposure CNI. We applied the iBox system (NCT03474003), an integrative and validated risk score which used the parameters measured at 1 year after randomization (primary end point time line) and projected patient's individual long-term allograft survival.

A total of 1872 patients (940 in the everolimus and 932 in the MPA arm) reached the 1 year after transplant primary endpoint. Mean estimated glomerular filtration rate was 55.5 $\pm$ 19.9 mL/min/1.73 m^2 in the everolimus arm vs 56.1 $\pm$ 19.0 in the MPA arm. The mean protein/creatinine ratio was 0.33 $\pm$ 0.68 g/g in the everolimus arm vs 0.25 $\pm$ 0.62 in the MPA arm. The incidence of active ABMR and acute TCMR of 7.1% and 7.2% in the everolimus arm *vs* 6% and 7.1% in the MPA arm. The rate of circulating anti-HLA DSA was 13.8% in the everolimus arm *vs* 16.1% in the MPA arm. These immunological, functional and histological parameters were entered into the iBox risk prediction system, which translated to an overall patient graft survival at 3, 5 and 10 years after randomization of 94.2 *vs* 94.7% %, 91.2% *vs* 92.0% and 83.3% *vs* 84.9% in the everolimus and MPA arms respectively (95%CI $-$3.1% to 0.2%, below the non-inferiority margin of 10%) Figure 1.

The iBox system confirms the non-inferiority of everolimus vs MPA 10 years after patient's randomization in the RCT. Given the unmet need for surrogate end point for clinical trials, this study shows the potential of a clinical trial simulation tool to fast track the development and approval of pharmaceutical agents.

Figure 1: Projected long term allograft survival between the everolimus and MPA arms using the iBox clinical trial simulation tool



Mean projected allograft survival

Everolimus - CNI	94.2%	91.2%	87.6%	83.3%
MPA - CNI	94.7%	92.0%	88.7%	84.9%

LIVER TRANSPLANTATION

O73 TORQUE TENO VIRUS VIRAL LOAD COULD PREDICT IMMUNOSUPPRESSION LEVEL AFTER LIVER TRANSPLANTATION

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Torque teno virus, a main constituent of the human virome, is considered a commensal virus. Our aim was to evaluate its viral load (TVL) as a biomarker of under or over-immunosuppression after liver transplantation (LT).

Patients are from the French ANRS 23 CUPILT cohort, which included 695 HCV transplant patients who received direct antiviral treatment. Subjects were selected according to the occurrence of events, either rejection or infection. Event-free controls were matched (1:1) on age, sex, time between LT and inclusion, HIV status, number of immunosuppressive agents at baseline and stage of fibrosis. The plasma TVL was determined before and during or after the event and at a comparable post-TH delay compared to controls and expressed in $\log_{10}$ IU/mL.

One hundred and five patients (mean age 60.8 ± 8.9 years, 67% males) were included in the infection group with a mean delay of 6.8 years from LT. The sites of infections were mainly pulmonary (35%), ENT (17%) and urinary (13%). The TVL before and after the event was 3.99 [2.4–4.9] and 3.86 [2.5–5.0] ($p = 0.95$) respectively. The TVL was 3.25 [2.5–4.5] in the control group ($p = 0.15$). Fifteen patients (mean age 53.3 ± 5.4 years, 73% males) were included in the rejection group 2.1 years after LT. Median Banff score was of 5 [4–6]. The TVL was not significantly different between the rejection group and the controls (3.71 [2.5–4.6] versus 3.96 [2.4–6.5], respectively ($p = 0.51$).

Among the 234 transplant patients, 35 patients had an undetectable TVL with a longer delay between transplantation and inclusion (7.8 [3.5–11.3] versus 4.0 [1.1–8.8, $p = 0.007$). In contrast, the 29 patients with TVL ≥ 7 log had more immunosuppressive agents ($p < 0.001$) and a lower BMI (22.4 [21.3–24, 9] versus 24.5 [22.2–28.4] kg/m^2, $p = 0.01$).

After LT, TVL is not different in patients with infection or rejection compared to the control group. However, extreme viral loads, undetectable or ≥7, are associated with under- and over-immunosuppression factors.

