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Transplant International

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frontiers

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October 19—21, 2022, Europahaus, Mayrhofen/Zillertal, Austria

Table of Contents

Welcome to the Austrotransplant 2022

Dear colleagues,

Dear friends, guests and supporters of the Austrotransplant Annual Meeting,

It is a special pleasure and honour for us to welcome you all to this year's congress of the Austrian Society for Transplantation, Transfusion and Genetics at the Europahaus in Mayrhofen in the Zillertal valley.

Already the name of the event location reflects in a way the theme of our congress: Europe as a symbol for the strength of a common appearance and the mastering of challenges with united forces #teamworkmakesthedreamwork.

As representatives of all professional groups in medicine and science, we experience in our everyday lives time and again how much the desired outcome of a transplant or a research project depends on each individual link in the chain. We know this so well because we all share a single, clearly defined goal: to give patients the best possible life in the short and long term.

The fact that we can only be strong and effective together and thus make dreams come true is not only the motto of our annual congress this year and a hashtag in 2022, but our very personal aspiration for our joint event. This year's congress should include all aspects of transplantation with its challenges. It is particularly important to us to dedicate a focus of the congress to organ donation, as the basic prerequisite of every transplantation.

We will provide a stage as well as a discussion forum for all participants and emphasise inter- and multidisciplinarity. From the opening evening to the farewell on Friday, you will experience sessions that we hope will not only inform you about the latest developments in organ donation, preparation for transplantation, transplantation itself and post-transplant

care, but also bring you closer to far-reaching aspects and perspectives of the different professional groups. International experts allow us to look beyond the Austrian horizon and inspire us to cooperate in the clinical and scientific fields.

We would also like to take this opportunity to thank the numerous sponsors, without whom an event with this special character would not be possible.

With this programme from us to you, we look forward to an exciting and wonderful time together in Tyrol!

Julia Dumfarth & Annemarie Weißenbacher
Austrotransplant 2022 Conference Organisation

Marion Frank
Conference President Nursing

Kidney

01

Validation of the optimal Torque Teno virus range for risk stratification of graft rejection and infection in kidney transplant recipients by a commercial PCR

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BACKGROUND

The quantification of the non-pathogenic and ubiquitous Torque Teno virus (TTV) was suggested for risk stratification of graft rejection and infection in the first year post kidney transplantation. A previous optimal TTV-range has been defined applying an in-house PCR. Recently, a commercial PCR, the TTV R-GENE® kit, has been CE certified for clinical use. The present study was designed to validate and refine the optimal TTV range applying the commercial PCR.

METHODS

Patients were selected from the prospective TTV-POET trial including 628 consecutive adult recipients of a kidney allograft transplanted at the Medical University of Vienna, between January 2016 and July 2020. Patients were followed for 12 months post-transplant or until drop out. TTV was quantified longitudinally by the TTV R-GENE® kit. The primary outcome was biopsy-proven graft rejection and the secondary end-point was infection.

RESULTS

After reaching steady state in month 3 post-transplant, a total of 78 patients with 85 graft biopsies (rejection, n=18) and 274 patients with 80 infectious events following TTV quantification were selected. The risk for rejection decreased significantly by 25% with every log level increase in TTV load (RR 0.75, 95% CI 0.67-0.85; p<0.001). For TTV loads <5log10 c/mL a high specificity of 90% for rejection was calculated. The risk for infection increased by 6% with every log level increase of TTV load (RR 1.06, IQR 1.00-0.12; p=0.047). For TTV loads >7log10 c/mL a high specificity of 91% for infection was calculated. Multivariate modelling revealed an independent association between TTV and rejection and infection.

CONCLUSION

This study supports the value of TTV for risk stratification of graft rejection and infection post kidney transplantation applying a commercial PCR. The optimal TTV-range refined by these data will be applied in an interventional randomized controlled trial to assess the safety of TTV-guided immunosuppression: the TTVguideIT trial.

02

Tailored immunosuppression with LCPT extended release tacrolimus based on NFAT-regulated gene expression

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INTRODUCTION

There is a narrow therapeutic window for immunosuppression (IS) with calcineurin (CNI) inhibitors. The immunosuppressive effect of CNIs differs between individuals. Therefore, the drugs` trough levels do not reflect IS and should be replaced by pharmacodynamic monitoring. Since nuclear factor of activated T-cells (NFAT)-depending gene expression correlates with cyclosporine induced IS, this study was designed to evaluate the effect of LCPT extended release Tac on NFAT regulated residual gene expression (RGE).

METHODS

Gene expressions of interleukin-2, interferon-γ and granulocyte-macrophage colony-stimulating factor and three reference genes were measured with droplet digital polymerase chain reaction (ddPCR) in whole blood samples at day 2, 7, 14, month 1 and 6 until 1 year after LT in 23 patients transplanted between February 2019 and June 2020. The RGE after Tac intake was calculated as $c_{peak}/c_0 x100$, where c_0 is the adjusted number of transcripts at the Tac predose level and c_{peak} is the number of transcripts at peak level. IS consisted of LCPT extended-release Tac introduced directly after LT, mycophenolic acid, and a corticosteroid-taper for 3 months. All reported p-values are two-sided. $P \leq 0.05$ are considered statistically significant. To quantify the relationship between Tac peak levels and NFAT-RGE the

bivariate nonparametric correlation coefficient by Spearman was calculated. To describe time to infection a Kaplan Meier method was used. All statistical analysis was performed using SAS 9.4.

RESULTS

Tac peak levels and NFAT-RGE showed a strong inverse correlation (r=-0,8). Our descriptive analysis shows that although patients show a Tac trough level within the targeted therapeutic window, RGE might be too low, resulting in a higher risk for infection. Infection free survival was significantly different between RGE groups <30 and ≥30 (p<0.0001), while Tac trough values were comparable between the groups. Estimated glomerular filtration rate (eGFR) and creatinine were not different between the groups.

CONCLUSION

Tailored IS monitored with NFAT-RGE is promising to decrease infectious complications by optimization of the IS level in LT recipients on LCPT extended release Tac.

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03

Robotic-assisted donor nephrectomy – a single center experience

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BACKGROUND

Robotic-assisted living donor nephrectomy (LDN) was implemented at the Medical University of Vienna in May 2017. The robotic device used was a Da Vinci Si ®, Intuitive Surgical, Inc., 1020 Kifer Road, Sunnyvale, CA 94086.

METHODS

Patients that received a robotic-assisted LDN between 05/2017 and 06/2022 were retrospectively analyzed. Preoperative parameters included sex, age, body mass index (BMI), computed tomography (CT) scans with angiography, magnetic resonance imaging (MRI) urography/fluoroscopy with proportional kidney function left vs. right and blood samples. Intraoperative parameters were side of the nephrectomy, number of arteries and veins, warm ischemia time (WIT), operation time, intraoperative complications and need for conversion. Postoperative complications, creatinine levels and length of hospital stay were documented.

RESULTS

Between 05/2017 and 06/2022 thirty patients underwent a robotic-assisted LDN. The sex distribution was even. Median age was 56.1 years (min. 29.1 to max. 80.7). Median preoperative BMI was 24.5 (min. 20.2 to max. 32.4). Nephrectomy side was predominantly left (90%), median kidney function of the explanted kidney was 48.5% of total kidney function and most patients had a single renal artery (83.3%) and a single renal vein (96.7%). Warm ischemia time (WIT) was 135 seconds (IQR 120-213.5). Median operation time was

265 minutes (IQR 217-290). Two patients needed a conversion to open surgery (6.7%) due to bleeding. These two cases both occurred within the first 8 months after the start of the robotic-assisted LDN program. No other intraoperative complications happened since then. Postoperative complications were observed in 8 patients (26.7%), 6 graded class 1 (20%) and 2 graded class 2 (6,7%) in the Clavien-Dindo classification. Median hospital stay was 7 days. All donated kidneys were transplanted with good primary graft function.

CONCLUSIONS

Robotic-assisted living donor nephrectomy is feasible and safe. Warm ischemia time is short and graft function is excellent. Due to more flexibility of the instruments the robotic-assistend approach is the favoured technique in obese donors or patients with complex vascular anatomy. Our future perspective is the implementation of robotic-assisted kidney transplantation in obese recipients.

04

Vascular reconstructions in living donor renal transplantation. A single center experience over the last 16 years

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BACKGROUND

In living donor renal transplantation (LDRT), vascular anastomosis is more difficult due to missing arterial patches and shorter renal veins. Thus sometimes, and especially in case of multiple arteries, vascular reconstruction or multiple anastomosis are mandatory. However, using a variety of reconstruction techniques, renal transplantation is feasible in most cases of complex donor vascular anatomy and results are similar to standard procedures. Here we report the results of our center of LDRT with vascular reconstruction.

METHODS

We reviewed the records of all LDRT in our center from the beginning of the program in 2005 until 2021 for vascular reconstructions. The cohort was divided into two groups: transplantation with vascular reconstruction and standard transplantation. These groups were compared for operative parameters, short- and long-term result. Statistics: Chi square test was used for comparison of dichotomous values, for metric values with normal distribution standard T-test was used.

RESULTS

From 2005 to 2021 201 LDRT were completed in our unit. In 16.6% of these cases a vascular reconstruction was performed, including single ostium side to side anastomosis, end to side anastomosis, patch reconstruction and vein interposition.

There was no significant difference in operative time (180 min vs. 169 min; p = 0.118), mean time for anastomosis (28 min vs. 27 min; p =0.59) between groups. Also, postoperative complications (5.7% vs. 7.4%; p = 0.72) and the need for reoperation or postoperative interventions (2.9% vs. 6.8%; p = 0.391) was rather equal. However, the risk of organ loss over the follow-up period was significantly higher after vascular reconstruction: (45.5% vs. 12.6% p = 0.010).

CONCLUSIONS

Vascular reconstructions are frequently used in LDRT. Short-term results are similar to standard procedures. However, in long term follow up, the risk of organ loss is significantly higher.

05

ABOi living donor kidney transplantation at a single center: Long-term follow up

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BACKGROUND

Clinical outcomes of ABOi living donor kidney transplantations (ABOi LDKT, n=39) were compared with those of ABO-compatible LDKT (n=144).

PATIENTS AND METHODS

In total, from 2010 to 2022 183 donors were retrospectively analyzed. Prenephrectomy measures were age, body mass index (BMI, kg/m^2), pre-existing arterial hypertension, scintigraphic left and right renal function, number of arteries and veins, operative times as time of anastomosis and operation, warm and cold ischaemia, arterial reconstructions, unusual venous anatomy, conversion and postoperative complications, compared in both groups. Relationship between donor and recipient, laparoscopic versus open nephrectomy, median duration of hospital stay, pre- and postoperative creatinine, pain, malignancies and long term follow up of donors was listed. For the recipients age, gender, implantation side, individual number of prior kidney transplantations, risk factors for graft loss, graft survival, malignancies and pregnancies were obtained.

RESULTS

Between 2010 and 2022 39 ABOi LDKT (18,39% of all LDKT) underwent open donor nephrectomy (ODN) (n=4) versus laparoscopic donor nephrectomy (LDN) (n=35), in ABOc group 31 ODN versus 113 LDN, overall survival was 100%. 17,36% arterial reconstructions in ABOc group, 8,57% in ABOi group.

Clavien Dindo IIIb 4,8% (7/144) in ABOc LKDT, 5,1% (2/39) in ABOi LKDT. 10,41% (15/144) graft loss in ABOc group, in the ABOi group 12,82% (5/39) because of higher biopsy proven acute rejection in 3 cases (IgA-renephritis). During 12 years follow-up, 92,9% donors attended all recommended visits. All of them had a stable renal excretory function (mean creatinine 1,2 mg/dl). Graft survival in 34 recipients in ABOi (n=39) and 129 recipients in ABOc (n=144).

CONCLUSIONS

ABOi LDKT allows increasing the donor numbers. It is an adaequate option for those without compatible donors.

06

Systematic digitalization and assessment of patient-reported outcomes in pediatric kidney transplantation in clinical routine: A pilot study.

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BACKGROUND

Patient-Reported Outcomes (PROs) are measurements of a patient's perception of his/her disease and corresponding treatment, without interpretation by healthcare personnel. In pediatric chronic kidney disease PROs fill an important gap to achieve optimal disease control and general well-being. Digitally collected patient history provides additional information compared to traditional methods. However, neither PROs nor digital patient history systems are frequently used in clinical routine. The aim of this pilot study is to develop and implement a digital system for the collection and evaluation of patient history and PROs for pediatric patients with kidney transplantation and analyze it in context of clinical outcomes.

METHODS

Pediatric kidney transplantation patients will receive a tablet with 19 questions for the collection of patient history and PROs at their regular visits at our outpatient clinic. The analysis of these data in context of clinical surrogate outcomes (e.g., creatinine) will be conducted by unsupervised cluster analysis and dimensionality reduction techniques.

EXPECTED RESULTS

The pediatric kidney transplant patients are 66%:34% male:female, with a median age of 13.5 (IQR 11-16) and a median post-transplant time of 59 (IQR 30.5-120) months. 46% were living donors. The median graft function at baseline is 0.91 (IQR 0.7-1.2) mg/dl creatinine. The unsupervised cluster and dimensionality reduction will be conducted at baseline to identify different patient cohorts by different ePRO patterns in context of graft function surrogate parameters.

CONCLUSIONS

Regular and structured follow-up of (pediatric) patients with kidney transplantation renders this patient cohort ideal for the implementation of digital patient history and ePRO systems in clinical routine. This pilot study displays that even singular ePRO measurements at baseline enable the identification of different patient cohorts in context of graft function. The longitudinal utilization of these systems could aid the early identification of complications (e.g., over- and/or underimmunosuppression, adherence) and facilitate subsequent early intervention.

07

Survival benefit of kidney transplantation for women and men in Austria: A retrospective cohort study using target trial emulation

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BACKGROUND

Kidney transplantation is considered the optimal treatment strategy for eligible end stage renal disease patients. However, it remains unclear whether the anticipated survival benefit from receiving a kidney transplantation is different for women and men. Previous studies comparing transplant outcomes between women and men showed inconclusive and conflicting results. The aim of this study is to investigate survival differences of kidney transplantation compared to remaining waitlisted on dialysis between female and male transplant candidates applying causal inference methodology.

METHODS

We included all dialysis patients recorded in the Austrian Dialysis and Transplant Registry who were waitlisted for their first kidney transplant between 2000 and 2018. In order to estimate the causal effect of kidney transplantation on 10-year restricted mean survival time, we mimicked a series of controlled clinical trials and applied inverse-probability of treatment and censoring weighted sequential Cox models.

RESULTS

This study included 4408 patients, one third of them were women and the mean age was 52 years. Glomerulonephritis was the most common primary renal disease both in women (27%) and men (28%). We found that kidney transplantation led to a gain of 2.22 years (95% CI 1.88, 2.49) compared to remaining on the waitlist over a 10 year follow-up. The effect was slightly smaller in women (1.95 years, 95% CI: 1.38, 2.41) than in men (2.35 years, 95% CI: 1.92, 2.7). Across ages the survival benefit of transplantation over a follow up of 10 years was smaller in younger women and men and increased with age, showing a peak for both, women and men aged about 60 years.

CONCLUSIONS

Our study provides robust evidence based on state-of-the-art causal inference methodology for survival benefit after kidney transplantation compared to remaining on the waitlist for women and men.

Kidney/Liver

08

Detection of biomarkers during hypothermic machine perfusion and prediction of liver graft function

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BACKGROUND

The increasing number of patients awaiting liver transplantation necessitates the recruitment of marginal donors (e.g., steatotic livers, elderly donors), that are associated with increased risk of graft dysfunction. Hypothermic machine perfusion (HMP), in which the graft is perfused at a temperature of 10-14°C, has been reported to reduce ischemia/reperfusion injury and thus graft damage. However, there are not many predictors of graft function that can be assessed during HMP. FMN (flavin nucleotide) measured during HOPE could predict post-transplant liver function.

METHODS

HMP has been routinely used at the Medical University of Vienna since May 2018. 50 patients that received a liver subjected to HMP between November 2018 and October 2020 were included. FMN, GOT, GPT and LDH was measured in perfusate samples collected at 0,60 and 120 minutes. Primary endpoint was the development of early allograft dysfunction (EAD), secondary endpoints included biliary complications, graft and patient survival.