O74 SELECTING PATIENTS WITH DECOMPENSATED CIRRHOSIS AND ACUTE-ON-CHRONIC LIVER FAILURE (ACLF) ADMITTED TO THE INTENSIVE CARE UNIT FOR LIVER TRANSPLANTATION

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Background: ACLF is a decompensation of cirrhosis associated organ failure (s) secondary to an acute decompensated event. The aim of this prospective study was to evaluate the outcome and the factors associated with a selection to liver transplant (LTx) in this population.
Methods: All consecutive patients admitted to the ICU with cirrhosis and ACLF, were recruited. Patient with age <18 years or with fulminant hepatitis were excluded.
Results: We included 155 cirrhotic patients in ICU. Mean age was 55.6 ± 11.3 years (71.6% Male). Cirrhosis was due to alcohol in 78.1 % of the patients. ACLF grading at admission was: 44.5% ACLF3 (n = 60), 21.3% ACLF2 (n = 33), 14.8% ACLF1 (n = 23), and 19.4% ACLF0 (n = 30).Of the 155 patients, 46.5% (n = 72) were considered to be eligible for a transplant. The main reasons were alcohol abuse (66.3%, n = 55), death within 7 days after admission (32.5%, n = 27) and improvement of the liver disease. Of the eligible patients 47.2% (n = 34) were transplanted. Twelve patients died on the waiting list (24% of the listed patients), mainly of septic shock. Among those who were assessed for LTx but not listed (n = 21), 76.2% died before the listing (n = 16) and 23.8% were not listed because of severe comorbidities (n = 5). The global mortality rate was 56.8% (n = 88). The 28 and 90 days rate mortality were respectively 42.9% and 56.2%. The overall 3-month survival was respectively 97% and 26% in the transplant and non-transplant group ($p < 0.001$). Among eligible patients, factors associated with the absence of LTx, were mechanical ventilation (HR 8.95; 95% CI [2.75; 29.06], $p < 0.001$) and age over 60 years (HR 3.32; CI 95% [1.04; 10.63], $p < 0.001$).
Conclusion: Cirrhotic patients in ICU should be evaluated for eligibility to LTx. Half of the patients were eligible and 22% patients were transplanted. Among those eligible, patients over 60 years and under mechanical ventilation during early ICU stay would less likely to survive and be selected for LTx.

O75 ESTIMATE OF RENAL FUNCTION BEFORE LIVER TRANSPLANTATION

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Introduction: Renal function is a major factor in pre- and post-liver transplant mortality. Its estimate is complex in cirrhotic and the standard evaluation methods are not valid. This leads to significant over or underestimation of renal function. The gold standard remains the measurement of the DFG by the clearance of an exogenous tracer but this method is not applicable in current practice. The aim of this work is to determine, in the absence of French recommendations, the most appropriate estimation formula for the cirrhotic patient.
Methodology: This is a monocentric retrospective study, performed at Toulouse University Hospital. All patients who had a pre-liver transplant assessment including a measurement of glomerular filtration rate by inulin between 01/01/2006 and 31/12/2017 (n = 470) were included. Patients who have been grafted in a super-emergency without measure of GFR were excluded.
Results: CKD EPI creatinine and MDRD4 overestimated GFR (bias at 14.5 and 23.2). The formula CKD EPI cystatin underestimated GFR (bias at 23.2). The most accurate estimate was obtained from MDRD6 and CKD EPI creatinine-cystatin formulas with a bias of less than 2, a degree of correlation (measured DFG-estimated DFG) greater than 0.75, and a precision of 30% for

more than 80% of patients. For GFR <60 ml/min/1.73 m^2, CKD EPI cystatin allowed to minimize the bias. However, its 30% accuracy level was similar to that of the combined MDRD6 and CKD EPI creatinine-cystatin formulas. Although the degree of accuracy is lower for high scores, the severity of liver injury (MELD and CHILD) did not impact the estimation method to be used.
Conclusion: We therefore recommend an early estimation of renal function by the MRDR6 or CKD EPI creatinine-cystatin formula in all cirrhotic patients, regardless of the degree of renal impairment or the severity of hepatic injury.

O76 ALCOHOL RECURRENCE AND OUTCOME IN PATIENTS TRANSPLANTED FOR ALCOHOLIC CIRRHOSIS: IMPACT OF THE 6 MONTHS RULE

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Introduction: Liver transplantation (LTx) is generally recommended for patients with decompensated alcoholic cirrhosis (Meld > 15) with a time from alcohol abstinence to LTx > 6 months. The latter rule is still debated as the 6-month per says could not contraindicate alone LTx in the last guidelines.
Methods: This is a retrospective study that recruited in our center all LTx patients for alcoholic cirrhosis during the period of 2013–2017. Patients were stratified into 3 groups according to period of abstinence prior to LTx: >6 months (group 1); <6 months (group 2) and biopsy-proven acute alcoholic hepatitis (AAH) refractory to medical treatment (group 3). Alcoholic recurrence was defined by any alcohol consumption reported by the clinicians, or on oriented/protocol liver biopsies and prospectively by a specific survey send to all patients. The survey allowed characterizing the recurrence via the AUDIT-C score.
Results: Among the 225 LTx patients recruited in the study, 28 and 17 patients were respectively in group 2 and 3. The mean MELD score at time of LTx was respectively 21 ± 10.9, 32 ± 9.6 and 34.7 ± 7.6 (Group 1, 2 and 3). The 1- and 5-year patient survival was, respectively, 93%, 81% and 100% and 76%, 72% and 100% (Group 1, 2 and 3, global Log-rank, p = 0.088). Overall, 60 patients had post-transplant alcohol recurrence. Alcohol recurrence rates were respectively 24%, 25% and 53% in groups 1, 2 and 3 (p = 0.17). In the multivariate analysis, factors associated with alcohol recurrence were AAH {OR = 3.51 95% CI (1.1–11.27), p = 0.035} and consumption of toxic substances prior to LTx {OR = 2.94, 95% CI (1.15–7.51), p = 0.025}.
Conclusion: The absence of differences in survival and recurrence rate between group 1 and 2 support the fragility of the 6-month rule and the importance of a multi-disciplinary and a multifactorial approach for optimal selection of these patients to LTx.

O77 EARLY VERSUS LATE HEPATOCELLULAR CARCINOMA (HCC) RECURRENCE AFTER LIVER TRANSPLANTATION FOR HCC: PATTERNS AT RECURRENCE AND LONG-TERM OUTCOME

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Aims: Analyze the patterns and outcome of patients who developed HCC recurrence according to post-transplant time of recurrence.
Patients and Methods: Consecutive patients who underwent LT for HCC between 2000 and 2017 at our center were recruited. Characteristics of patients, recurrence, modalities of treatment and outcome were collected retrospectively. Patients were divided according to time of recurrence: early (≤2 years post-transplant) and late (>2 years post-transplant).
Results: 433 patients (mean age: 57.8 ± 8.5 years; 83.8% were males). Mean follow-up was 74.6 ± 58.6 months. 75 patients (17%) developed HCC recurrence with a mean time to recurrence of 64.9 ± 31.8 months. Patient who developed recurrence had more tumors outside Milan and UCSF criteria, high AFP score and microvascular invasion at pathology. Early recurrence developed in 46 patients (61.3%) and late recurrence in 29 patients (38.7%). The median survival times from the diagnosis of HCC recurrence were similar 15 and 17 months respectively in the early and late recurrence groups (p = 0.12). The mean AFP level at the time of diagnosis of early HCC recurrence was 1061 ± 466 ng/mL and 292 ± 402 ng/mL in the late HCC recurrence group. Among the patients who developed an early HCC recurrence the overall 5, 10 and 15-year survival rates were 6.7%, 0%, 0% but significantly shorter than those patients with late recurrence respectively at 5.10 and 15 years, 64.0%, 27.1% and 0% (log-rank p < 0.0001). In the multivariate logistic regression analysis, independent predictors for early recurrence were bi-lobar tumor at first diagnosis of HCC (OR = 86.23; p = 0.016), and at time of transplant Child-Pugh score A/B vs. C (OR = 28.65/61.99; p = 0.016) and higher number of nodules (OR = 2.65; p = 0.035).
Conclusion: In this large cohort with long-term follow-up, late HCC recurrence has been associated with a good long-term survival. Early HCC recurrence had very bad prognosis mostly in relation to bi-lobar and high number of nodules.

O78 MULTIPLE CANCER AFTER LIVER TRANSPLANTATION MUCAALT, A FRENCH NATIONAL MULTICENTER STUDY

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Despite the great progress made in recent decades, post-liver transplant de novo cancer is one of the leading causes of late complications and mortality after LT.

Using data from the French Biomedicine Agency's national database, our objective was to see if survival was different with one or more cancers.

114 French patients who had LT between 1993 and 2012 were followed until June 2016 or until death.

After an average follow-up of 9.8 ± 5.1 years, 52 patients developed 1 cancer, 49 had 2 cancers and 13 had 3 cancers. Univariate analyzes showed that the reduction in survival time was significantly related to the metastatic stage (Hazard Ratio (HR) = 2.19, 95% confidence interval (CI) [1.20–3.98], p = 0.0102, ref. "Localized cancer"), ENT cancer and / or respiratory system (HR = 4.61, 95% CI [2.28–9.35], p < 0.0001, ref. "Genitourinary system") and smoking (HR = 3.14, 95% IC [1.55–6.36], p = 0.0015). While the recurrence of cancer (p = 0.514, ref single cancer), the type of primary IT (Tacrolimus: p = 0.1409, Cyclosporine: p = 0.2809, ImTor: p = 0.1707) and the alcohol (p = 0.5836) did not significantly influence the survival time of our cohort. Duration under IT was found to be significantly related to survival (HR = 0.76, 95% CI [0.70–0.82], p < 0.0001). In multivariate analysis, due to a lack of probable potency, only the duration of IT and the location of (metastatic) cancer remained significant factors affecting survival.

ENT cancer and / or respiratory system have a shorter survival time than a genitourinary cancer. In univariate analysis, the metastatic stage and tobacco were risk factors for decreased survival. Cancer recurrence, alcohol and type of IT were not significant. Pre-transplant cancer could not be studied because of a large quantity of missing data.