RESULTS

In total, 13/50 (26%) patients developed EAD. Survival analyses revealed a three-months patient survival of 100% in the non-EAD group, whereas patient survival for patients who developed EAD was 76.9% (p = .013). Relations between FMN and perfusate laboratory parameters GOP, GPT and LDH measured at 0, 60 and 120 minutes indicate strong correlations, r= .47 to .70. Additionally, ROC analysis for the criterion EAD displayed cut- off values for perfusate FMN to be 12.72 ng/dL (AUC 78.6%) at 0 min, 29.31 ng/dL (AUC 77.9%) at 60 min, and 34.53 ng/dL (AUC 73.5%) at 120 min. Moreover, the cut-off value of FMN at 0 minutes shows a sensitivity of 84.6%, while the specificity is only 69.4%.

CONCLUSIONS

Intraoperative FMN perfusate at 0 minutes may be suggested as a biomarker for prediction of EAD as well as for graft and patient mortality in the sense of a risk factor.

09

Perfusate IL-6 levels during liver NMP might be predictive for hemodynamic response and catecholamine demand after reperfusion in the recipient

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BACKGROUND

Normothermic liver preservation (NMP) has become a clinical routine at several transplant centres. Reperfusion-syndrome occurs less often in recipients of NMP-livers compared to cold stored livers. We hypothesized that perfusate interleukin (IL)-6 during liver NMP correlate with recipient hemodynamics in the post-reperfusion period.

METHODS

Consecutive NMP-liver transplants at a single-centre were prospectively analysed. Perfusate samples were collected at 1 and 6 hours of NMP and at the end of perfusion and analysed for IL-6 levels. Median arterial pressure (MAP) and catecholamine need during surgery were recorded. The anhepatic phase was defined as baseline for MAP and catecholamine requirements.

RESULTS

Over a period of 36 months, IL-6 perfusate measurements were assessed in 77 livers undergoing NMP and transplantation; 15/77 (19.5%) were DCD organs. The median donor age was 61 (15-87) years, median recipient age was 60 (19-73) years. Median (IQR) cold ischemia time was 6.2 (2.1) hrs, NMP-time and overall preservation time were 17.6 (10.4) hrs and 23.6 (10.6) hrs. Median (IQR) IL-6 levels (ng/L) after 1, 6 hrs and NMP-end were 52 (175), 278 (674) and 174 (2171). Neither duration of CIT nor NMP correlated with IL-6 levels over time. NMP-livers were stratified for the median of the last IL-6 measurement. Recipients receiving NMP-livers with perfusate IL-6 levels above the median developed significantly lower post-reperfusion MAP (dropping 20% from baseline) and displayed a significant higher demand of catecholamines (increase of 25% from baseline) up to 30 minutes after reperfusion (figure 1A-B). Perfusate IL-6 did not correlate with the occurrence of early allograft dysfunction.

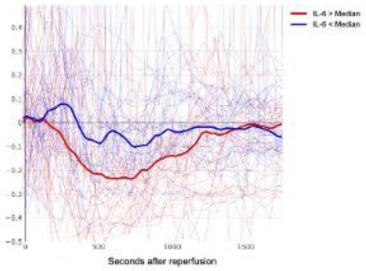

Figure 1A) MAP compared to baseline

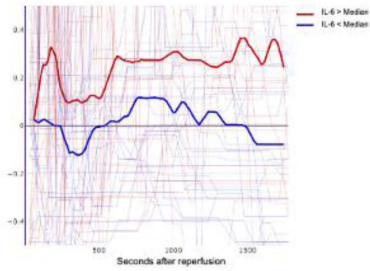

Figure 1B) Catecholamine demand compared to baseline

FIGURE 1

CONCLUSION

Perfusate IL-6 levels during liver NMP are clinically relevant as they help to predict the post-reperfusion hemodynamics in recipients.

10

Mitochondrial respiration in human kidney allografts after cold storage reflect distinct donor characteristics

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BACKGROUND

ATP production by oxidative phosphorylation (OXPHOS) plays a central role in the physiological kidney function. Pre-existing pathologies of donors may deeply influence graft quality. However, it is not fully understood how these factors affect renal mitochondrial function after cold storage. Therefore, we aimed to investigate bioenergetic patterns of baseline donor characteristics and pathologies in the mitochondrial respiration of the allograft.

METHODS

Biopsies of the renal cortex were taken in 55 human kidney grafts after static cold storage. The mitochondrial respiration was assessed by high-resolution respirometry in tissue homogenates. Mitochondrial substrate pathway- and coupling-control of the electron transfer system were measured and correlated with the donor's age, sex, body mass index (BMI), history of hypertension, ECD- and DCD-status, final creatinine levels, kidney donor risk indices and length of the preceding SCS.

RESULTS

Final donor creatinine levels correlate inversely with ATP production efficiency (linear regression $R^2 = 0.3079$, $p < 0.0001$), OXPHOS-capacity ($R^2 = 0.1477$, $p = 0.0045$) and with the maximum capacity of the electron transfer system

(R^2 = 0.1794, p = 0.0016) if using succinate as substrate. The NADH-linked mitochondrial respiration is higher in kidneys of donors with higher BMI (R^2 = 0.155, p = 0.0047 for the OXPHOS-respiration and R^2 = 0.2221, p = 0.0006 for the electron transfer capacity, respectively). DCD kidneys show elevated mitochondrial outer membrane damage. Other donor parameters showed weak to no correlation with pre-transplant mitochondrial function.

CONCLUSIONS

We found decreased succinate-linked OXPHOS and ATP production efficiency in donor kidneys with impaired function. Interestingly, a higher donor BMI resulted in increased NADH-linked respiratory capacity, possibly as a result of an altered energy status in overweight donors. By showing a clear impact of specific donor parameters on mitochondrial respiration, the predictive capacity of mitochondrial function as a possible biomarker may be exploited.

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11

The global burden of immunosuppression and its association with BK-virus-associated morbidity in ABOi vs. pre-transplant DSA-positive kidney transplant recipients

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BACKGROUND

ABO blood group-incompatible kidney transplantation (ABOi) may be associated with increased BK virus (BKV) replication. The reasons for this remain unclear, but might be attributable to more intense immunosuppression and/or use of rituximab. Global burden of immunosuppression can be estimated via quantification of Torque-Teno-Virus (TTV) in recipient blood and offer insight into this ABOi-specific phenomenon.

METHODS

Longitudinal TTV-PCR was assessed in 38 ABOi and 143 pre-transplant DSA+ patients (Tx 2007-2018). TTV load was determined at baseline and at months 3, 6, 12 and 18. BKPyV-DNAemia was defined as at least two consecutive positive BKV-DNA detections in blood. Additionally, we recorded frequencies of presumptive (>10.000c/mL, without biopsy) or definite BKPyVAN (biopsy-confirmed).

RESULTS

CD20 antibody rituximab was used in 63% of ABOi patients and ATG plus semi-selective immunoadsorption in 89% of DSA+ patients. TTV loads in ABOi patients were 7.6x10^4 at baseline and 1.5x10^9, 4.0x10^9, 5.3x10^6, and 9.1x10^5 at M3, M6, M12 and M18. In DSA+ patients, baseline TTV load was 5.3x10^3 and 1.1x10^8, 6.9x10^6, 9.7x10^5 and 9.8x10^4 at M3, M6, M12 and M18, respectively. Comparing ABOi with DSA+ we found higher TTV levels in ABOi at baseline ($p=0.04$), with significant differences at M6 ($p=0.018$) but not at M12 ($p=0.64$) or M18 ($p=0.31$). Incidences of any BKPyVDNAemia did not differ between groups (ABOi 23.7% vs. 30.8% in DSA+; $p=0.53$). The same was true for presumptive BKPyVAN (ABOi 15.8% vs. 11.9%, $p=0.6$), but definite BKPyVAN were observed more frequently in ABOi patients (13.2% vs. 3.4%, $p=0.03$). Interestingly 17.4% of presumptive BKPyVANs occurred 18 months or later after transplantation.

DISCUSSION

The overall higher TTV load in ABOi recipients may reflect the use of rituximab before transplantation. As suggested by the literature BKPyVAN rates were higher in ABOi patients, although BKPyVDNAemia did not differ between groups. Prolonged BKPyVDNAemia screening may be considered in these specific patient groups.

Transplant International

12

Levels of donor-derived cell-free DNA and chemokines in BK polyomavirus-associated nephropathy

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BACKGROUND

BK polyomavirus-associated nephropathy (BKPyVAN) carries a risk of irreversible allograft injury. While detection of BK viremia and biopsy assessment are current diagnostic gold standard, the diagnostic value of biomarkers reflecting tissue injury (donor-derived cell-free DNA [dd-cfDNA]) or immune activation (C-X-C motif chemokine ligand [CXCL]9 and CXCL10) remains poorly defined.

METHODS

For this retrospective study, 19 cases of BKPyVAN were selected from the Vienna transplant cohort (biopsies performed between 2012 and 2019). Eight patients with T cell-mediated rejection (TCMR), 17 with antibody-mediated rejection (ABMR) and 10 patients without polyomavirus nephropathy and rejection served as controls. Fractions of dd-cfDNA were quantified using next-generation sequencing and CXCL9 and CXCL10 were detected using multiplex immunoassays.

RESULTS

BKPyVAN was associated with a slight increase in dd-cfDNA (from 0.21% [median; interquartile range: 0.12-0.34%] in non-rejecting control patients to 0.38% [0.27-1.2%]; p=0.005). Levels were far lower than in ABMR (1.2% [0.82-2.5%]; p=0.004]), but not different from TCMR (0.54% [0.26-3.56%]; p=0.52). Within the BKPyVAN cohort, we found no relationship between dd-cfDNA levels and the extent of tubulo-interstitial infiltrates, BKPyVAN class and BK viremia/viruria, respectively. In some contrast to dd-cfDNA, concentrations of urinary CXCL9 and CXCL10 exceeded those detected in ABMR, but similar increases were also found in TCMR.

CONCLUSION

BKPyVAN can induce moderate increases in dd-cfDNA and concomitant high urinary excretion of chemokines, but this pattern may be indistinguishable to that of TCMR. Our results argue against a significant value these biomarkers for reliably distinguishing BKPyVAN and rejection.

13

Optimum timing of anti-thymocyte globulin in relation to adoptive Treg cell therapy

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BACKGROUND

Regulatory T cell (Treg) therapy is under clinical investigation for immunomodulation in kidney transplantation. Reducing the recipient's T-cell pool is considered to increase the efficacy of Treg therapy. This necessitates timing of anti-thymocyte globulin (ATG) administration early enough before adoptive cell therapy (ACT), so that residual serum ATG does not deplete the transferred Tregs. The optimum time-point in this regard has not been defined. Herein we report pharmacodynamics and pharmacokinetics of ATG and the effects of residual serum ATG on the Treg product viability in a clinical trial for ACT in kidney transplantation.

METHODS

Cell therapy patients (n=4) received ATG monotherapy (6mg/kg), *without* concomitant immunosuppression, 2-3 weeks before kidney transplantation and Treg therapy (NCT03867617). Control group patients (n=3) received standard of care ATG induction (4x 1.5mg/kg, starting at transplantation) *with* concomitant immunosuppression. Total ATG, Treg-specific ATG and anti-ATG IgG/IgM were measured in patients' sera. T cell depletion was followed by flow-cytometry.

RESULTS

ATG led to profound T-cell depletion (>90%) in both groups, but T-cell reconstitution was faster in the cell therapy group. Treg-specific and total ATG levels were significantly lower in the cell therapy group compared to the control group 14 and 21 days after ATG administration (Treg-specific ATG on day 21; cell therapy group: mean=0.09$\pm$0.19µg/ml; control group: mean=0.90$\pm$0.27µg/ml; p=0.01). The rapid ATG decline was associated with the development of anti-ATG IgM and IgG in 4/4 cell therapy group patients (and clinical episodes of serum sickness), while 0/3 control group patients developed anti-ATG IgM or IgG. *In-vitro* viability assays using the actual Treg product under clinical investigation demonstrated that even ATG serum levels <1µg/ml, previously reported as subtherapeutic, drastically reduce the viability of the Treg product.

CONCLUSION

ATG levels need to decline to levels lower than previously thought for efficacious Treg transfer. In 3 of 4 patients such levels were reached within 14 days.

14

Transplant*ieren*: A psychoeducational programme for children and caregivers before and after solid organ transplantation

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BACKGROUND

Due to the mostly excellent short-term outcome, the care of children and adolescents with organ transplantation mainly focuses on the preservation of long-term graft function, associated complications, and on psychosocial development of these patients into young adulthood. Accordingly, high-quality education of patients and their caregivers is highly important to adherence formation. Particularly in, e.g., pediatric kidney transplantation (KTX) medication non-adherence and subclinical rejection remain the most common causes of long-term graft failure. Therefore, the aim of this project coalesces at adequate education of children and adolescents and their families/caregivers concerning key information, treatments and measures most important for long-term graft and overall survival after organ transplantation (TX).

METHODS

To support families in their preparation for an upcoming KTX, the psycho-educational programme "Valentin and the Water Slide" was developed. Each family is given a book and a teddy bear, *Valentin,* that had a "surgery" and was equipped according to the respective child's organ replacement therapy (e.g., haemodialysis catheter). The age-appropriate approach to these topics enables the family to deal with the topic of TX in a low-threshold way in several sensory qualities (reading, listening, looking, touching). In a second step the book "Finally Transplanted" was developed, continuing the story of *Valentin*.

RESULTS

In an interdisciplinary effort of psychologists, clinicians, and dieticians this psychoeducational programme is being extended to all departments of our center offering TX: Transplan*tiere*. An animal mascot is assigned to each organ, with particular emphasis on the meaning of the animal names, and respective illustrative books and physical mascots are being developed: Kidney: Bear *Valentin* ("to be strong"), Liver: Fox *Frieda* ("power"), Heart: Tiger *Toni* ("worth the price), Lung: Elephant *Ella* ("the sunny one")

CONCLUSIONS

In the future, Transplan*tiere* will represent their own trademark to create better media visibility and public relations for pediatric TX.

Basic Science I

15

Possible role for CD8+ cells in Treg-mediated prevention of humoral response

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BACKGROUND

Recently our group succeeded in significantly prolonging graft survival in a murine model of fully mismatched skin transplantation by an approach based on selective in vivo expansion and activation of Tregs via IL-2 coupled to a specific antibody against IL-2 (IL-2cplx). Here we investigate the effect of alloreactive CD8+ T cells in Treg mediated skin graft survival.

METHODS

Recipient C57BL/6 mice received IL-2cplx, Rapamycin and a short term treatment of anti-IL-6 mAb in addition to fully mismatched BALB/c or single MHCII mismatched BM12 skin grafts (no CD8 T cell alloreactivity). Indicated groups of recipients additionally received anti-CD8 mAb to study the impact of CD8+ T cells in this model. To dissect the mechanisms of skin graft rejection we assessed development of donor-specific antibodies, T cell alloreactivity as well as graft infiltrating leucocytes.

RESULTS

The combined treatment of IL-2cplx with Rapamycin and anti-IL-6 mAb extended single MHCII mismatched skin graft survival to a median survival time of 77.5 days versus 30.5 days for fully mismatched skin grafts and additionally resulted in prevention of recipient sensitization for the latter. Notably,

if CD8+ cells were depleted no further prolongation of skin graft survival was achieved and in stark contrast to non-depleted recipients, donor-specific IgG1 was detectable early after rejection. Furthermore, an increase of donor-reactive Th2 cells and higher recipient CD4+ effector T cells infiltrating the skin grafts by day 20 post transplantation were seen in CD8+ cell depleted mice. Moreover, analyses of Tfh as well as Tfr levels in the spleen were increased in mice devoid of CD8+ alloreactivity if compared to non-depleted/fully mismatched mice.

CONCLUSIONS

Absence of CD8+ cells suggests no beneficial effect in skin allograft survival and results in - albeit delayed - donor-specific antibody formation suggesting a profound role of a CD8+ cell population for sustainable prevention of sensitization.

16

The frequency of HLA-specific IgE antibodies in humoral immune response and *de novo* changes of allergen-specific IgE in solid organ transplant recipients

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BACKGROUND

Antibody mediated rejection, elicited by donor-specific antibodies (DSA), is a leading cause of graft loss. The occurrence of HLA-specific IgE antibodies, including IgE-DSA, was recently described in literature. Here, we investigated prospectively the frequency of pre-existing and *de novo* anti-HLA IgE in organ transplantation and assessed whether atopic patients have a predisposition to develop anti-HLA IgE.