O79 NODULAR REGENERATIVE HYPERPLASIA IS A SEVERE COMPLICATION AFTER LIVER TRANSPLANTATION

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Nodular regenerative hyperplasia (NRH) represents 27% of non-cirrhotic portal hypertension in Europe. In the liver transplantation (LT) settings, NRH could recur on the graft for patients transplanted for NRH, but also 10% of patients transplanted for another indication develop *de novo* NRH. Some of them will develop portal hypertension that may lead to death or reLT. The primary objective of this study is to describe natural history of symptomatic NRH in patients with histologically proven NRH after LT.

This is a retrospective, monocenter, cohort study. The inclusion criteria were age >18 years, history of LT independently of the cause, NRH histologically proven after LT. We collected all liver biopsies with NRH after LT from 2007 to 2017. Events related to NRH were defined as ascites, esophageal varices (EV) with or without bleeding, hepatic encephalopathy (EH), portal thrombosis, reLT and death related to NRH. Then, a research of predictive factors for a symptomatic RNH was conducted.

We identified 118 patients with a mean time follow-up of 8.9 ± 9 years since LT. Mean age was 52 ± 14 years. At the time of diagnosis, mean bilirubin was 22.1 ± 56 μmol/l, INR: 1.2 ± 0.4. 4 (3%) patients presented a recurrence of RNH and 114 patients (97%) presented *de novo* RNH. 29 patients (24.6%) experienced events with the mean time follow-up of 8.3 ± 9.9 years after LT: 18 (15.3%) patients developed ascites, 12 (10.2%) EV, 7 (5.9%) variceal bleeding, 3 (2.5%) HE, and 8 (6.8%) portal thrombosis. 6 patients (5.1%) were treated with TIPS and 1 (0.8%) patient with PCA. 9 patients (7.6%) were retransplanted with a meantime of 12.6 ± 9.7 years after previous LT but only 6 (5.1%) for symptomatic RNH. 16 (13.6%) patients died

with a meantime of 12.7 ± 9.5 years after LT. The overall and graft survival at 5-year was 87% and 81%. respectively.

NRH is a severe complication that should be screened. Predictive factors of events among these patients will be presented during the meeting.

O80 LONG-TERM OUTCOME OF CHILDREN TRANSPLANTED DURING CHILDHOOD IS STILL A MATTER OF INVESTIGATION

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The aim of our study was to evaluate the short- and long-term outcomes of children regarding surgical and medical complications according to the type of grafts.
Methods: The choice of the type of graft depended upon recipient's age and weight, the degree of LT urgency or parent's willing for live donation.
Results: From 1991 to 2010, 1061 LT were performed in our institution. Among them, they were 160 LT done in 151 children (85 females and 75 males) with a mean age of 5 ± 4.9 years (range 0.3–17) and a mean weight of 18 ± 14.6 kg (range 0.5–94). The mean waiting time was 106 ± 190 days (range 0–1404). Whole grafts accounted for 53 (33.1%) and 107 partial grafts (66.9%); among partial grafts there were 64 from split livers and 43 from live donors. Comparing whole and partial liver transplantations, waiting time was shorter and there were significantly more surgical complications in the later group which accounted for younger, smaller and more sick recipients. The 50% rate of acute cellular rejection was comparable in the three groups whereas children having received living donor graft experienced significantly less late acute and chronic rejection. Chronic rejection and graft loss were significantly associated with the presence of Class II DSA and high MFI. Progression of graft fibrosis over years is slow and multifactorial. Overall patient and graft survival was 84.7% and 79.3% respectively after a mean follow-up of 13.5 ± 8.7 yrs (range: 0–29). Whole and partial graft overall survival was 86.7% and 75.7% respectively ($p = 0.07$), moreover overall partial graft survival dramatically improved in the second half of the series at 94.5%.
Conclusion: Long-term outcomes in pediatric liver transplant recipients is excellent whatever the type of graft in spite of frequent surgical complication mainly in small recipients.

O81 LIVER TRANSPLANTATION IN CHILDHOOD FOR AUTOIMMUNE LIVER DISEASE: A EUROPEAN MULTICENTER EXPERIENCE

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Background: Autoimmune liver diseases (autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC)) are rare indications for LT in children with well-recognized complications (graft rejection and disease recurrence).
Patients and Methods: Retrospective data from 30 children diagnosed with AIH or PSC who underwent a first liver transplantation from January 1988 to February 2018 were collected in 4 European centers in France and Switzerland.
Results: The study population consisted of 18 girls and 12 boys, transplanted for AIH type 1 (n = 14 (47%)), AIH type 2 (n = 7 (23%)) or PSC (n = 9 (30%)). Mean age at LT was 11.8 ± 5.2 years. Median interval between diagnosis and LT was 34.2 months (range 0.1–11.4 months). Steroids before LT were used in 16 cases (53%) with a median duration of 2 years (range 0.1–7.0). The main indications for LT were fulminant hepatitis, n = 11 (37%), complications of portal hypertension, n = 10 (33%) or end-stage liver failure, n = 9 (30%). Initial immunosuppression included steroids (100%), tacrolimus (57%), cyclosporine (43%), azathioprine (40%), mycophenolate mofetil (20%). Steroids were maintained in 14/30 of the patients (46%). Graft rejection occurred in 19 patients (63%) with a total of 41 episodes of rejection; 6 pts (31%) required retransplantation (rLT) for chronic rejection. Recurrence of initial disease was observed in 6 patients (20%), all of them with type 1 AIH, after a median time of 42 months (range 14–265 months), requiring rLT in 2 cases. Finally, 8 patients (26%) died (all AIH), from whom 5/8 had had LT for fulminant hepatitis: 4 died early after LT (3 from multiorgan failure and 1 from sepsis), and 4 beyond 3 months after LT (2 from sepsis and 2 from AIH recurrence).
Conclusions: LT is the only therapeutic option in case of pediatric end-stage autoimmune liver disease. Long-term patients and graft survival are impaired in patients with AIH because of consistent complications such as rejection and disease recurrence.

PIERRE-OLIVIER DENUÉ & BENJAMIN RAMUS SESSION BEST ABSTRACTS

O82 RENAL, EFFICACY AND SAFETY OUTCOMES USING AN EVEROLIMUS (EVR)-BASED CALCINEURIN INHIBITOR (CNI)-FREE REGIMEN VERSUS STANDARD TACROLIMUS (TAC) AFTER LIVER TRANSPLANT (LTX): FOUR-YEAR FINDINGS FROM CERTITUDE

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Background: EVR-based CNI-free therapy may preserve renal function and reduce CNI-related complications after Ltx but long-term data are sparse.
Methods: The prospective CERTITUDE trial follows Ltx patients [pts] to 5 years post-Ltx after completing the 6-month [M] SIMCER study, in which deceased-donor pts were randomized at month 1 post-Ltx to (i) EVR + TAC withdrawn by month 4 or (ii) standard TAC, both with basiliximab induction, mycophenolic acid (MPA) ± steroids to compare the glomerular filtration rate (GFR) after Ltx.
Results: 143 of the 188 pts randomized in SIMCER entered in CERTITUDE (65/93 EVR, 78/95 TAC) with 124 pts followed to M48 post-transplantation (57 EVR, 67 TAC). The leading indications for Ltx were alcoholic cirrhosis (75/143) and hepatocellular carcinoma [HCC] (35/143). Adjusted means (SEM) change in estimated GFR (eGFR; MDRD) from SIMCER randomization to M36 after adjusting for baseline eGFR was −10.6 (3.0) mL/min/1.73 m^2 with EVR and −18.9 (2.7) mL/min/1.73 m^2 with TAC; difference 8.27 [0.321; 16.213] mL/min/1.73 m^2 ($p = 0.04$). Observed mean (SD) eGFR at M48 was 70.9 ± 30.06 vs 69.2 ± 26.04 mL/min/1.73 m^2 with EVR vs TAC ($p = 0.04$). Treated biopsy-proven acute rejection [BPAR] affected 10 everolimus-treated pts and 7 tacrolimus pts until M48. Major adverse cardiovascular events (MACE) occurred in 4.6% and 7.7% of EVR and TAC pts, respectively ($p = 0.511$). The cumulative cancer occurrence at M48 was 15.4% and 10.3% respectively ($p = 0.357$). No patient on EVR experienced a recurrence for liver cancer whereas 5.1% on TAC treatment had HCC recurrence. . Study drug was discontinued due to adverse events in 30.8% of EVR pts and 12.8% of TAC pts.
Conclusions: EVR and MPA with early TAC withdrawal preserves renal function to year 4 post-Ltx, without increased risk of rejection.

O83 SELECTING COSTIMULATION DOMAIN FOR DONOR HLA-TARGETED CAR-TREGS IN TRANSPLANTATION

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Donor-specific regulatory T-cell (Treg) therapy has emerged as a very potent strategy to promote immune tolerance in experimental transplantation.

However, a major stumbling block in the clinical use of allospecific Tregs is due to their very limited number. Recently, the potential of chimeric antigen receptor (CAR) technology was investigated to redirect antigen-specificity of Tregs toward a relevant alloantigen. However, whether the type of CAR costimulatory domain (CSD) impacts the stability, persistence and function of CAR-Tregs remain largely unexplored.