METHODS

Anti-HLA IgE antibodies were measured in 105 transplant recipients (60 kidneys, 15 heart, 15 liver and 15 lung) by a single-antigen bead-based assay. Using an *in vitro* basophil degranulation assay, functionality of IgE was determined. Th1/Th2 cytokines were measured in serum by flow cytometry. Allergy-specific IgE sensitization was investigated with a high-throughput multi-allergen chip.

RESULTS

10% of the kidney recipients had HLA-specific IgE before transplantation, including 3.3% with IgE-DSA, and showed effector functions *in vitro*. Among the heart, liver and lung cohort 4.4% were positive for HLA-specific IgE. Anti-HLA IgE developed *de novo* in 1.8% of the kidney and in 5% of the heart, liver and lung cohort. Th2 associated cytokines were increased in sera of recipients positive for HLA-specific IgE compared to controls (IL-4: *$p<0.05$; IL-5, IL-6, IL-10, IL-13: **$p<0.01$) and showed elevated IgG2 levels ($p<0.001$). Differences in allergen reactivity were observed among the different organ cohorts, but did not correlate with anti-HLA IgE production ($p>0.05$). Besides a 2 to 3-fold reduction of the sum of signal-intensity after one-year post-transplant, 8.4% developed *de novo* allergen-sensitizations.

CONCLUSION

Pre-existing and *de novo* HLA-specific IgE, in general IgE-DSA, were found in a subset of kidney, heart and liver recipients. The development of HLA-specific IgE antibodies is driven by a humoral Th2 response accompanied by the presence of significantly increased IgG2 antibodies.

The potential impact of the unique effector mechanisms of anti-HLA IgE and their possible role in ABMR remain to be established.

17

Cardiac allograft rejection in mice is accompanied by changes of immunoglobulin E-receptor positive cell subsets

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BACKGROUND

The role of IgE in allergy and other TH2 type diseases is well described in several publications. However, the presence of IgE specific for donor MHC in mice as well as human transplant patients raises the question of a possible pathomechanism of this antibody isotype in transplant rejection.

METHODS

In a murine model of acute antibody-mediated rejection (ABMR), CCR5KO recipients received fully mismatched BALB/c cardiac allografts without treatment. Wild type C57BL/6 mice (WT) recipients were used as controls. Donor-specific IgE antibodies were measured via an adapted ELISA using recombinant MHC class I and II monomers. Basophils, B cells and CD23 (IgE low-affinity receptor) expression levels were measured in peripheral blood using flow cytometry before transplantation and then every week thereafter. The ability of donor-specific IgE to form immune complexes was determined *in vitro* using a modified IgE antigen facilitated binding (FAB) assay.

RESULTS

MHC-specific IgE was detected in both recipient groups after cardiac allograft rejection with slightly elevated levels in CCR5KO recipients. Basophil levels

and basophil-bound IgE were significantly increased during rejection in CCR5KO mice in the periphery compared to WT recipients, indicating a possible role of MHC-specific IgE in allograft rejection. Notably, IgE+ CD23+ B cells could be detected in both recipient groups after untreated cardiac allograft rejection. Using a modified IgE FAB assay, we demonstrated *in vitro* the formation of IgE-MHC complexes in recipient serum and their subsequent binding to naïve B cells.

CONCLUSION

IgE immune complex formation is connected to and increased T cell activation and elevated antigen specific antibody levels in allergy. Therefore, the detection of IgE+CD23+ B cells *in vivo* after allograft rejection and the demonstration of MHC-IgE complex binding to isolated B cells *in vitro* suggest a possible pathomechanism of donor-specific IgE in solid organ rejection.

18

CYP3A4 activity after liver transplantation in the first 48h assessed by continuous Midazolam perfusion – the first 12 patients in a proof of principle study

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INTRODUCTION

Midazolam (MDZ), is a short-acting narcotic drug, and is almost exclusively metabolized by Cytochrome P450 3A4 (CYP3A4) to 1-OH-MDZ. Therefore, it is widely used as a marker substance to determine CYP3A4 activity. Currently there is no data available on the detoxifying function of the liver graft represented by MDZ clearance in the very early postoperative period. This study for the first time tries to implement a new method to assess MDZ clearance by continuous infusion during and after orthotopic liver transplantation (oLT).

METHODS

In this prospective study, MDZ was used as a marker substance to determine CYP3A4 activity. Patients scheduled for oLT after 2/2019 were given a microdose (5 µg/h) of MDZ intravenously as a continuous perfusion over 48h over a peripheral venous catheter. Blood was drawn at standardized time points during cava clamp and for the first 48 hours after reperfusion through a central line. Plasma MDZ and 1-OH-MDZ concentration were assessed using a LC-MS/MS method for each timepoint. Confounding factors were identified using patients' electronic charts.

RESULTS

Twelve patients underwent oLT (female n=2), 10 completed the MDZ evaluation process. Application of continuous MDZ infusion was well tolerated. No study-associated adverse event and no drug effect occurred during the study period. The highest MDZ serum levels observed were 407 pg/ml (Patient 9, figure 1). The median time to peak MDZ was 950 minutes after start of perfusion (range 529 to 1980 minutes) with a mean MDZ concentration of 263.2 pg/ml (±79.8pg/ml) at peak levels. Metabolism to 1-OH-MDZ could already be observed during the anhepatic phase. Median time to achieve steady state was 855 min (364-2486 min). Mean serum levels of 1-OH-MDZ during steady state were 35.6 pg/ml (± 7.9 pg/ml). Mean MDZ-Clearance was 602.7 ml/min (±177.0ml/min).

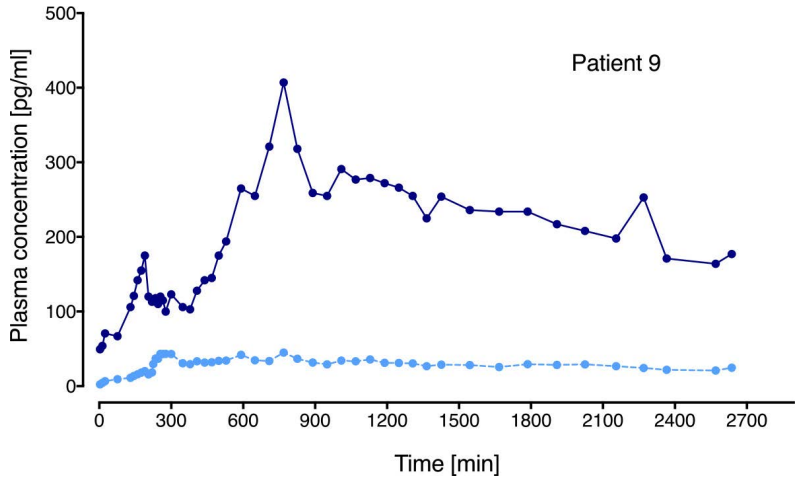

FIGURE 1: Plasma concentration of MDZ (dark blue) and 1-OH-MDZ (light blue) over time in patient nr. 9.

CONCLUSION

This proof of principle study reports the first data on the CYP3A activity after oLT during transplantation and within the first 48hours after reperfusion. No adverse drug effects occurred during our observational period, making this a safe technique to determine CYP3A4 activity even in a highly critical phase after oLT. Clinical implications on outcome still need to be evaluated.

19

ATG leads to B-cell activation mediated by CD4-/CD8- double-negative T-cells

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BACKGROUND

Anti-thymocyte globulin (ATG) is routinely used as induction therapy in solid organ transplantation. Due to its polyclonal nature, ATG binds a plethora of epitopes across virtually all leukocyte populations. Recent reports indicate that ATG, besides T-cell depletion, triggers interleukin-6 secretion in B-cells. We therefore hypothesized that ATG provides a pro-inflammatory stimulus that activates B-cells.

METHODS

Expression of activation markers CD86, MHC-II and CD40 on B-cells was assessed via flow cytometry in: (1) peripheral blood of 2 patients receiving 3mg/kg ATG monotherapy 3 weeks *before* kidney transplantation (within clinical trial: NCT03867617), (2) peripheral blood mononuclear cells (PBMC) from healthy volunteers (n=4) and end-stage kidney disease patients on dialysis (n=6) cultured with or without ATG (1µg/ml) and (3) B-cells flow-sorted from healthy volunteers cultured with sorted leukocyte populations (CD4+ T-cells, CD8+ T-cells, CD4-/CD8- T-cells, Monocytes/Granulocytes/macrophages) with or without ATG.

RESULTS

In PBMC from healthy volunteers, ATG triggered a substantial upregulation of CD86 on B-cells within 48h that persisted for up to 5 days (%CD86+ B-cells,

day 5: without ATG: mean=29.55±2.25; with ATG: mean=48.51±7.78; p=0.025). An increase in CD86 expression, was also seen with cells from end-stage kidney disease patients cultured for 3 days (without ATG: mean=17.74±6.46; with ATG: mean=30.59±9.42; p=0.001). Also, peripheral blood CD86+ B-cells increased by a factor of 4.5 within 24h after ATG administration *in-vivo* in kidney transplant patients. However, ATG did not directly induce activation in purified B cells *in vitro*. When selected leukocytes subsets were added to purified B-cells, only CD4- CD8- (double negative) T-cells restored the stimulating effect of ATG on B-cells (%CD86+ B-cells in B-cell + double negative T-cell cultures: without ATG: mean= 13.50±4.64; with ATG: mean=21.60±3.98; p=0.003).

CONCLUSION

ATG triggers rapid and persistent activation of B-cells *in-vitro* and *in-vivo*. This activating effect is indirectly mediated through CD4- CD8- T-cells and might enhance the potency of B-cells as antigen presenting cells.

20

Immunosuppression by tetrahydrobiopterin mobilizes regulatory T-cells and modulates TH1/TH2 cytokine balance in a murine heart transplant model

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BACKGROUND

Tetrahydrobiopterin has been shown to attenuate acute cellular rejection in a murine heart transplantation model, however, its direct effects on immune cells is still a matter of debate.

METHODS

To elicit the immunosuppressive effects of tetrahydrobiopterin on immune cells, a fully MHC mismatched mouse heart transplantation model was used.

RESULTS

Median graft survival showed a significant improvement in tetrahydrobiopterin-treated animals compared to untreated mice, and this improvement was similar to that of cyclosporine-treated mice. Histopathological analyses

consistently identified signs of severe rejection in untreated allografts and mild and no rejection in cyclosporine-treated and syngeneic grafts, respectively. Tetrahydrobiopterin-treated grafts contained mild to severe lymphocytic infiltrates. In the secondary lymphoid organs, regulatory T cells and mast cells showed a significant increase under tetrahydrobiopterin-treatment compared to controls, whereas frequencies of dendritic cells were decreased. Cytokine production in tetrahydrobiopterin-treated animals compared to controls as well as cyclosporine-treated animals revealed a shift of the balance between TH1 and TH2 cytokines towards TH2 cytokines, indicated by a significant increase in IL-10, IL-4 and IL-5 production, and of the transcription factor GATA-3 in the grafts.

CONCLUSION

The immunosuppressive role of tetrahydrobiopterin relies on an increased frequency of regulatory T cells and mast cells as well as on a modulation of TH1 and TH2 cytokines.

Basic Science II

21

Normothermic machine perfusion of metastatic livers: Establishing an ex-vivo tumor model

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BACKGROUND

Reliable tumor models are critical to advance the field of oncologic precision medicine. Currently, patient derived xenografts are considered the gold standard to investigate personalized precision medicine approaches, however they miss and cannot replicate the important stromal and immune microenvironment of the tumor. In the present study we aim to establish an ex-vivo colorectal cancer (CRC) tumor model by applying normothermic machine perfusion (NMP) to resected liver specimens. In a second step, we plan to assess and analyze tumor microenvironment, genetic profiles, bioenergetics, and viability characteristics.

METHODS

Following standard right hemihepatectomy for CRC liver metastases, the vessels and bile ducts of the resected liver specimens were reconstructed and prepared for cannulation. After cannulation, the resected specimens were connected to the OrganOx metra® device and NMP was initiated. Serial ultrasound-guided biopsies of tumor and liver tissue were obtained and analyzed using confocal microscopy, hyperspectral imaging, high-resolution respirometry and single-cell RNA sequencing (ScRNASeq).

RESULTS

Three liver specimens have been perfused so far. For the first two specimens perfusion was ended after 36 hours of NMP. For specimen number three perfusion was kept stable and viable for seven days. Viability assessment showed tumor viability to be greater than 90% following seven days of NMP, indicating a stable tumor model. ScRNASeq analysis revealed distinct cell clusters of CRC and immune cells. The CRC cell cluster exhibited a specific gene expression pattern and transcription factor activity profile.

CONCLUSIONS

The proposed tumor model has the potential to outperform standard tumor models due to its very close reflection of human physiology within ex-situ perfused metastatic organs containing stromal and immune components of the microenvironment. Ultimately, this tumor model may pave the way for ex-situ tumor therapy and organ repair with subsequent reimplantation of the respective organ.

22

Mitochondrial respiration in a normothermic machine perfusion model of the porcine kidney

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BACKGROUND

Normothermic machine perfusion (NMP) enables pre-transplant organ assessment and potentially active regeneration. Currently, kidney NMP is approved for maximal 6 hours in the clinical setting. Studies aim to prolong perfusion time, which requires knowledge on baseline bioenergetic markers and on their development during NMP. Therefore, we aimed for an in-depth assessment of mitochondrial respiration in a long-term normothermic perfusion model of the porcine kidney.

METHODS

In a cohort of 8 pigs, both kidneys were procured and after a short period of static cold storage, one kidney was perfused for up to 24 hours under normothermic conditions (Kidney Assist, XVIVO Perfusion). Mitochondrial respiration was assessed by high-resolution respirometry (HRR) before start and at the end of NMP.

RESULTS

Upon organ retrieval, the OXPHOS capacity of the combined fatty acid oxidation (FAO), NADH and succinate pathways was 147.8 $\pm$ 27.9 pmol·sec^{-1}·mg wet mass^{-1} (mean$\pm$SD). The succinate pathway contributes to 87%, while the

NADH-linked and fatty acid oxidation contribute 10 and 24% to overall mitochondrial respiration, respectively. There is a significant loss of about 50% of overall OXPHOS capacity during NMP; the cytochrome *c* control efficiency, marker for outer mitochondrial membrane damage, is twice as high on average after NMP, while the S-linked *P-L* control efficiency shows that the ATP production in the remaining functioning mitochondria is steady or even more efficient. Nevertheless, the above parameters were highly variable among experiments, with single kidneys remaining stable throughout the NMP.

CONCLUSIONS

During NMP, the mass-specific OXPHOS decreases, partly due to weight gain of the kidney during NMP. In some cases, there is an apparent dyscoupling and damage to the mitochondrial outer membrane. HRR has proven to be a useful tool for monitoring the mitochondrial respiration during NMP and may be an important aid for the improvement of perfusion protocols.

23

Precision-cut liver slices as an accompanying model to study perfusate composition during long-term liver perfusion

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BACKGROUND

Long-term normothermic machine (NMP) perfusion may open the opportunity for *ex vivo* regeneration of marginal organs. Thus, perfusion protocols need to be adapted for extended perfusion durations. One important point to consider is that perfusate electrolyte levels may exceed physiological levels during isolated liver perfusion since filtration is lacking. To this end, we developed a precision-cut liver slice (PCLS) model to evaluate the cellular effects of changing perfusate composition.

METHODS

8 mm punch biopsies were taken of cold preserved porcine livers prior NMP. PCLS (300 µM) were generated using a Leica 1200S vibratome and cultivated for 7 days in 24-well plates on a rocking platform in conditioned DMEM media containing defined concentrations of Na^+ (160 or 165 mmol/L), K^+ (7 or 15 mmol/L) and urea (200 or 400 mg/dL). To assess tissue viability and functionality MTS assay was performed and albumin production was assessed. LDH secretion into culture media was analyzed to evaluate cell damage.

RESULTS

Viable and metabolically active PCLS could be generated and cultivated for 7 days. Viability was maintained irrespectively of the utilized media with no significant differences compared to the control group and compared to viability after slicing. Albumin production was observed for all conditions with no significant differences, confirming the results of the MTS assay. However, due to the slicing process LDH release into the supernatant was observed. In the course of cultivation, LDH levels remained stable for all conditions. No significant differences between conditioned media and control were found, indicating elevated electrolytes or urea cause no further damage to liver tissue.

CONCLUSIONS

PCLS can be utilized to study long-term Na^+, K^+ and urea levels above the physiological range do not cause damage to PCLS. Thus, elevated perfusate levels of those analytes may not lead to tissue injury during long-term machine perfusion.

24

Feasibility of microdialysis in normothermic ex-situ heart perfusion – A porcine Model

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BACKGROUND

The current gold-standard assessment of myocardial viability in ex-situ heart perfusion (ESHP) is serial perfusate lactate measurements. The information about myocardial function and cell damage is limited. Microdialysis can measure markers of cell injury and metabolites in the interstitial fluid. The study aimed to investigate the feasibility of this analysis tool in a porcine ESHP model.

METHODS

12 German domestic pigs (65-75kg) were used to simulate two different organ donation protocols: "donation after brain death" (DBD) (n=6) and "donation after circulatory death" (DCD) (n=6). Microdialysis catheters (CMA 20 Elite 10mm, CMA Microdialysis AB, Kista, Sweden) were inserted in the myocardium of the left ventricle. Semi-continuous perfusate samples were taken every 10 minutes. Subsequently, lactate, pyruvate, and glycerol were analysed with the ISCUSflex (CMA Microdialysis AB, Kista, Sweden). The groups were compared at baseline (in-situ) and 20, 60, 180, and 360 minutes after implementation of ex-situ heart perfusion.

RESULTS

Interstitial levels of lactate, pyruvate, and glycerol did not differ at baseline between the two groups. DCD was associated with a significant increase in lactate levels with highest values after 20 minutes of ESHP (DCD 7.31±0.11 mmol/l vs. DBD 1.28±0.56 mmol/L, p<0.001). Pyruvate increased significantly faster in the DCD group once ESHP was implemented (*20min:* DCD 162.8 ±124.4 µmol/ vs. DBD 26.41 ±23.97 µmol/l, p=0.04) and stayed elevated over the whole course of ESHP (*360min*: DCD 455.93±104.59 µmol/l vs. DBD 129.58±72.46 µmol/l vs., p<0.001). Glycerol was stable during ESHP in the DBD group but was significantly higher in the DCD group with a rapid increase directly after reperfusion (20min: DCD 783.79±280.02 µmol/l vs. DBD 105 µmol/l±71.73, p<0.001).

CONCLUSIONS

Microdialysis in ESHP is feasible and able to detect metabolic changes in myocardial tissue. Glycerol as a marker of cell injury could emerge as a helpful parameter for myocardial injury and cell damage.

Young Investigator Awards

25

Adoptive cell transfer for allergen specific tolerance induction

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BACKGROUND

Transplantation of hematopoietic cells has mainly been investigated as strategy of tolerance induction in transplantation, but this approach could be extended also to other immune-mediated diseases. Recently, allergen-specific tolerance induction based on the transplantation of retroviral transduced allergen-expressing bone marrow cells has been developed. Transgenic BALB/c mouse that expresses Phl p 5 at the cell surface have been developed and now used as a cell donor. In this study, we investigated whether purified cell populations isolated from Phl p 5^+ mice are able to induce Phl p 5-specific tolerance in recipient mice.

METHODS

CD19⁺ B cells were isolated from spleens of the Phl p 5-transgenic mouse and transferred to recipient mice (BALB/c 8-10 weeks). Mice were treated with rapamycin and anti-CD40L antibody. Chimerism levels were analyzed in whole blood by flow cytometry over time. Tolerance was assessed upon 3 subcutaneous sensitizations with Phl p 5 and a control allergen, Bet v 1. Allergen specific antibody responses were analyzed in serum samples by ELISA. Whole body plethysmography (WBP) was performed to investigate the allergen-induced lung inflammation.

RESULTS

Transfer of purified CD19⁺ B cells induced chimerism levels in the recipient mice for up to 2-3 months. Phl p 5-specific IgE and IgG_1 antibody response were not detected in chimeric mice, in contrast to untreated but sensitized mice. Tolerance induction was specific for Phl p 5, as Bet v 1-specific antibody responses were detected in all mouse groups. WBP revealed preserved lung function in CD19⁺ B cell-treated mice in contrast to sensitized mice.

CONCLUSIONS

We demonstrated that transfer of mature Phl p 5-expressing CD19+ B cells can induce chimerism and allergen-specific tolerance until the end of experiment, 14 weeks after cell transfer. These findings underscore the potential of hematopoietic cell transplantation for inducing tolerance in a range of immunological diseases.

26

Early experience of 48-hour normothermic machine perfusion in human kidneys applying urine recirculation

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BACKGROUND

Normothermic machine perfusion (NMP) of the kidney has been studied extensively during the past decade. Short-term kidney NMP has demonstrated promising results, however currently transplant logistics cannot be improved and for organ treatment longer preservation periods might be necessary. As a proof of principle, we aimed to achieve 48-hour NMP by applying urine recirculation (URC) with a commercially available perfusion device.

METHODS

Discarded human kidneys were normothermically perfused on the XVIVO Kidney Assist perfusion device. The perfusate comprised packed red cells and 5% albumin. For volume management UR was applied. Air (21% O2) and CO2 were used for oxygenation of the circuit and monitored with an in-line blood gas analyser. Perfusate and urine samples as well as hemodynamics were regularly assessed.

RESULTS

Five discarded human kidneys underwent kidney NMP following hypothermic machine perfusion (HMP) and static cold storage (SCS). All but one kidneys were DBD organs. Median donor age (range) was 62 (41-68) years. Median (IQR) CIT and HMP were 19.9 (12.1) and 5 (7.2) hrs. An NMP duration of 48 hrs could be achieved in all kidneys. All kidneys were urinating throughout with

a median (IQR) output of 22.5 (30.5) ml/h. Overall median arterial flow (IQR) was 695 (383) ml/min. Median (IQR) pH was 7.2 (0.2). Overall median (IQR) perfusate sodium, chloride and potassium were 161 (14.7) mmol/l, 124.5 (11.5) mmol/l, and 6.5 (2.7) mmol/l. Median (IQR) perfusate lactate over time was 109 (55.2) mg/dl. Median perfusate sodium and chloride were significantly higher than corresponding urine values; 130 (27) mmol sodium and 120.5 (11.8) chloride over time, $p=0.02$ and 0.04. Median arterial flow over time was significantly higher in NMP kidneys with lower perfusate sodium levels; $p<0.001$, correlations coefficient (Spearman's rho) -0.461.

CONCLUSIONS

This early experience underlines the feasibility of extended ex-situ kidney NMP by applying URC. Hemodynamic stability and urine excretion were achieved for 48 hours.

27

Primary cilia in biliary regeneration – A potential approach to improve outcomes in liver transplantation

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BACKGROUND AND AIMS

Biliary complications (BC) are one of the most common complications after orthotopic liver transplantation. Up to 25% of liver transplant recipients will develop BC, a major factor determining long term patient survival. BC have been associated with pre-transplant cold storage, hypoxia and insufficient regeneration of biliary epithelial cells (BEC) following transplantation. BEC have primary cilia (PC), a unique organelle that is crucial to sense the extracellular environment and regulate cell proliferation.

In this study we investigate the impact of biliary PC on regeneration in the setting of BC.

METHODS

Human biopsies were used to study the structure/function of PC in liver transplant recipients with (N=7) and without BC (N=12).

We developed novel murine models of liver procurement, cold static preservation, and conditional ablation of PC (K19CreER^{T} KIF3A$^{flox/flox}$ mouse) in order to study the role of PC in BEC. Tubastatin A was used to stabilise PC and promote BEC regeneration following cold storage.

RESULTS

BEC's PC are shortened prior to transplantation in livers that later develop BC ($p=0.006$). We identify hypoxia as the main molecular mechanism responsible of this damage during cold-storage conditions.

Genetic PC ablation in BEC induces senescence *in vitro* and *in vivo*, a state of irreversible cell cycle arrest, impairing the regenerative capacity of BEC. These results indicate the presence of a feedback loop that reduces the regenerative response of BEC after liver transplantation.

Finally, inhibition of senescence (by means of p21$^{-/-}$ mice or by administration of senolytics) or stabilisation of PC structure, preserves PC prior to transplantation, improving BEC regeneration.

CONCLUSIONS

Pre-transplantation hypoxic conditions trigger the loss of PC in BEC, impairing biliary regeneration through cellular senescence. Our results suggest that PC represent a potential novel therapeutic target to improve biliary regeneration and prevent BC development following liver transplantation.

28

Perioperative IL-6 blockade promotes intra-graft regulation and prevents costimulation-blockade resistant rejection

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BACKGROUND

Our group has recently shown that CTLA4-Ig monotherapy leads to limited murine heart allograft survival associated with decreased Treg frequencies and early acute T-cell mediated rejection. Herein we investigated whether the perioperative blockade of interleukin-6 (IL-6) in combination with anti-thymocyte globulin (ATG) overcomes costimulation-blockade resistant rejection.

METHODS

C57BL/6 mice were grafted with a fully mismatched balb/c cardiac allograft under ATG induction (6mg/kg) and CTLA4-Ig maintenance (10mg/kg, days 0,4,14,28,56,84) with or without additional perioperative IL-6 blockade (anti-IL-6 mAB; 600µg day -1, 300µg days 3 and 6). Heart allograft survival was followed via palpation for 100 days. In selected groups, heart allografts were explanted 2 weeks after transplantation to assess intra-graft regulation via flow cytometry of graft infiltrating leukocytes (GIL) and immunofluorescence microscopy of tissue sections.

RESULTS

CTLA4-Ig monotherapy prolonged graft survival, but nearly all grafts were rejected by day 45 (MST=36 days). Additional ATG induction extended the median survival time to 80 days. Combined induction therapy with ATG and

anti-IL6 under CTLA4-Ig led to long-term (100 days) graft survival in all recipients (ATG+αIL6+CTLA4-Ig: 8/8 vs. ATG+CTLA4-Ig: 4/9; p=0.015). Perioperative blockade of IL-6 significantly increased Treg frequencies in peripheral blood (day 8, freq. within CD4; ATG+αIL6+CTLA4-Ig: 12.81±3.40% vs. ATG + CTLA4-Ig: 6.98±1.44%; p=0.002) and within the cardiac allograft itself (day 14, freq. within GIL; ATG+αIL6+CTLA4-Ig: 0.75±0.44% vs. ATG + CTLA4-Ig: 0.23±0.16%; p=0.035) early upon transplantation. Immunofluorescence microscopy showed a favorable Treg:CD8 T-cell ratio within areas of highest lymphocyte infiltration in tissue sections of recipients treated with additional IL-6 blockade compared to ATG + CTLA4-Ig. This shift towards Tregs within the graft remained detectable until the end of the follow up 100 days post transplant.

CONCLUSION

Perioperative blockade of interleukin-6 promotes intra-graft regulation and prevents costimulation-blockade resistant rejection.

29

Effect of CLAD phenotypes on the outcome after lung retransplantation – A retrospective single center data analysis

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BACKGROUND

The last possible therapeutic option for Chronic lung allograft dysfunction (CLAD) is retransplantation. Based on published evidence, outcomes appear to be worse in patients with restrictive allograft syndrome (RAS) or mixed phenotype compared to bronchiolitis obliterans syndrome (BOS). Therefore, non-BOS phenotypes are considered as contraindication to retransplantation. We hypothesized that retransplantation for CLAD is associated with good outcomes irrespective of the phenotypes.

METHODS

This study was a retrospective single center analysis including patients undergoing lung retransplantation due to CLAD between 2012 and 2021.

RESULTS

A total of 44 patients were included in the analysis. 71% of patients had BOS, 18% a mixed phenotype and 11% RAS. No difference was observed in terms of intraoperative use of erythrocyte concentrates (BOS 2400, 1500-3750 ml vs non-BOS 2240, 1500-7650 ml, p=0.255), fresh frozen plasma (BOS 2800, 1700-3400 ml vs non-BOS 2400, 1950-9300 ml, p=0.220), thrombocyte concentrates (BOS 0, 0-266 ml vs non-BOS 0, 0-411, p=0.369), Beriplex

(BOS 0, 0-1500 I.E. vs non-BOS 500, 0-2375 I.E., p=0.522) and fibrinogen (BOS 1750, 0-3000 I.E. vs non-BOS 2000, 0-2000 I.E., p=0.988). 30% of the cohort (BOS 33% vs non-BOS 31%, p=0.869) needed at least one revision after retransplantation, Length of mechanical ventilation (BOS 2, 1-7 days vs non-BOS 4, 2-6 days, p=0.389), prolonged ECMO (p=0.443), need for tracheostomy (p=0.894) and ICU time (BOS 10, 4-23 days vs. non-BOS 6, 5-26 days, p= 0.790) was comparable between the groups. Furthermore, survival between the groups did not differ with overall and graft survival rates at 90 days, 1 and 3 years of 97%, 71% and 58% for BOS and 85%, 59% and 59% for non-BOS (p=0.998).

CONCLUSIONS

In contrast to published evidence, our retrospective analysis showed that non-BOS retransplant patients had comparable outcomes with BOS patients. This implicates that retransplantations should be considered in all CLAD patients irrespective of the phenotype.

30

Anti-interleukin-6 antibody clazakizumab in late antibody-mediated kidney transplant rejection: Effect on levels of donor-derived cell-free DNA and urinary C-X-C motif chemokine ligand 10

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BACKGROUND

Therapeutic antibodies that antagonize interleukin-6 (IL-6) or its receptor have been shown to counteract donor-specific antibody (DSA) production and the activity of antibody-mediated rejection (ABMR). To date, it is unclear whether or to what extent IL-6 antagonism modulates biomarkers indicative of tissue injury and inflammation, such as donor-derived cell-free DNA (dd-cfDNA) or urinary chemokine C-X-C motif chemokine ligand /CXCL)10.

METHODS

Here, we report a secondary endpoint analysis of a phase 2 trial of anti-IL-6 antibody clazakizumab in late ABMR (ClinicalTrials.gov, NCT03444103). Twenty kidney transplant recipients were randomized to receive monthly subcutaneous injections of clazakizumab versus placebo over 12 weeks (part A), followed by an extension where all recipients received clazakizumab through week 52 (part B). Biomarkers were evaluated at three predefined time points (baseline; after 12 and 52 weeks).

RESULTS

Plasma dd-cfDNA fractions did not significantly change, without any inter-group differences at the end of part B and only a slight, non-significant decrease of dd-cfDNA fractions over the 12-month study period, after at least 9 months of clazakizumab treatment (median dd-cfDNA at baseline vs. week 52: 1.5% [median; interquartile range: 0.8-2.8%]) vs. 1.0% [0.6-1.7%]; P=0.14). Likewise, urine CXCL10, which was found to correlate with the MFI of immunodominant DSA at baseline, was not different between groups and did not change over the study period (CXCL10 [pg/mg creatinine]: 81.0 [49.1-113.8] at baseline to 67.4 [41.5-132.0] at 52 weeks; P=0.32). The same was true for CXCL10 in serum. Individual changes in dd-cfDNA or chemokine levels over time did not correlate with the observed decline in DSA MFI or molecular ABMR activity.

CONCLUSION

Our study suggests that IL-6 blockade may not trigger significant changes in dd-cfDNA and CXCL10 levels, at least over a 9 to 12 month treatment period. Early monitoring of these biomarkers not have clinical utility to detect subtle responses to this new therapeutic principle.

31

Pre-transplant mitochondrial respiration in human kidney allografts predicts clinical outcome upon transplantation

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INTRODUCTION

With the increasing use of extended criteria donors for kidney transplantation biomarkers with robust predictive capacity are necessary. The renal cortex has low ischemia tolerance as proximal tubuli have the second highest mitochondrial density in the human body and oxidative phosphorylation (OXPHOS) is essential for ATP synthesis. Furthermore, post-reperfusion mitochondrial respiration is associated with delayed graft function (DGF) [1]. Therefore, we evaluated the predictive value of pre-transplant mitochondrial respiration towards graft function after transplantation.