Here, we used HLA-A2-targeted CAR-Tregs incorporating either 4-1BB or CD28 CSD to study their effect on Treg biology. *In vitro*, CAR-Tregs maintained their regulatory phenotype and stability, regardless of the CSD. Moreover, CAR-Tregs mediated HLA-A2-specific suppression *in vitro*. We found that the type of CSD dramatically influenced the proliferative capacity, immunometabolism (glycolytic pathway, mTOR activation), and activation/differentiation of CAR-Tregs *in vitro*. The CAR construct selected based on *in vitro* experiments was subsequently used for *in vivo* models. *In vivo* bioluminescent tracking of HLA-A2-targeted CAR-Tregs demonstrated their homing to secondary lymphoid organs. In addition, HLA-A2-targeted CAR-Tregs were fully able to prevent xenogeneic graft versus host disease induced by the co-transfer of HLA-A2+ peripheral blood mononuclear cells in a humanized mouse model.

Together, our data provide not only proof of concept but also new insights to optimize human CAR-Tregs engineering and manufacturing on the path toward clinical development.

O84 LONG-TERM FOLLOW-UP OF KIDNEY TRANSPLANT RECIPIENTS WITH POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS: LESSONS FROM THE FRENCH REGISTRY

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Introduction: Post-Transplantation Lymphoproliferative Disorders (PTLD) are a serious adverse event after solid organ transplantation with about 50% of mortality. Data regarding the very long-term prognosis of the surviving patients are scarce.

Patients and methods: The French Registry of PTLD occurring after kidney transplantation enrolled adult patients with a diagnosis of lymphoma between 1/1/1997 and 31/12/2007. Patients were initially followed until the 1st July 2010. We already reported 252 deaths leading to a 47% 5-years mortality rate and we described the risk factors associated with a bad prognosis. A survey was sent to the centers to obtain a long-term follow-up of the surviving patients.

Results: Among the 248 surviving patients, we obtained a follow-up in 199 patients. Among them, 11 passed away during the initial study period (before 1/7/10). Then, 188 surviving patients are included in the present study. We recorded 64 additional deaths including 2 due to PTLD relapse. Other causes of death were 17 cardio vascular, 14 infectious, 5 neoplastic, and 26 other causes. 33 patients lost their graft during the long-term follow-up, due to kidney chronic rejection possibly related to immunosuppression lowering in 22 of them. Only 5 of these 188 patients developed a late PTLD relapse after 31, 60, 87, 94 and 151 months. Overall, 35 patients were retransplanted after a mean delay of 8.3 years [2.7 to 18] with a favorable evolution. 34 patients developed another neoplasia (NMSC in 53% of cases). Patient global survival was 39% and graft survival was 60% 10 years after PTLD diagnosis. Factors associated with patient and graft survival will be presented.

Conclusion: This study confirmed that PTLD is a severe complication after kidney transplantation, with a high rate of mortality in the first years after lymphoma diagnosis. However, long-term prognosis of the surviving patients seems acceptable with a very low rate of PTLD relapse.

O85 SHIELDING ISLETS WITH HUMAN AMNIOTIC EPITHELIAL CELLS PROTECTS ISLETS AGAINST HYPOXIA AND ENHANCES ISLET ENGRAFTMENT AND REVASCULARIZATION AFTER TRANSPLANTATION IN A MURIN DIABETIC MODEL

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Background: Hypoxia is a main cause of considerable islet loss during first days after intra-portal transplantation. Human amniotic epithelial cells (hAECs) possess regenerative, immunomodulatory and anti-inflammatory properties and present particular interest in the context of islet transplantation to protect transplanted islets against immune attack, hypoxic and inflammatory injury. The aim of this work was to investigate whether covering islets with a shield of hAECs improves islets survival under hypoxic conditions *in vitro* as well as islet engraftment and survival *in vivo*.

Methods: Shielded islets were generated on microwells by mixing islets and hAECs at ratio of 100 hAECs per islets. The ability of hAECs to adhere to islets was analyzed by confocal microscopy. Engineered rat shielded or neat islets were cultured under normoxic and hypoxic conditions. For all conditions, cell viability and islet function were assessed by static insulin release in response to glucose in vitro. Next, function of shielded islets was tested in vivo. For this, 1200 human shielded or neat islets were transplanted under the kidney capsule of diabetic SCID mice. Blood glucose was monitored regularly. Intravenous glucose tolerance test was performed 1 month after transplantation. Graft morphology and vascularisation were evaluated by immunohistochemistry.

Results: Islets shielded with hAECs had an increased glucose-stimulated insulin secretion in vitro. Transplantation of shielded islets resulted in considerably earlier normoglycemia and vascularization and improved glucose tolerance, both in rat and in human islet transplantation experiments.

Conclusion: Co-transplantation of islets with hAECs had a profound impact on the engraftment process, maintaining islet organisation and improving islet revascularisation. Moreover, hAECs improved the capacity of islets to reverse hyperglycaemia.