METHODS

In a prospective study, cortex biopsies were taken in 40 human kidneys at the end of static cold storage (SCS) and/or hypothermic machine perfusion (HMP). Mitochondrial respiration was assessed by high-resolution respirometry. OXPHOS capacity, maximal mitochondrial respiration and ATP production efficiency with the respiratory substrate succinate were evaluated. Additionally, conventional histology was graded after Remuzzi *et al.*

RESULTS

We found significantly lower OXPHOS capacity (53.4±17.6 *vs.* 74.2±23.0 $pmol^{-1} \cdot s^{-1} \cdot mg$ wet $mass^{-1}$ [mean±SD], $p = 0.0083$), maximal respiration (60.9±22.9 *vs.*

91.1±29.0 $pmol^{-1} \cdot s^{-1} \cdot mg$ wet $mass^{-1}$, $p = 0.0029$), and ATP production efficiency (0.73±0.12 *vs.* 0.82±0.06, $p = 0.0023$) in biopsies of kidneys developing delayed graft function as compared to those with normal post-transplant function. These values also correlated significantly with the 7-day creatinine and glomerular filtration rate (GFR) values. The OXPHOS capacity in the biopsy after HMP inversely correlated with the 3-month creatinine values (Pearson r = -0.41, $p = 0.039$). The Remuzzi score did not correlate with DGF, 7-day or 3-month creatinine and GFR values.

CONCLUSION

In kidney grafts eventually developing DGF, mitochondrial respiration and ATP production efficiency are heavily impaired at the end of SCS and HMP. Pre-transplant mitochondrial respiration also correlates with the 3-month creatinine values. Thus, mitochondrial respiratory function is a highly promising biomarker with predictive capacity towards kidney function in transplantation, integrating both chronic alterations and acute subcellular damage.

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32

Perfusate lactate during the first 6 hours of liver normothermic machine perfusion predicts clinical outcome – A multicenter study

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BACKGROUND

While already many livers undergo normothermic machine perfusion (NMP) before transplantation, biomarkers with robust predictive capacity towards clinical outcome are still lacking. To aid the decision making for transplantation, we investigated lactate clearance as a basic function of liver viability during the first 6h of NMP in a multicenter study.

METHODS

504 livers underwent $\geq$6h of NMP before transplantation in 6 centres in the UK, Germany, and Austria. The donor age was 49.74$\pm$16.30y (mean$\pm$SD), DRI was 1.97$\pm$0.68, 29% of livers stemmed from DCD and cold storage time was 412$\pm$124min. All centers applied a back-to-base approach and used the OrganOx metra system for NMP. The perfusate lactate levels at the start (5-15min), at 1h, 2h, 4h and 6h of NMP were assessed individually and as AUC and correlated with MEAF and L-GrAFT.

RESULTS

The total NMP time was 723±334min. EAD occurred in 26%, MEAF was 4.86±1.86 and L-GrAFT at 7 and 10 day was 0.53±1.25 and -0.21±1.25. The 1-year patient and graft survival were 86% and 80%. Lactate at 1h, 2h and 6h correlated significantly with MEAF. The correlation increased in robustness over time. Rather than a binary assessment with a cut-off value <2.5mmol/L at 2h, the actual 2h lactate level correlated with the MEAF ($p=0.0306$ *vs* $p=0.0002$, Pearson $r=0.01087$ *vs* $r=0.1734$). Further to the absolute lactate concentration at 6h, the AUC of 0-6h and 1-6h ($p<0.0001$, $r=0.3176$) has strong predictive value towards MEAF after transplantation. We did not find any correlation between perfusate lactate and L-GrAFT.

CONCLUSION

Lactate AUC up to 6h but also lactate levels at 6h correlate strongly with risk of liver allograft dysfunction upon transplantation. With duration of NMP, the predictive value of lactate is increasing. The time frame of monitoring lactate levels should be extended to at least 6h of NMP to retrieve meaningful data.

Heart

33

Highly feasible assessment tools in *ex-situ* heart perfusion – A functional evaluation in a pig model

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BACKGROUND

Ex-situ heart perfusion (ESHP) enables the resuscitation and assessment of potentially unusable donor hearts. Therefore, a comprehensive analysis of myocardial function and metabolism is crucial. Currently, the only used assessment tool for quality control is sequential lactate measurement from the perfusate. The aim of this study was to investigate new and highly feasible assessment tools in ESHP.

METHODS

12 German domestic pigs were used as heart and blood donors. "Donation after brain death" (DBD) (n=6) and "donation after circulatory death" (DCD) (n=6) were simulated and 6 hours of normothermic ESHP was performed. Analysis were performed at 1 (T1), 3 (T2) and 6 (T3) hours of perfusion. Different assessment tools were used to analyse myocardial damage (myoglobin, high-sensitive [hs] troponin t), functional status (left ventricular pressure balloon [LVPB], visual cardiac score [VCS]) and metabolomic measurements (perfusate lactate level). Data were compared with t-test. Spearman correlation was performed independently of group and timepoint.

RESULTS

Parameters of myocardial damage increased in both groups and were significantly higher in the DCD group: myoglobin (T1: DCD 1154±444.7 vs. DBD 385.2±113.8µg/l, p=0.011; T3: DCD 2002±571.4 vs. DBD 652±117.2 µg/l, p=0.003), hs troponin T (T1: DCD 44796±46581 vs. DBD 12229±6447ng/l, p=0.159; T3: DCD 446742±315830 vs. DBD 102496±33448 ng/l, p=0.044). Functional assessment revealed a decline during ESHP in both groups. LVPB did not differ between the groups (T1: DCD 160±97 vs. DBD 204±83mmHg, p=0.354; T3: DCD 66±38 vs. DBD 104±40mmHg, p=0.250), whereas VAS was significantly lower in DCD group (T1: DCD 7.3±0.8 vs. DBD 7.8±1.2, p=0.490; T3: DCD 2.7±1.0 vs. DBD 5.8±1.5, p=0.002). Lactate levels did not correlate with functional tests, whereas myoglobin had a strong correlation: VCS (rho=-0.663) and LVPB (rho=-0.590).

CONCLUSIONS

Biomarker levels for cardiac damage are correlating with impaired left ventricular function and should be considered in ex-situ heart perfusion as additional and highly feasible tool.

34

Preservation of mitochondrial function in ex-situ heart perfusion – A porcine model

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BACKGROUND

Due to the high ATP-consumption of the myocardial tissue, cardiac function is extremely dependent from an efficient mitochondrial respiration. Ischemia and reperfusion injury (I/R) have severe impact on the function of the mitochondrial respiratory system. *Ex-situ* heart perfusion (ESHP) is able to minimize I/R injury. We aimed to investigate the mitochondrial respiration using high-resolution respirometry (HRR) in a porcine model.

METHODS

6 German domestic pigs (65-75kg) were used as heart and blood donors. ESHP was performed over 6 hours. Homogenate of porcine myocardium was assessed by HRR using substrate-uncoupler-inhibitor protocols. Samples were obtained at baseline (b), and after 1, 3 and 6 hours of ESHP. Data were expressed as mean and standard deviation. Comparison of repeated measurements were performed with one-way ANOVA with Tukey's post hoc test.

RESULTS

The combined oxidative phosphorylation capacity with NADH, fatty acid and succinate fuel substrates remained stable during 6 hours of ESHP (b: 198±59.7,

1h: 196.5±66.7, 3h: 207.5±48.1, 6h: 200.5±27.9 $pmol^{-1} \cdot s^{-1} \cdot mL^{-1}$; p=0.707). The flux control ratio of the NADH-pathway (b: 0.43±0.07, 1h: 0.43±0.05, 3h: 0.47±0.05, 6h: 0.44±0.07 $pmol^{-1} \cdot s^{-1} \cdot mL^{-1}$; p=0.549) and succinate-pathway (b: 0.49±0.06, 1h: 0.49±0.05, 3h: 0.48±0.01, 6h: 0.5±0.05 $pmol^{-1} \cdot s^{-1} \cdot mL^{-1}$; p=0.814) did not change during perfusion. The mitochondrial outer membrane damage was significantly lower after 6 hours of ESHP (b: 0.39±0.07, 1h: 0.27±0.06, 3h: 0.18±0.03, 6h: 0.17±0.02; p=0.0124).

CONCLUSIONS

We performed the first in-depth analysis of mitochondrial respiratory function during *ex-situ* heart perfusion. ESHP is able to preserve mitochondrial respiration in donor hearts. Importantly, the initial mitochondrial outer membrane damage recovered over time. Next, the predictive value of HRR might be evaluated in clinical practice to promote organ acceptance in the future.

Lung

35

Atypical single-site dual-stage cannulation for extra corporal membrane oxygenation before and after lung transplantation

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BACKGROUND

Extra corporal membrane oxygenation (ECMO) support with single site dual-lumen catheters can provide advantages to standard dual-site cannulation, including improved patient mobilization, reduced recirculation and reduced risk of infection. While dual-lumen cannulation is typically only achieved through the right internal jugular vein, some scenarios can make this venous access unfeasible. This multicenter case series aims to demonstrate that single site cannulation via an atypical venous access is a safe and effective alternative in patients with an inaccessible right internal jugular vein (RIJV).

METHODS

We performed a multi-institutional analysis of adult patients receiving dual-lumen ECMO support through an atypical venous access before and after lung transplantation. We collected baseline demographic data including underlying diagnosis, type of respiratory failure, treatment goal, reason for atypical

cannulation and outcome reports. Additionally, we collected technical data as well as complications related to the cannulation.

RESULTS

Nine patients received atypical dual-lumen cannulation for hypoxemic and/or hypercapnic respiratory failure as a bridge to transplantation or recovery. Venous access was achieved through the left internal jugular vein (n=2), right (n=2) and left (n=2) subclavian vein and right femoral vein (n=3) with cannula sizes from 19 FR up to 28 FR. While 3 patients had bleeding at cannulation site, no serious adverse events occurred during cannulation. 6 out of 9 patients were not intubated and awake on ECMO support. Five patients were successfully bridged to lung transplantation, one patient died before transplantation due to bleeding after liver biopsy and 3 patients after lung transplantation were successfully bridged until allograft recovery.

CONCLUSION

In this multicenter case series, we demonstrated the feasibility of dual stage cannulation as way to treat respiratory failure in patients with inaccessible RIJV. ECMO flow rates and outcome reports were satisfactory with most patients being awake and not intubated to avoid further physical deterioration.

36

Effect of combined CMV prophylaxis on the incidence of CMV infections, CLAD and survival after lung transplantation: Single-center experience of 1100 patients

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BACKGROUND

Cytomegalovirus infection and disease continue to be a significant cause of morbidity and mortality in lung transplant recipients (LTR) however, the optimal prophylactic strategy remains a matter of debate. At the Vienna lung transplant center all LTR receive a CMV prophylaxis combining Ganciclovir/Valganciclovir for 3 months (or 12 months for high-risk patients D+/R- since 2006) together with CMV- IVIG during the 3 weeks (Day 0,7,14,21) after LuTX (1mg/kgBW).

METHODS

All consecutive patients receiving a primary lung transplantation between 01/2010-12/2020 were included in this retrospective analysis (n=1100). The incidence of CMV infections (disease, viremia) was analyzed and correlated to CMV status, type of induction therapy, survival and incidence of CLAD.

RESULTS

A total of 34 (3.1%) patients developed CMV-infection and 267 (24.3%) viremia. The rate of CMV infection was higher in seropositive LTR (32% D+R- and 29% D+R+ vs. D-/R- 6% and D-/R+ 17%). There was no correlation between CMV infection/disease and survival or incidence of CLAD. Also the type of induction treatment had no influence on the incidence or outcome of CMV infections in our cohort.

CONCLUSION

The incidence of CMV viremia and disease was extrelmy low in our center compared to the published series (see table). We hypothesize the use of CMV-IG in combination with Valganciclovir prophylaxis, the use of alemtuzumab induction therapy followed by low-dose maintenance immunsupression and the use of TTV (Torque Teno Virus) for tailoring the immunosuppressive therapy protects LTR from CMV associated complications.

Literature	patients	CMV Viremia
L. G.-Gallo **2015**	159	61% D+/R- 35% R+
Ruttmann **2006**	68	70% D+/R- (GAN) 34% D+ (GAN and CMV-IVIG)
Weill **2003**	38+48	7.9% CMV diaease (CMV-IVIG and GAN) vs. 33% GAN
Kruger **2003**	44	59% (R+ with GAN) 36% Pneumonitis 73% R+ IVIG 50% Pneumonitis
Ranganathan **2009**	599	36% pediatric patients

37

Longterm results of different induction therapy regimes after bilateral lung transplantation in Innsbruck

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BACKGROUND

Induction therapy is a particularly intensive immunosuppression used at the beginning after transplantation to reduce acute rejection. The successful prevention or reduction of acute and chronic rejection after transplantation of allografts essentially determines the outcome and long-term survival of patients, especially in lung transplantation, as rejection leads to chronic lung allograft dysfunction.

METHODS

This retrospective data analysis examines long-term outcomes following the use of three different induction therapy regimes after lung transplantation: Induction using daclizumab (interleukin-2 antagonist), antithymocyte globulin (ATG, monoclonal antibody), alemtuzumab (polyclonal antibody) and an induction therapy-free regimen.

177 Patients were included who received a bilateral lung transplantation at the University Hospital of Cardiac Surgery Innsbruck between November 1993 and January 2020 and one of the four mentioned therapy regimes in a standardized fashion. Observation period ended in August 2021. Patient survival, rejection-free survival, time to diagnosis of bronchiolitis obliterans syndrome,

development of forced expiratory volume in 1 second and occurrence of CMV reactivation or neoplasia were analyzed.

RESULTS

Regarding rejection and the development of bronchiolitis obliterans syndrome, there were significant differences between the study groups (bronchiolitis obliterans syndrome: $p = 0.045$, rejection: $p = 0.002$). The results after antithymocyte globulin or alemtuzumab administration tend to be better than those of the other two groups. The forced expiratory volume in 1 second, develops particularly favorably after antithymocyte globulin administration in our study population.

CONCLUSION

Inductions therapy regimens are favorable to no induction therapy. Antithymocyte globulin or alemtuzumab show promising results although observation period is shorter in these two groups.

38

Prioritizing heart procurement in organ donors after circulatory death does not jeopardize lung transplant outcomes

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BACKGROUND

Organ donation after circulatory death (DCD) has become a standard in liver, kidney and lung transplantation. With recent innovations in ex-vivo heart perfusion, more and more heart transplant centers have now started to accept DCD heart allografts. As the heart has a very limited tolerance to warm ischemia, changes to the DCD organ procurement procedures will be required. However, for the lungs this entails delayed ventilation and prolonged warm ischemia. It is unclear if this leads to negative effects on lung allograft function.

METHODS

We performed a retrospective data analysis of DCD lungs transplanted between 2012 and February 2022 at the Medical University of Vienna. Two groups were distinguished: 'heart+lung' consisted of cases where the heart was procured by the cardiac team for subsequent normothermic ex-vivo perfusion (EVP) before the lungs were perfused or ventilated. A control group ('lungs') was formed by cases where only the lungs were explanted. In 'heart+lung' group cases, prioritized heart procurement was employed. This meant that heart perfusion cannulas were placed first after circulatory death and a hands-off time, donor blood for EVP was collected and rapid

organ perfusion performed. Then, the heart was explanted. Up to this point the lung procurement team only stood by, and no concurrent ventilation of the lungs or perfusion of the pulmonary artery was performed. After cardiac explantation, ventilation was initiated and lung perfusion was performed directly through both pulmonary arteries. This study analysed procedural explant times using this protocol, as well as postoperative outcomes, PGD, length of mechanical ventilation and ICU stay as well as early survival.

RESULTS

A total of 56 DCD lungs were transplanted within the study period. In 7 cases (12.5%), the heart was procured before the lungs ('heart+lung'). In the remaining 49 cases (87.5%), only the lungs were explanted ('lung'). Donor demographic parameters were comparable between groups. Median time from circulatory arrest to lung perfusion (24min vs 13.5min; p=0.002) and skin incision to lung perfusion (14min vs 5min; p=0.005) were significantly longer for 'heart+lung' explants. Meanwhile, post-transplant PGD scores at 0 h (p=0.851), 24 h (p=0.856), 48 h (p=0.929) and 72 h (p=0.874) were similar. At 72 h after transplantation, none of the lungs in the 'heart+lung' but 1 (2.2%) in 'lung' group were in PGD3. Median length of mechanical ventilation (50 h vs 41 h; p=0.801), ICU stay (8 d vs 6 d; p=0.951) and total hospital stay (27 d vs 25 d; p=0.814) were comparable. In-hospital mortality was only recorded in one patient of the 'lung' group (2.2%).

CONCLUSION

Although prioritized DCD heart explantation is associated with delayed ventilation and significantly increased warm ischemic time to the lungs, early post lung-transplant outcomes are not affected. Prioritizing heart perfusion and explantation in the setting of DCD procurement can be considered acceptable.