O86 EVIDENCE FOR INVERTED DIRECT ALLORECOGNITION IN DONOR-SPECIFIC ANTIBODY GENERATION AFTER SOLID ORGAN TRANSPLANTATION

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Background: Generation of de novo DSA post-transplantation is a major cause of graft loss. The current immunologic dogma holds that the differentiation of recipient's allospecific B cells into DSA-producing plasma cells requires the help of recipient's CD4+ T cells of indirect allospecificity: i.e. able to recognize the complexes made of recipient's MHCII/processed alloantigen on the surface of allospecific B cells.

Using a translational approach, we herein challenge this vision and provide evidence that passenger CD4+ T cells from donor's origin are able to trigger DSA generation by direct recognition of recipient's MHC class II molecules on allospecific B cells.

Methods and results: Despite being devoid of CD3+ T cells, CD3εKO C57BL6 mice develop a fast (but transient) DSA response after transplantation with a fully mismatched CBA ($H2^k$) heart graft.

CD4+ T cells can be isolated from the heart of CBA mice and are efficiently depleted by administration of anti-CD3 or anti-CD4 monoclonal antibodies. T-cell depletion in the donor abrogates DSA generation in CD3εKO recipient mice.

Interaction between donor's (CBA) T cells and recipient's (C57BL6) B cells were further evidenced in vitro, allowing clarifying the molecular mechanisms involved in this non-canonical DSA generation.

Finally, the clinical relevance of our experimental findings was suggested by the fact that renal graft perfusion liquids (n = 20) do contain donor's lymphocytes, including T follicular helper cells.

Conclusion: Our work demonstrates that, in addition to recipient's CD4+ T cells of indirect allospecificity, donor CD4+ T cells transplanted with the graft can also provide help to allospecific B cells through a previously overlooked « inverted direct » pathway.

O87 INDUCTION THERAPY WITH ANTI-LYMPHOGLOBULIN OR BASILIXIMAB IN HIGHLY SENSITIZED KIDNEY TRANSPLANT PATIENTS WITHOUT PREFORMED DSAS

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Two large prospective studies have shown that the incidence of acute rejection is significantly lower in highly sensitized kidney transplant patients given polyclonal antibodies compared to those given anti-IL2R blockers. However, these studies were performed before the era of Luminex. Hence, some patients included in these studies could have preformed donor-specific antibodies (pDSAs) at inclusion. The aim of this prospective pilot randomized French multicenter study was to compare Grafalon (n = 32) and basiliximab (n = 27) in highly sensitized kidney transplant patients without pDSAs. Patients with a cPRA ≥ 50% and having at least one antibody with a mean fluorescence intensity ≥5000 without historical pDSA or pDSA at the day of transplantation were included in the study. The primary endpoint, i.e. the 6 and 12-months survival without acute rejection, graft loss or death, was similar in both arms. Survival without acute rejection at 6 and 12 months were similar in both arms (96.4% and 90.4% with Grafalon and 84.4% and 76.8% with basiliximab). One TCMR and one borderline rejection were observed in Grafalon-treated patients. One ABMR and 4 borderline rejections occurred in basiliximab-treated patients. Only one patient who received basiliximab developed a *de novo*DSA. At 6 and 12 months, patients' and grafts' survivals, kidney function, histological lesions observed on protocol kidney biopsies, infection rate, and immunosuppressants' tolerance were similar in both groups.

In summary, in highly sensitized kidney transplant patients without pDSAs, Grafalon and basiliximab have the same efficacy as induction therapy. A large prospective study is required to confirm our data.

O88 OPTIMIZATION OF ADOPTIVE IMMUNOTHERAPY IN BK VIRUS NEPHROPATHY VIA CRISPR/CAS9

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Introduction: Among kidney transplant recipients, BK virus reactivation is associated with adverse outcomes, including graft loss. The only widely treatment approach for this condition is a decrease in the intensity of immunosuppression, which in turn, increases the risk of graft rejection. Adoptive T-cell (Tc) immunotherapy, which consists in the injection of ex vivo stimulated pathogen-specific Tc autologous or allogenic, is a promising approach to confer pathogen-specific immunity without important risks of graft rejection. One of the limitations of this strategy is the survival or an insufficient reactivity of these cells after the transfer, especially in the context of persistent Tc immunosuppression. The immunophilin FKBP12 is required for the effects of the Tacrolimus. CD5 is well known to inhibit the TCR signal. The goal was to use the CRISPR/Cas9 strategy to delete FKBP12 or CD5 in BK virus-specific Tc and to assess the impact on proliferation and functionality of these Tc in the presence and absence of Tacrolimus.
Materials and Methods: We generated BK-Specific T-cell lines from peripheral blood mononuclear cells (PBMC) pulsed with Dendritic cells presenting VP1 and LTA. Crispr/Ribonucleoprotein (crRNP) was delivered through electroporation. A model of Tc activated CD3/28 was also used. Using Sanger sequencing, Flow cytometry, and ELISpot, we evaluated FKBP12 or CD5-deleted T cells.
Results: For FKBP12, we observed a similar proliferation in Tc activated CD3/28 electroporated for crRNP targeting FKBP1A with or without FK-506, while control Tc was markedly inhibited by the drug. We obtained 42 to 78% of CD5 negative cells among Tc BK specific. Using ELISpot, we confirmed that genetic editing did not compromise the generation of BK-specific Tc relative to unmanipulated controls.
Conclusion: The knock-out of FKBP1A or CD5 using CRISPR/Cas9 is possible on BK-specific Tc and seems a promising avenue for adoptive immunotherapy.