39

Recurrence of acute respiratory distress syndrome after bilateral lung transplantation

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BACKGROUND

Main causes for early respiratory failure after lung transplantation include primary graft dysfunction (PGD), acute rejection and infection. In this report we describe a case of unclear early respiratory failure after bilateral lung transplantation for extensive Covid-19 induced acute respiratory distress syndrome (ARDS).

METHODS

We reviewed the patient file to investigate the course of the functional decline and evaluate reasons for early graft failure. Analyzed data included crossmatch results, biopsy results, leukocyte antigen (HLA) antibodies testing, bronchoalveolar lavages, respiratory parameters and medications.

RESULTS

The patient had an excellent initial postoperative course but developed progredient respiratory failure with bilateral opacities and a Pa02/Fi02 ratio <100mHG after postoperative day 5, eventually making re-implantation of extra corporal membrane oxygenation (ECMO) support necessary. Crossmatch results were negative and antibody monitoring revealed no HLA antibodies before and after transplantation. Performed transbronchial biopsies showed no sign of rejection. The patient was on constant antibiotic prophylaxis and multiple bronchoalveolar lavages did not show any common or opportunistic pathogens. Despite the low likelihood of acute rejection, multiple courses of anti-rejection treatment were given. Since the patient showed no signs of improvement to any treatment, lung protective ventilation with intermitting

prone position was initiated. The patients respiratory situation and bilateral opacities slowly improved over the next few weeks and ECMO support could eventually be discontinued.

CONCLUSION

With no evidence for PGD, rejection or infection, recurrent ARDS caused by a systemic immunological process was seen as the only plausible cause for the patients respiratory failure after lung transplantation. The fact that ARDS can develop extrapulmonary without direct viral or bacterial damage, makes us conclude that the preceded systemic activation and recruitment of immune cells by the primarily injured lung could potentially lead to recurrence of ARDS even if the injured organ is removed.

Liver

40

Normothermic machine perfusion of liver grafts in the clinical routine: A single center experience

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BACKGROUND

Normothermic machine perfusion (NMP) has been shown to be a safe preservation method for liver grafts and has become part of the clinical routine at our liver transplant center. Yet, many questions, such as the definition of optimal viability criteria and expected outcomes in the setting of NMP, remain unanswered. This study reports on experiences and outcomes of normothermically preserved and transplanted livers at the Medical University of Innsbruck (MUI).

METHODS

All liver grafts undergoing NMP at the MUI between February 2018 and December 2021 were included in the study. NMP was performed using the OrganOx metra® device. Outcomes following liver transplantation (LT) were compared for low-risk (benchmark) and high-risk (non-benchmark) cases. Chi-square and rank-sum tests were applied as appropriate to analyze and compare outcomes following LT. Kaplan-Meier-plots and the log-rank test were used to analyze patient and graft survival.

RESULTS

165 liver grafts have been perfused normothermically, 120 (73%) were ultimately transplanted; 36 (30%) would not have been accepted for LT without prior viability assessment. The ECD rate was 75% with 18% of grafts being from DCD donors. 62.5% of cases were classified as non-benchmark cases. Median NMP time was 15.5 hours. The overall 1-year patient survival was 83%; 1-year graft survival was 96% for benchmark cases compared to 71% for non-benchmark cases (p=0.002). The incidence of early allograft dysfunction (35.6% vs. 29.3%, p=0.478), ischemic type biliary lesions (4.4% vs. 8.6%, p=0.479) and hepatic artery thrombosis (0.0% vs. 6.7%, p=0.077) was similar between benchmark and non-benchmark cases.

CONCLUSIONS

NMP offers the possibility to assess the viability of marginal organs which would otherwise not be considered for transplantation. Thus, applying NMP potentially increases the donor pool while keeping waitlist mortality low. The definition of viability criteria in the setting of NMP continues to evolve and needs to be refined.

41

Ex vivo liver perfusion program - Medical University Vienna

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BACKGROUND

With the establishment of different machine perfusion strategies, optimal protocols for different donor graft indications are currently discussed. The Vienna General Hospital has the unique opportunity of using both hypothermic oxygenated machine perfusion (HOPE) and normothermic machine perfusion (NMP) in clinical routine. HOPE is the center standard for every transplanted liver since 2018, NMP was established in 2021 predominantly for extended criteria donor (ECD) grafts that needed additional assessment.

METHODS

Our aim is that all liver grafts offered to our center receive either HOPE or NMP. Depending on their and the recipient's individual risk profile, the transplant surgeon decides which method is applied. A team of medical students is on call as perfusionists. They prepare the machine, monitor the perfusion, and collect samples. The transplant surgeon performs back-table preparation and connects the liver to the machine. NMP takes place in a dedicated perfusion operating room (OR) where the liver remains until hepatectomy is finished and then the machine is transferred to the recipient OR. HOPE takes place in the same OR as the transplantation as the perfusion is always performed parallel to hepatectomy.

RESULTS

161 hypothermic and 27 normothermic perfusions were performed since May 2018. A biobank with samples (serum, perfusate, effluent, bile, biopsies) of all perfusions and recipients was built up for future research projects. The establishment of a dedicated perfusion-OR was a big step forward, but the recruitment and training of perfusionists is still challenging, as well as logistics of machine-perfusion, especially in case of NMP.

CONCLUSIONS

HOPE is our standard procedure for liver grafts in order to improve preservation of bile ducts and NMP for liver grafts when pre-transplant viability assessment is required. As for our knowledge no approach has shown superiority over the other regarding all possible indications until now.

42

Gene expression profiling during normothermic machine perfusion of human donor livers

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BACKGROUND

Normothermic machine perfusion (NMP) has been successfully implemented in clinical routine of liver transplantation over the past years. However, little is known about the mechanisms how NMP impacts on the transcriptome of a human donor liver. We herein examined gene expression profiles in transplanted and non-transplanted livers over NMP time.

METHODS

45 livers subjected to NMP were included in this study. 30 were transplanted after a maximum of 24 hours (h) perfusion, while 15 were discarded due to poor performance. Biopsies were collected pre, 1h, 6h, 12h, 20h of NMP and after reperfusion. Next-generation sequencing was applied in liver biopsies to assess differential gene expression over perfusion time. Perfusate samples were collected regularly to monitor liver function.

RESULTS

Comparison in differential gene expression between pre and 20h NMP showed 415 upregulated and 727 downregulated genes. Most significantly upregulated genes were associated with extra cellular matrix organization, cell growth/differentiation processes and cytokine signaling. A set of genes were

identified which were significantly differentially expressed in non-transplanted vs transplanted biopsies, especially at 12 and 20h of NMP.

CONCLUSIONS

This study demonstrates that NMP significantly upregulates gene expression in human donor livers over perfusion time, with different transcriptomic profiles in transplanted and non-transplanted livers at later time points. Our data provides deeper understanding of molecular mechanisms during human liver NMP and may be serve as groundwork in the decision process whether to transplant a liver or not.

43

Endothelial glycocalyx damage marker Syndecan-1 measured during hypothermic oxygenated machine perfusion correlates with early allograft dysfunction after liver transplantation

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BACKGROUND

Hypothermic oxygenated machine perfusion (HOPE) allows transplantation of extended criteria donor organs. During different stages of organ damage, the endothelial glycocalyx is degraded and can be used as an indicator for damage extent. Syndecan-1 (Sdc-1), the main component of endothelial glycocalyx, is released into serum upon its degradation. We aimed to assess glycocalyx damage during hypothermic oxygenated machine perfusion in the context of liver transplantation.

METHODS

HOPE was performed on 40 livers prior to transplantation with the Organ Assist® perfusion system. Sdc-1 was measured by ELISA in samples of: perfusate, effluent and serum. Sdc-1 levels were analyzed in patients who did and did not develop early allograft dysfunction (EAD) using Mann-Whitney U test, Pearson correlation and receiver operating characteristics (ROC).

RESULTS

Patients that developed EAD showed elevated Sdc-1 concentrations in perfusate compared to non-EAD patients: after 0 min [598 (±526) vs. 276 (±150) ng/ml; p=0.076] and 60 min [1099 (±739) vs. 521 (±382) ng/ml; p=0.016] of perfusion. The 15 patient samples (4 with EAD) of the effluent showed a similar trend: [2074 (±1273) vs. 443 (±226) ng/ml; p=0.001]. Sdc-1 levels correlated with EAD: at 0 min (R=0.433; p=0.006), at 60 min (R=0.471; p=0.003) and in the effluent (R=0.769; p<0.001). Additionally, an association between Sdc-1 concentrations and EAD could be shown by ROC: perfusate at 60 min (AUC=0.704; p=0.018) and effluent (AUC=1; p=0.004 (n=15, 4 with EAD)). Sdc-1 was not associated with graft survival (p=0.339) in cox regression analysis, however, patients who developed EAD showed a significantly reduced graft survival (log-rank=0.009) compared to those without EAD.

CONCLUSIONS

With this translational approach, we could show that the level of glycocalyx degradation measured during hypothermic oxygenated machine perfusion can predict liver transplantation outcome regarding EAD. Therefore, Sdc-1 could be a potential biomarker for organ assessment during HOPE.

44

Comparability of bioenergetic fingerprints in the human and porcine liver and influence of normothermic machine perfusion

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BACKGROUND

Large animal models are increasingly used for development of extended *ex vivo* normothermic machine perfusion (NMP) protocols and organ regeneration. The crucial role of mitochondrial ATP synthesis and injury during liver transplantation and NMP is well known. In the translational research, comparability of biomarkers is essential. Therefore, we (1) tested the bioenergetic capacity in human and porcine livers after static cold storage (SCS); (2) evaluated the effect of reperfusion on the bioenergetics during NMP; and (3) the stability of these parameters over a 5-day-perfusion period in a porcine model.

METHODS

Mitochondrial respiration was assessed by high-resolution respirometry in human livers after SCS (N=32) and in porcine livers after SCS and during NMP (N=19).

RESULTS

Both in human and porcine livers, the succinate-pathway alone contributes to 100% of OXPHOS capacity after SCS. The fatty acid oxidation (FAO) accounts for 25% in porcine and for 30% in human livers, while the NADH-linked respiration is higher in pigs. The succinate-linked OXPHOS was not different, while human livers have lower ATP production efficiency (0.79 *vs.* 0.86), probably due to longer cold storage (6.1h human *vs.* 0.5h porcine; median) and donor-specific reasons. In the porcine model, the respiration and ATP production efficiency decreased while the mitochondrial outer membrane (OMM) damage increased upon reperfusion. FAO- and NADH-linked respiration selectively decrease after reperfusion. No further changes were detected during the later perfusion. OMM damage correlated inversely with the cumulative bile production (Spearman r=-0.633, p=0.041).

CONCLUSIONS

We found a good bioenergetic comparability between human and porcine livers which allows for a translational approach also on a mitochondrial level. Porcine livers are sensitive to reperfusion injury, as demonstrated by the OMM damage and decreased bioenergetic efficiency on the first day of perfusion. Importantly, all bioenergetic markers remained stable until day 5 of NMP, also correlating with bile production.

45

Changes of glutathione excretion during normothermic machine perfusion of livers and potential influencing transplant factors

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BACKGROUND

Normothermic machine perfusion (NMP) is a diagnostic tool for liver assessment prior to transplantation. Recent literature on liver NMP supports the importance to analyse the composition of bile during liver NMP. Glutathione (GSH) is known to be one of the major determinants of bile flow and the osmotic driving force in acid-independent bile formation. It is known that biliary GSH efflux is impaired after ischemia. Our aim was to analyse bile GSH in NMP livers over time and hypothesize that it correlates with transplant factors.

METHODS

Consecutive NMP livers were prospectively included in the study between 2018-2019. After one and four hours, as well as at the end of the perfusion bile was analysed biochemically. An ELISA assay was performed to detect changes in GSH content during perfusion and correlated with clinical and perfusate parameters.

RESULTS

Overall, 41 of 58 perfused livers were transplanted after NMP. 49 (90.7%) were from extended criteria donors (ECD) and 16 (27.6%) from donors after circulatory death (DCD). Total mean±SD preservation time was 1365.8±403.6 min, NMP duration was 978.8±377.2 min and mean cold ischemia time (CIT) 387±158.7 min. The GSH content in bile showed a significant increase over time (hour 1: 24.1±30.3µM vs. end: 96.6±85.0µM, $p<0.001$). In 14 (34.1%) recipients, early allograft dysfunction occurred. GSH after one hour of NMP correlated negatively with bile lactate ($p=0.018$). GSH at four hours correlated significantly with bile pH ($p=0.0391$), bile bicarbonate ($p=0.047$) and negatively with the difference of perfusate lactate and bile lactate ($p=0.019$).

CONCLUSIONS

Our data indicates that there is an active increase of GSH in bile during liver NMP and GSH content correlates with bile composition. The negative correlation between lactate levels and GSH content might indicate the important role of GSH in protecting cells from oxidative damage and maintaining redox hemostasis.

Immunology/Covid-19

46

Humoral response after a third and fourth dose of mRNA-based SARS-CoV-2 vaccine in previously seronegative kidney transplant recipients

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BACKGROUND

Growing evidence shows diminished response to mRNA-based SARS-CoV-2 vaccination in kidney transplant recipients. We aimed to investigate the seroconversion rate after a 3rd and 4th dose of mRNA vaccination in kidney transplant recipients without prior antibody response to two or three vaccination doses.

METHODS

This retrospective study included 324 prevalent kidney transplant recipients of a single tertiary transplantation center without prior seroconversion defined as anti-Spike-antibody titer <7.1 BAU/ml after dose two or three of mRNA-based SARS-CoV-2 vaccination. Maintenance immunosuppression was not changed. The median patient age was 60.6 (IQR 51.4 to 68.1) years, 66.9% were male. Positivity for anti-S-antibodies (≥7.1 BAU/ml) was measured 4 to 5 weeks after administration of a 3rd and 4th vaccine dose.

RESULTS

Seroconversion rates were 63.9% after a 3rd dose and 29.3% after a 4th dose of vaccine. Cumulative prevalence of seropositivity for anti-S-antibodies was 51.5% after two doses, 80.5% after three doses and 84.2% after four doses.

CONCLUSION

Seroconversion can be achieved in most of the kidney transplant recipients by administrating three or four doses of mRNA vaccine without changing maintenance immunosuppression.

47

Incidence and outcome of SARS-Cov-2 infection in kidney transplanted children – The Vienna Cohort

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BACKGROUND AND METHODS

Here, we report on the incidence and outcome of SARS-Cov-2 infection in a cohort of 43 pediatric renal transplant patients routinely followed at the Division of Pediatric Nephrology and Gastroenterology (median age 12.2 years and median post-transplant time 19 months).

RESULTS

Until July 2022, 26 of 43 patients were tested positive for SARS-CoV-2 confirmed by PCR (60%). The majority of the infections (20 out of 26) was registered after January 2022. This is mainly due to the high infectious property of the omicron variant.

20 of the 26 infected patients were vaccinated at least once, the majority of the children had received two or three vaccine doses according to the actual vaccination policy before / at the time of infection.

The main symptoms of SARS-Cov-2 infection were fever, higher temperature, fatigue, rhinorrhea and coughing.

None of the patients required hospitalization and no changes were made to the immunosuppressive regimen. 6 children was treated with sotrovimab infusion and 1 patient received remdesivir therapy. The antibody sotrovimab has not been given since April 2022.

Long-lasting symptoms (National Institute for Healthcare Excellence (NICE) definition of long-COVID) have not been present in any of the children.

CONCLUSIONS

The incidence of SARS-CoV-2 infection was high in our cohort. Most patients were infected with the omicron variant and fortunately, the disease course was mild for all patients.

Stem Cell

48

Retrospective evaluation of the predictive value of the CD4: CD8 ratio in allografts on major outcomes of allogeneic hematopoietic stem cell transplantations at various graft versus host disease prophylaxis regimens

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BACKGROUND

A high CD4/CD8 T cell ratio in allografts was observed to predict graft-versus-host disease (GVHD) and non-relapse mortality (NRM). However, the differential impact of the CD4/CD8 ratio in settings of various GVHD-prophylaxis regimens has not yet been systematically addressed.

METHODS

This retrospective monocentric study included all consecutive HSCT performed with bone marrow (BM) or G-CSF mobilized peripheral blood stem cells (PBSC) between January 2000 and June 2021 (n=641). The impact of the graft CD4/CD8 ratio was analyzed in three cohorts defined by GVHD-prophylaxis: cyclosporin A/methotrexate (CSA/MTX; n=195), CSA/mycophenolate mofetil (CSA/MMF; n=307), and posttransplant cyclophosphamide (PTCy)/tacrolimus/MMF (PTCy/Tac/MMF; n=139). The CD4/CD8 ratio cut-off was defined by the overall cohort's 75th percentile (2.38).

RESULTS

In the entire cohort, grafts with a high CD4/CD8 ratio (> 2.38) had a significantly decreased overall survival in the multivariate analysis (Hazard ratio [HR] 1.43; P=0.005). Likewise, in the CSA/MMF subgroup, a high CD4/CD8 ratio was associated with decreased overall survival (HR 1.47; P=0.02), but not so in the CSA/MTX subgroup (HR 1.10; P=0.71), and in the PTCy/Tac/MMF subgroup (HR 1.72; P=0.09). Further, a high CD4/CD8 ratio was associated with a significantly higher risk of acuteGVHD-associated mortality in the overall cohort (sub-Hazard ratio [sHR] 1.83; P=0.003) and in the CSA/MMF subgroup (sHR 2.24; P=0.002).

CONCLUSIONS

A high CD4/CD8 ratio in the allograft may have an adverse impact on overall and GVHD-associated mortality, particularly in HSCT applying CSA/MMF as GVHD-prophylaxis. PTCy- or particularly MTX based prophylaxis may partly overcome the adverse impact of a high CD4/CD8 ratio.

49

Stromal-immune cell interactions regulate establishment of tissue residency in the skin after hematopoietic stem cell transplantation

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BACKGROUND

Tissue-resident memory T cells (TRM) are important for immune defense and maintenance of homeostasis at barrier sites. Due to a lack of adequate models, factors determining human TRM development and function in specific tissues are understudied. In the skin of patients undergoing hematopoietic stem cell transplantation (HSCT), host skin TRM survive radio-chemotherapy, while donor T cells can home to the skin to form a new TRM pool, which exists beside host TRM. To discriminate host and donor origin of immune cells and study pathways involved in the development of TRM, we performed a longitudinal analysis of skin and blood of HSCT patients at single-cell resolution. Additionally, integrative analysis with stromal skin cell types uncovered aspects of tissue-immune regulation and cell-cell communication within the skin after transplantation.

METHODS

We performed single-cell RNA and T cell receptor (TCR) sequencing on skin and blood-derived $CD45^+$ and $CD45^-$ cells of patients before and after HSCT (days -7, 0, +14, +100) to uncover changes in their transcriptional state,

define dynamics of T cell clonality in parallel in two compartments and assess cell-cell interactions occurring in the skin.

RESULTS

We recovered leukocytes and stromal cells of all longitudinal samples. Immune cells after transplantation were annotated to host and donor origin based on the genotype. Interestingly, distinct T cell subsets displayed time-dependent expression patterns related to TRM function and metabolism, indicating formation of a specialized local immune memory. Furthermore, skin fibroblasts changed their expression profiles at the day of transplantation: immune signaling was enriched whereas genes associated with matrix remodeling were downregulated. A preliminary cell-cell interaction analysis between immune and stromal cells revealed enhanced communication after transplantation.

CONCLUSIONS

Our study suggests that stromal-immune cell communication is required to establish new tissue-resident immune cell populations after transplantation. We detected involvement of some previously unrecognized pathways that we plan to validate in functional *ex vivo* experiments.

50

Autologous and allogeneic stem cell transplantation as salvage treatment options for relapsed/refractory multiple myeloma: A single-center experience over 20 years

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BACKGROUND

Despite new therapies, multiple myeloma remains an incurable disease with poor outcome. So far, allogeneic stem cell transplantation is the only potentially curative treatment option.

METHODS

We retrospectively analyzed the outcome of myeloma patients undergoing an allogeneic (allo-SCT; n=34) or autologous stem cell transplantation (ASCT; n=41) as salvage treatment in the relapse/refractory (r/r) setting.

RESULTS

After a median observation period of 79.9 months in the auto group and 15.7 months in the allo group, the 5- and 10-year OS were 54% (95% CI, 38%-71%) and 44% (95% CI, 26%-63%) in the auto group and 17% (95% CI, 2%-31%) and 4% (95% CI, 0%-12%) in the allo group (p=0.0002). The 5- and 10-year disease-free survival in the auto group were 21% (95% CI, 8%-35%) and 8% (95% CI, 0%-17%) and 14% (95 CI, 2%-27%) and 5% (95% CI, 0%-14%) in the allo group (p=0.0142). The 5- and 10-year cumulative incidence of relapse/progression in the auto group were 69% (95% CI, 55%-86%) and 82% (95% CI, 70%-96%) and 64% (95% CI, 49%-84%) and 69% (95% CI, 54%-88%)

in the allo group (p=0.0759). The 5- and 10-year non-relapse mortality in the auto group was significantly lower [5% (95% CI, 1%-19%) *versus* 45% (95% CI, 31%-67%) (p=0.0001)].

CONCLUSION

Although limited by low patient number and a potential bias towards a higher proportion of patients with more aggressive disease in the allo group as reflected by a significantly shorter time interval from diagnosis to allotransplant, a second autotransplant in selected r/r patients offers an acceptable long-term outcome partly due to a significantly lower treatment-related morbidity and mortality.

51

Early autologous and allogeneic peripheral blood stem cell transplantation for adult patients with acute B- and T-cell precursor neoplasms: A 12-year single center experience

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BACKGROUND

Adult acute lymphoblastic leukemia/lymphoma (ALL/LBL) is a rare and heterogeneous malignancy characterized by uncontrolled proliferation of B- or T-cell precursor cells.

METHODS

Here, we retrospectively analyzed the outcome of early autologous stem cell transplantation in standard-risk patients in first complete remission (n=24) and of allogeneic transplantation in high- and highest-risk, and relapsed/refractory patients (n=35).

RESULTS

The 10-year overall survival after autologous transplantation was 45%. The 10-year overall survival after allogeneic transplantation was 58%. The cumulative incidence of relapse was 29% after allogeneic and 67% after autologous transplantation. The cumulative incidence of non-relapse mortality was 0% after autologous and 12% after allogeneic transplantation.

CONCLUSION

This retrospective single center analysis in a limited number of standard-risk patients clearly demonstrates that early autologous transplantation in first complete remission leads to an acceptable long-term outcome with a short overall treatment duration of less than six months compared with more than two years with conventional chemotherapy. More sensitive and standardized methods to detect minimal residual disease (MRD) will further help to identify those patients more accurately who are most likely to benefit from such a short and intensive treatment strategy (i.e. MRD negative standard-risk patients) or those who require early targeted therapy (e.g. blinatumomab) in case of MRD positivity. Early allogeneic transplantation results in long-term survival/cure in nearly two-thirds of all high- and highest-risk, and relapsed/refractory patients.

Poster Presentations

Abdomen

52

Viability assessment during normothermic machine perfusion

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BACKGROUND

Normothermic machine perfusion (NMP) as an approach to tackle organ shortage by using extended criteria donor organs (ECD) has its major benefit in the possibility of viability assessment. For organs donated after circulatory death (DCD) the viability of the biliary system is especially important, due to their greater susceptibility to biliary complications.

METHODS

24 perfusions of predominantly ECD livers (Mean donor risk index 1.885 (SD: 0.41)) were performed since 01/2021. Graft Viability was assessed based on hepatocellular and cholangiocellular criteria (pH and glucose content in perfusate and bile, perfusate lactate clearing) during hour 2 and 4 of the perfusion. Median follow-up after transplantation is 13.6 months.

RESULTS

Out of the 24 perfusions performed, 14 organs were transplanted successfully after evaluation. The 10 secondarily discarded organs were declined for

e.g., low bile quality, non-lactate clearing or extensive fibrosis in the frozen section. The number of transplanted DCD grafts at our center increased steadily since the introduction of NMP. From the 14 patients who received a graft that was perfused normothermic, 5 developed biliary complications (3 anastomotic strictures, 1 bilioma and 1 hepaticus necrosis) but no case of ischemic-type biliary lesions occurred. All biliary complications were successfully treated (endoscopic stenting, punctation of the bilioma and a hepaticojejunostomy for the hepaticus necrosis). There was no need for re-transplantation. 3 recipients out of 14 died during follow-up due to liver unrelated reasons (necrotizing pancreatitis, disseminated Kaposi sarcoma and ischemic stroke). Median comprehensive complication index during hospital stay following transplantation was 32.9 (range: 79.1).

CONCLUSIONS

Due to implementation of NMP, livers that otherwise would have been discarded have been transplanted successfully. Considering the risk profile of ECD organs, the outcome after NMP is promising. Further validation of the viability criteria in use in larger, randomized trials is warranted.

53

Influence of gender-mismatch on post-reperfusion hemodynamics in liver transplantation

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BACKGROUND

It is known that donor to recipient gender mismatch worsens graft outcome after liver transplantation. Hemodynamic instability immediately after liver graft reperfusion in the recipient has negative impact on recipient morbidity and mortality and it is not clear whether gender mismatch has an impact on post-reperfusion hemodynamics. Here we investigate the influence of gender mismatch on the hemodynamics of the post-reperfusion phase in liver transplantation.

METHODS

In 77 (43 gender-match, 34 gender-mismatch) patients, mean arterial pressure (MAP) and catecholamine consumption was recorded throughout the surgery at one minute intervals. To allow comparison of the different catecholamines used, the formula "total catecholamines= Norephinephrine + Epinephrine + Dopamin/100 +Vasopressin*2.5" was applied. MAP and total catecholamine consumption was calculated for the first 30 minutes of the post-reperfusion phase for every patient and set in proportion to the anhepatic phase. The change in total catecholamine requirement and MAP during the post-reperfusion phase in relation to the anhepatic phase was statistically analysed between the two groups using the Welch Two sample t-test.

RESULTS

There was no difference in MAP in the post-reperfusion phase between the gender-match and gender-mismatch group ($t = 1.15$; $p = 0.2537$).

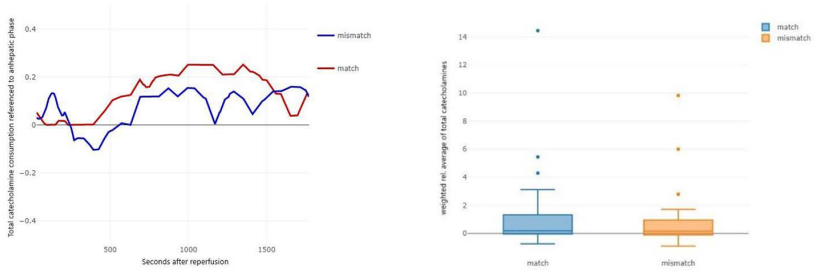

FIGURE 1

Total catecholamine requirements increased in both groups after reperfusion, but no difference was seen between the two groups (t = 0.53; p = 0.599).

CONCLUSION

This work in 77 patients shows no difference in post-reperfusion hemodynamics and catecholamine consumption between patients who received a graft of the same gender and patients who were transplanted with a graft of the opposite gender. Possible limitations however, could be the heterogeneous patient population and the multifactorial genesis of haemodynamic instability after liver graft reperfusion.

54

Depicting immune cell dynamics and inflammation using single-cell RNA sequencing in normothermic machine perfusion of the liver

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BACKGROUND

Normothermic machine perfusion (NMP) enables prolonged preservation, evaluation, modification and treatment of human organs *ex vivo*. Using single-cell RNA sequencing we provide a first comprehensive single cell atlas of human livers perfused *ex vivo*, characterized cell composition and assessed molecular mechanisms.

METHODS

In-depth cell mapping was achieved by whole transcriptome single-cell RNA sequencing (scRNASeq) prior and at the end of NMP and upon transplantation in 4 livers. Resident immune cells where visualized and localized. At corresponding time points, passenger leukocytes and inflammatory profile were quantified and characterized in the perfusate of 26 human donor livers during NMP.

RESULTS

A human liver cell atlas was constructed integrating 56.560 cells uncovering the single-cell transcriptome landscape of immune cells during NMP. The abundance of inflammatory $CXCR2^{+}$ neutrophils increased while tissue-resident neutrophils decreased during NMP. Concordantly, a massive influx of passenger leukocytes (2537/µl [2003, 3215]) with predominance of neutrophil granulocytes (1957/µl [1510, 2511]) was observed in the perfusate at 1h NMP. NMP induced a pro-inflammatory milieu which increased with perfusion time, wherein neutrophils and Kupffer cells constituted the main source of immunomodulatory cytokines/chemokines.

CONCLUSIONS

We provide a comprehensive transcriptomic cell atlas of the human donor liver prior, during and after NMP, and describe a previously unrecognized dominance of neutrophils and Kupffer cells as critical inflammatory cell populations. Together with the characterization of a massive mobilization of neutrophils into the perfusate these findings enhance the understanding of liver biology during NMP and transplantation and may set the stage for future modification.

55

Mitochondrial integrity and function partially recover during long-term normothermic perfusion of the liver

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BACKGROUND

Long-term normothermic machine perfusion (NMP) of the liver could represent a novel platform with the potential for organ regeneration and repair. As a prerequisite, detailed insights into the cellular metabolism and bioenergetic processes during NMP are required.

METHODS

Attempting to delineate the consequences of long-term organ procurement on mitochondrial integrity and function, a porcine model of 7-days NMP was applied. Liver biopsies were obtained before the initiation of perfusion, as well as on day 1, 5, 6 and 7, and analysed by high-resolution respirometry (HRR; O2k, Oroboros Instruments, Innsbruck, Austria).

RESULTS

OXPHOS capacity showed a continuous decline in throughout perfusion (day 0: 49.1 $\pm$ 24.4, day 1: 40.4 $\pm$ 23.7, day 7: 28.3 $\pm$ 6.3 pmol s^{-1} mg wet $weight^{-1}$).

Comparison of mitochondrial efficacy of ATP production before initiation of NMP and after 24 hours revealed an initial decline (*P-L* coupling efficiency on day 0: 0.84 ± 0.05 vs. day 1: 0.75 ± 0.10; p = 0.016). Importantly, ATP production efficiency recovered on day 5 (0.81 ± 0.03; p= 0.188) remaining stable on day 6 (0.8 ± 0.04; p= 0.125) and 7 (0.82 ± 0.04; p= 0,437). Potential damage to the outer mitochondrial membrane was assessed by analysis of the cytochrome c control factor. A discrete elevation was observed after 24 hours (day 0: 0.21 ± 0.11 vs day 1: 0.33 ± 0.06; p<0.05). However, recovery from this initial damage was indicated by lowered levels after day 5 (0.19 ± 0.07; p= 0.625) of perfusion, remaining unaltered until day seven (day 7: 0.2 ± 0.07; p=0.593).

CONCLUSION

Our data indicate that, mitochondrial integrity and function, can be maintained stable during long-term-NMP. A time-dependent decrease of mass-specific respiration is counterbalanced by stable ATP production efficiency. Importantly, a discrete impairment after 24 hours reveals to recover in the long-term perfusion setting.

56

Successful pregnancy in a kidney-pancreas transplanted patient on LifeCycle Pharma tacrolimus (LCPT)-based immunosuppression: A case report

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BACKGROUND

As no experiences concerning LifeCycle Pharma tacrolimus (LCPT) in pregnancy after simultaneous pancreas kidney transplantation (SPK) are published so far we retrospectively analyzed the long-term graft function, obstetric/neonatal course, LCPT dosage, tacrolimus (TAC) levels, concomitant medication and complications in a 25-year-old female SPK recipient at our center, who gave birth to a child in posttransplant month 32.

METHODS

Due to TAC fast metabolism she was converted from a standard TAC formulation to LCPT in the first month posttransplant. Her long-term immunosuppression including the obstetric and peripartal course consisted of LCPT, prednisolone, azathioprine.

RESULTS

She kept an excellent function of both grafts at the observation time of 48 months posttransplant. All (mostly infectious) complications were reversible and no relapse of her pretransplant episode of atypical haemolytic uremic syndrome with critical deterioration of her general condition (requiring clinically indicated early termination of her first pregnancy prior to SPK) occurred posttransplant. Her child is in good health at the age of 12 months without any malformations.

CONCLUSION

We conclude from this single case experience that pregnancy in SPK under LCPT is feasible. Further experiences on this subject are of interest in order to expand the empirical knowledge surrounding tacrolimus.