O89 DONOR–RECIPIENT MATCHING BASED ON PREDICTED INDIRECTLY RECOGNIZABLE HLA EPITOPES (PIRCHE) AND HLAMATCHMAKER IN LIVER TRANSPLANTATION

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Introduction: Production of de novo DSA (dnDSA) is associated with an increased risk of antibody-mediated rejection after liver transplantation. Antibodies not only recognize the entire antigen but are able to bind specific functional epitopes present on the HLA molecule surface. The HLAMatchmaker and the PIRCHE (predicted indirectly recognizable HLA epitopes) algorithms are able to determine predictive epitope mismatches scores and de novo DSA (dnDSA) synthesis based on alloreactive eplets' identification.

The study's purpose was to assess, for the first time in liver transplantation, the complementarity between these two algorithms.
Patients and Methods: We performed a retrospective study between 1991 and 2019 in Lyon and Montpellier University Hospital. We analyzed two independent cohorts of 407 adult and 133 pediatric liver transplant patients without preformed DSA.

HLA antibodies were detected by single antigen bead assay. HLA typing of the donor-recipient pair was achieved by serological and/or DNA-based techniques. Missing typing was extrapolated from HLA-ABCDRDQ-haplotype frequencies (HaploStats). PIRCHE and HLAMatchmaker algorithm were then applied on both groups.
Results: During the follow-up 27% of adults and 38% of children developed dnDSA. HLA-DRB1 and DQB1-PIRCHE and HLAMatchmaker scores were significantly higher in dnDSA group compared to no DSA group for both pediatric and adult patients (except for PIRCHE HLA-DRB1 locus score in pediatrics).

ROC curves allowed determining score thresholds classifying patients in low and high risk of dnDSA synthesis. Kaplan-Meier curves showed a mean predicted incidence of dnDSA of 34% in the low-risk group compared to 59% in the high-risk group (log-rank <0.05) 20 years after adult liver transplantation, with a good negative predictive value.
Conclusion: HLAMatchmaker and PIRCHE algorithms both are effective tools to identify anti-HLA immunization risk and to predict dnDSA formation after liver transplantation.

O90 TRAJECTORIES OF ESTIMATED GLOMERULAR FILTRATION RATE AND PROGRESSION TO END-STAGE RENAL DISEASE AFTER KIDNEY TRANSPLANTATION

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Introduction: Although the current gold standard of kidney allograft patients monitoring relies on glomerular filtration rate (GFR) assessment, little is known about the profiles of long-term GFR trajectories and their determinants at a population level. Such information would have substantial value for improving risk stratification in kidney transplantation.
Methods: We assembled an international cohort of kidney transplant recipients at 15 referral centers (10 in Europe and 5 in the US) and from 7 randomized controlled trials (RCT). Patients underwent assessment of clinical, histological and immunological parameters, as well as repeated estimated GFR measurements (eGFR, MDRD equation). Latent class mixed models (LCMM) were used to determine profiles of patient's eGFR trajectories. Multinomial regression models were used to assess patient and allograft characteristics associated with the eGFR trajectory profiles.
Results: A total of 14,312 patients were included (n = 4,140 in the development cohort, n = 10,172 in the validation cohorts), with 403,497 eGFR measures analyzed (median follow-up time post-transplant of 6.5 years). Overall, we identified 8 latent classes of eGFR. The determinants of the latent classes were the donor age and the following assessed at 1-year post-transplantation: eGFR, proteinuria level, allograft scarring, interstitial inflammation and tubulitis, microcirculation injury, and circulating anti-HLA DSA. We confirmed that the same 8 phenotypes of eGFR trajectories and their determinants were conserved in validation cohorts and in the RCTs.
Conclusion: With this population-based study, we identified for the first time universal profiles of eGFR trajectories. These profiles allow to stratify the long-term evolution of renal function in kidney recipients. Our results provide the basis for a dynamic approach of the risk stratification in kidney transplantation.