57

Prognostic value of magnetic resonance imaging in patients with kidney allograft dysfunction - A short term follow-up analysis

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INTRODUCTION

The diagnostic- and prognostic value of magnetic resonance imaging (MRI) is becoming increasingly important in various areas of transplant medicine. A previous study conducted at our center revealed that advanced interstitial fibrosis (ci) of allografts was associated with apparent diffusion coefficients (ADC) and higher T1 relaxation times in kidney transplant recipients. In the present post hoc analysis of the clinical course of enrolled subjects we aimed to assess the value of a single baseline MRI as a surrogate for predicting subsequent deterioration of graft function.

MATERIALS AND METHODS

In a prospective study design, study participants (n=32; median age 53.5 years) underwent allograft biopsies (indication or surveillance biopsies after a median of three years) and, at the same time, non-contrast MRI including ADC, T1- and T2-mapping sequences (recruitment period between December 2017 and January 2019). The MRI protocol included measurements in 3 axial (cranial, middle, and caudal) and 3 coronal planes (anterior, middle, and posterior parts of the kidney). MRI results were analyzed in relation to graft survival and the course of serum creatinine (SCr-mg/dL) over a period of 24 months.

RESULTS

Seven of the 32 included recipients(21.9%) lost their allograft during follow-up. Higher axial and coronal T1, but not ADC, showed significant correlations with the absolute SCr values(T1 Axial/3-month-SCr r=0.515, p=0.003, T1 Axial/24-month-SCr: r=0.393; p=0.039; T1-Coronal/3-month-SCr: r=0.476; p=0.007; T1-Coronal/24-month-SCr: r=0.381; p=0.045). Patients with a 20% increase in SCr over 24 months showed significantly higher T1 times (coronal and axial planes;cranial pole of the graft).

CONCLUSION

The results of our study suggest that T1 times at baseline correlate with the course of renal function and may therefore be a useful surrogate predicting transplant outcomes. Further research is needed to confirm our results in large validation cohorts, to standardize MRI-based assessment of renal fibrosis and to analyze the role of sequential MRIs as a surrogate of progressive allograft injury and long-term survival.

58

Comparison of an in-house and a commercial CE-marked real-time PCR assays for plasma TTV-DNA monitoring post kidney transplantation

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BACKGROUND

Plasma viral load of the highly prevalent, non-pathogenic torque teno virus (TTV) is associated with immunosuppression after solid organ transplantation. An optimal TTV range has been defined for risk stratification of graft rejection and infection in the first year post kidney transplant applying an in-house PCR. Recently, a commercial PCR, the TTV R-GENE® kit, has been CE certified for clinical use. In this analysis, the commercial TTV R-GENE® was compared with the Vienna in-house TTV PCR.

METHODS

Patients were selected from the prospective TTV-POET trial including 628 consecutive adult recipients of a kidney allograft transplanted at the MUV, between January 2016 and July 2020. Patients were followed for 12 months post-transplant. TTV was quantified longitudinally by the TTV R-GENE® and our in-house PCR. Analyses for both assays were performed in parallel using the same nucleic acid extracts.

RESULTS

A total of 342 plasma samples from 306 renal transplant recipients were tested. All but three samples (n=339) were tested TTV positive with both assays.

Mean log10 c/mL TTV load was 7.52 (SD 1.98) and 6.16 (SD 1.62) for in-house PCR and TTV R-GENE®, respectively. The results of both assays were highly associated (intercept: estimate -0.86, 95% CI -1.04 to -0.67; R 0.91). Bland-Altman analysis showed a mean log10 TTV load of -1.38 c/mL detected by TTV R-GENE® kit compared to in-house PCR. Only 13 samples were quantitatively discordant with a difference in TTV load of >2 log10 and were subjected to TTV single strain analysis.

CONCLUSIONS

Quantitative results of in-house and commercial TTV PCR are highly comparable. The absolute difference is due to different calibration curves. Few discordant samples are due to detection of TT midi virus by the commercial PCR.

59

Emergency colectomy in a patient with cytomegalovirus colitis after kidney transplantation

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BACKGROUND

Colitis induced by cytomegalovirus (CMV) is a rare but potentially life-threatening complication of immune compression. In addition, transplant patients have the risk of CMV reactivation of the donor organ.

CASE REPORT

A 50 year old male patient sustained toxic megacolon due to CMV colitis 9 months after his second kidney transplantation. Despite immediate antiviral therapy, the patients suffered from a septic shock with sopor, tachycardia and anuria. Laparotomy revealed a pathologically dilatated colon especially of the caecum and the transversal colon with livid discoloration of the bowel wall. In an emergency approach subtotal colectomy with end ileostomy was performed. The patient recovered quickly under intensive care and the transplanted kidney resumed its function after three days of haemodialysis. However, the postoperative course was prolonged due to a bacterial pyelonephritis and a continuing CMV viremia and was successfully treated with maribavir and atovaquone at the end. Four months after the operation he was discharged from the hospital with a creatinine of 2.6 mg/dl.

CONCLUSIONS

A toxic megacolon is rarely triggered by CMV-Colitis, but immunocompromised patients are at higher risk, especially if the immunosuppression is in context

with transplantation of an organ from a seropositive donor to a seronegative recipient. Then patients should receive an antiviral prophylaxis. In most of the cases, CMV colitis is successfully treated with antiviral and antibiotic therapy, although in literature mortality is described to be up to 6,5-9,2 %. Surgical treatment is indicated in case of therapy resistant colitis, bleeding, perforation or intraabdominal abscesses.

In cases of massive CMV reinfection, intensive interdisciplinary collaboration with medical specialists, surgeons and intensive care medicine is necessary for successful treatment of the patient with CMV colitis and septic shock.

60

Gene expression profiles of peritubular capillarits in chronic antibody-mediated rejection

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PURPOSE

Chronic antibody-mediated rejection (ABMR) is a significant cause of late allograft loss. Diffuse ptc (extent >50%) was associated with worse graft survival independent from the ptc score. Nevertheless, current ptc thresholds are arbitrarily defined and may not reflect pathophysiological phenotypes accurately. We hypothesize that re-assessment of ABMR biopsies with the Nanostring-NCounter based gene expression analysis allows the definition of novel thresholds of ptc extent, reflecting molecular ABMR phenotypes more accurately.

METHODS

We retrospectively analyzed 25 patients with ABMR/chronic ABMR and presence of donor specific antibodies, treated at two centers (Medical University of Vienna and Ordensklinikum – Elisabethinnen Linz). PTC was re-evaluated by an experienced external nephropathologist (M.M.) and included the ptc score as well as the ptc extent (focal ptc: 10-50%, diffuse: >50%). We performed Nanostring nCounter Gene expression analysis with a customized gene set corresponding to the recommendations in Banff 2017 guidelines. Gene expressions above the first quartile ($ABMR^{Q>1}$) were considered as positive values for ROC analysis.

RESULTS

Biopsies with diffuse ptc had significant higher gene expressions with the ABMR gene set [63/55-83 vs. 32/27-52; (median/IQR); p=0.012], the ABMR exhaust gene set (390/245-609 vs. 245/128-358; p=0.022), the Eculizumab gene set (180/143-339 vs. 65/57-133; p=0.0027) and the TCMR gene set (48/40-75 vs. 25/19-35; p=0.001). Sensitivity analysis revealed improved AUCs for predicting biopsies with ABMR gene expressions over the 1st quartile with a ptc cutoff of 35% compared to ptc cut-off of 50% [$ptc^{>35}$: AUC 0.76/0.61-0.90 (95% CI), p=0.013; $ptc^{>50}$: AUC: 0.71/0.54-0.88, p=0.039].

CONCLUSIONS

With the application of gene expression-based Nanostring platform we were able to identify a new threshold of ptc extent. The newly proposed cut off >35% may reflect molecular phenotypes of ABMR more accurate than the current one and could improve early diagnosis of ABMR.

61

Gore-Tex vascular graft as the key to success in a pediatric kidney transplant with azygos continuation of the inferior vena cava

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BACKGROUND

A five-year-old girl (17 kg) with two different chromosomal deletion syndromes with multiple organ involvement (6p25.1p23, TFAP2A) developed end-stage kidney disease requiring peritoneal dialysis treatment from April 2020 onwards. Pre transplant work-up revealed azygos continuation of the inferior vena cava precluding adequate renal venous outflow from a conventional renal allograft.

METHODS

The patient received a living donor kidney transplant from her grandmother (58 years, MM 1-1-0, D/R CMV -/- and EBV +/-). Following mobilization of the right lobe of the liver and right-sided nephrectomy, the left adult-sized donor kidney was transplanted in an orthotopic fashion. The donor renal artery was anastomosed end-to-side to the abdominal aorta. The donor renal vein was anastomosed to the suprahepatic inferior vena cava (IVC). To achieve adequate vessel length a ringed Gore-Tex graft (10 mm) was interposed as a vascular conduit attaching the prosthetic vascular graft end-to-side to the

suprahepatic IVC and end-to-end to the orifice of the donor renal vein. The urinary tract was reconstructed via an end-to-end ureteroureterostomy.

RESULTS

The kidney graft functioned immediately with appropriate diuresis and a 24-hour creatinine decline to 1 mg/dl. Postoperative anticoagulation included heparin for the first 3 days followed by dual platelet anticoagulation (aspirin, clopidogrel). Apart from an abdominal wall hematoma that required surgical evacuation the postoperative course was uneventful. The girl was discharged with an eGFR of 127 ml/min/1.73m^2 (0.39 mg/l creatinine).

CONCLUSION

We herein report the first case of a prosthetic vascular graft interposition in kidney transplantation to lengthen a donor renal vein and subsequently achieve adequate venous outflow in a patient with congenital vascular anomalies.

Basic Science

62

Eight micro-RNAs show differential expression twelve months after lung transplantation: Preliminary data from a high throughput technology

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BACKGROUND

Over the last years, the use of alemtuzumab as induction agent and the consequent reduction in CNI led to an improvement of the long-term outcomes after lung transplantation. Alemtuzumab leads to a long-lasting depletion of several immune cell subsets, thereby reducing the alloresponse against the newly implanted allograft. Until now, the mechanisms underlying immune reconstitution after alemtuzumab induction therapy are still unknown. We hypothesized that miRNAs could potentially play a fundamental role.

METHODS

We prospectively included recipients, who received a primary lung transplantation between 2018 and 2021 in our institution. All patients received alemtuzumab induction therapy followed by low-dose CNI-based immunosuppression. Plasma samples were collected at different timepoints including pre-transplant and 12 months after the procedure. The FirePlex miRNA Immunology-V2 panel (Abcam) was selected for multiplex analysis of 68 miRNAs in each sample. Samples were lysed prior to performing the assay according to the FirePlex panel protocol. Quantification was performed using CytoFLEX S Flow Cytometer (Beckman Coulter).

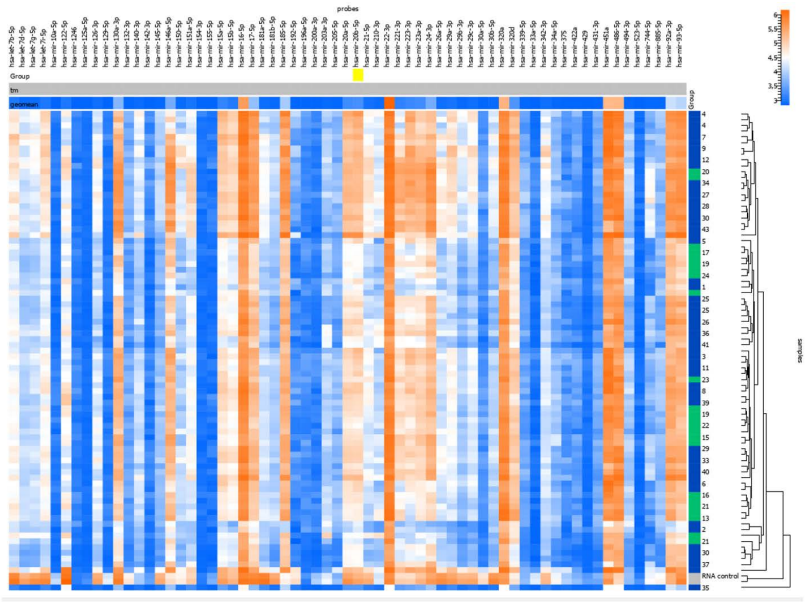

FIGURE 1

RESULTS

A total of 31 baseline pre-transplant samples and 12 follow-up samples after 12 months were analyzed. Eight miRNAs were found differentially expressed 1 year after transplantation: hsa-miR-20b (fold-change 1.98, p<0.001), hsa-miR-93 (fold-change: 2.04, p<0.001), hsa-miR-223 (fold-change: 2.75, p<0.001), hsa-miR-17 (fold-change: 1.96, p<0.001), hsa-miR-20a (fold-change 2.02, p=0.010), hsa-miR-29b (fold-change: 2.01, p=0.015), hsa-miR-744 (fold-change: 2.5, p=0.018), hsa-miR-21 (fold-change 2.1, p=0.049).

CONCLUSIONS

Our preliminary data show that 8 miRNAs involved in immune cell subsets development are differentially expressed in a cohort of lung transplant recipients after alemtuzumab induction therapy. Inclusion of a larger cohort is necessary to confirm our results.

Thorax

63

Single coronary ostium in a donor heart – Case report of successful heart transplantation

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BACKGROUND

Single coronary ostium is a very rare coronary anomaly with an reported incidence of 0.024% in angiographic series. Due to the progress in organ donor evaluation, coronary angiography is available in more and more donor hearts identifying patients with congenital anomalies.

CASE REPORT

We present a case report of a 54 year old female organ donor suffering from subarachnoid haemorrhage. Echocardiography revealed normal left and right ventricular function. Due to the history of strong smoking coronary angiogram was performed. Right coronary ostium could not be intubated selectively but there was clear evidence of a posterior descending artery arising from the left circumflex. An interdisciplinary discussion with heart failure surgeons and cardiologist was conducted evaluation the risk of suboptimal distribution of organs preservation due to this anatomic variance. There was concern that the right ventricle might suffer from ischemia as a boundary zone of the left coronary perfusion. In clear contrast to this risk evaluation was the normal echocardiographic results and the absence of cardiac events in the donor's past medical history. Therefore, the donor heart was accepted for a 61 year old male patient in high urgency status due to ongoing hypoperfusion

syndrome based on ischemic cardiomyopathy. Organ procurement went uneventful and inspection of the explanted donor heart clearly identified a prominent right coronary artery. Following an ischemic time of 209 minutes the cardiac performance was excellent and the patient could be discharged three weeks after transplantation.

CONCLUSIONS

Coronary anomalies are rare but will be of interest if coronary angiography is included in donor evaluation more often. We conclude that an atypical rise of the right coronary artery from the left without evidence of prior coronary ischemia, is associated with good graft outcome and should therefore not be considered contraindication for organ acceptance.

64

Constructive pericarditis after lung transplantation

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BACKGROUND

Constrictive pericarditis is a rare long-term postoperative complication after lung transplantation. The reported rate from 0,4% in the literature is restricted to small case studies at individual institutions. The incidence of constrictive pericarditis after lung transplant may be underestimated due to the subtlety of the clinical findings. We present our institutional experience with constrictive pericarditis after lung transplant in an effort to focus more awareness of this diseases entity.

METHODS

From January 2011 to June 2022, 1224 patients underwent lung transplantation at the Medical University of Vienna. An institutional database was queried to identify incident patients and determine baseline clinical data. At a median of 12,13 months (interquartile range = 2-36 mo), 7 patients (0.57%) developed constrictive pericarditis. Simple descriptive statistics were used to describe cohort characteristics and identify variables associated with constrictive pericarditis after lung transplantation.

RESULTS

The indication for transplantation at index operation was idiopathic pulmonary fibrosis in 4 of 7 patients (1.5% of the 262 restrictive lung disease patients transplanted in the same time period) and COPD in 3 patients. All 7 patients presented with worsening dyspnea and pleural effusions. Echocardiography and cardiac MRI confirmed constrictive physiology in all cases. Five patients

underwent total pericardiectomy via sternotomie and 2 patients were managed with pericardfenestration and diuretic therapy. Low perioperativ mortality and improved spirometry, kidney funktion, quality of life and survival were observed.

CONCLUSIONS

Diagnosis of constrictive pericarditis should be considered in patients with new-onset right-sided heart failure symptoms or recurrent pleural effusions. Pericardiectomy is a safe and effective treatment for posttransplant constrictive pericarditis.

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