
ESOT
18th - 20th
October 2023
Transplant
International
AUSTRO
TRANSPLANT
2023
Austrotransplant 2023
Transfusion und Genetik
Eisenstadt
Transplant International
frontiers

Introduction

Ebook ISBN: 978-2-8325-3587-5; 9782832535875
DOI: 10.3389/978-2-8325-3587-5

Citation - Georg Györi, Julia Jedamzik, Jakob Eichelter and David Pereyra. (2023). Austrotransplant 2023, 36. Tagung der Österreichischen Gesellschaft für Transplantation, Transfusion und Genetik.

Ladies and Gentlemen
Dear colleagues,

It is with great pleasure that we cordially invite you to the upcoming Austrotransplant, which will take place from October 18th to 20th, 2023 in Eisenstadt.

As a leading platform for the exchange of knowledge and experiences in the field of transplantation medicine, the conference has established itself over the last decades as an important event for researchers, clinicians, nurses and everyone interested in the progress of organ donation and transplantation.

This year Austrotransplant has an inspiring theme: "Innovation and collaboration: overcoming boundaries, changing lives". We will look intensively at the latest developments, challenges and solutions in transplant medicine, with a strong focus on innovation and the importance of collaboration.

Eisenstadt, the capital of Burgenland, is the perfect location for this unique conference. The city is known for its rich history, impressive architecture and picturesque surroundings. With the Eisenstadt Congress Center we offer you a modern and comfortable event venue that offers ideal conditions for professional exchange, discussions and lectures.

In addition to the scientific sessions, Austrotransplant will also offer a high level evening program and there will be sufficient time for informal discussions and the exchange of ideas in order to create an inspiring atmosphere.

We hope that Austrotransplant 2023 will offer you new perspectives and exciting discussions. Join us to push the boundaries of transplant medicine and to change lives together.

We look forward to welcoming you to Eisenstadt!

Priv. Doz. Dr. George Györi
Dr. Julia Jedamzik
Dr. Jacob Eichelter
Dr. David Pereyra
(for the organization team)

Table of contents

01 - Young Investigator Awards

Oral Presentation

01

Prediction Of Humoral And Cellular Immune Response To COVID-19 mRNA Vaccination By TTV Load In Kidney Transplant Recipients And Hemodialysis Patients

Marianne Graninger[1#], Julian Stumpf[2,3#], Gregor Bond[4], Irene Görzer[1], David Springer[1], Friederike Kessel[2], Hannah Kröger[2], Kerstin Frank[5], Torsten Tonn[6,7], Christian Hugo[2,3†], Elisabeth Puchhammer-Stöckl[1†*]

[1]Center for Virology, Medical University of Vienna, Vienna, Austria

[2]Medizinische Klinik und Poliklinik III, Universitätsklinikum, Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[3]KfH-Nierenzentrum Dresden, Dresden, Germany

[4]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria

[5]Institut für Transfusionsmedizin Plauen, DRK-Blutspendedienst Nord-Ost gemeinnützige GmbH, Plauen, Germany

[6]Institute for Transfusion Medicine, German Red Cross Blood Donation Service North-East, Dresden, Germany

[7]Faculty of Medicine Carl Gustav Carus, Transfusion Medicine, Technische Universität, Dresden, Germany

[#] These authors have contributed equally to this work and share first authorship.

[†] These authors have contributed equally to this work and share last authorship.

Background

Immunosuppressed individuals such as kidney transplant recipients (KTR) and hemodialysis patients (DP) show impaired immune responses to COVID-19 vaccination. Plasma Torque Teno Virus (TTV) DNA load is used as surrogate for the individual degree of immunosuppression. We now assessed the association of TTV load at time of COVID-19 vaccination with humoral and cellular immune response rates to vaccination in KTR, DP, and healthy medical personnel (MP).

Methods

A total of 100 KTR, 115 DP and 54 MP were included. All were SARS-CoV-2 seronegative at the time of vaccination with either BNT162b2 or mRNA-1273. Plasma TTV loads were assessed at the time of first vaccination. After two-dose vaccination, seroconversion (*de novo* detection of SARS-CoV-2 S1-IgA and/or IgG) was determined. In addition, cellular responses as assessed by interferon γ release and neutralizing antibodies were assessed in a subset of participants. ROC analyses were performed to define TTV load cut-offs predicting specific immune responses to vaccination.

Results

Plasma TTV loads at the time of first vaccination were negatively associated with seroconversion after two-dose vaccination in KTR (OR 0.87, 95% CI 0.76-0.99). TTV loads were significantly lower in KTR who developed humoral and cellular immune responses to vaccination compared to non-responders (p=0.0411 and 0.0030, respectively). Of patients with TTV loads above 10^6 copies/ml, none developed cellular immune responses against SARS-CoV-2, and only 2 of 17 (12%) seroconverted in response to vaccination.

Conclusion
Plasma TTV loads at the time of first vaccination in immunosuppressed individuals may be useful to predict individual vaccine-specific immune responses.

02

Mitochondrial Flavin Mononucleotide Measured During Hypothermic Machine Perfusion Can Predict Graft Dysfunction After Liver Transplantation

Jule Dingfelder, Dagmar Kollmann, Laurin Rauter, Effimia Poumpouridou, David Pereyra, Sertac Kacar, Gerd Silberhumer, Andreas Salat, Thomas Soliman, Gabriela Berlakovich, Georg Györi

Medical University Vienna, Vianna

Background
Flavin mononucleotide (FMN) is a respiratory chain compound that is released from complex I during anoxia, reflects directly on mitochondrial preservation damage and the remaining metabolic capability of the cell. Its release into the perfusate at perfusion start is the base of its reliable prediction of graft dysfunction. FMN is currently the only option for organ assessment during hypothermic oxygenated machine perfusion (HOPE).

Methods
FMN was measured during 50 hypothermic perfusions and correlated with standard laboratory and follow-up parameters including liver transaminases, need for dialysis, complications according to Clavien-Dindo classification(1), early allograft dysfunction (EAD) as defined by the Olthoff criteria(2), duration of ICU stay, biliary complications, graft and patient survival. FMN was measured by fluorescence spectroscopy, levels were displayed in artificial units and a standard curve was generated so levels could be displayed as concentrations.

Results
The area under the curve (AUC) for prediction of EAD at 5 minutes of perfusion was 0.74, the identified cut-off was at 10.65 ng/dL (sensitivity of 87%, specificity of 63%). FMN levels at 5 minutes were higher in grafts whose recipients had a higher morbidity, especially in cases with recipient death ($p<0.001$), graft loss ($p=0.007$), as well as trends in development of other complications. For prediction of patient survival, AUC at 5 minutes was 0.921. The determined cut-off of 23.5ng/dL (sensitivity of 86 % and specificity of 95 %) was used to discriminate between high and lower risk cases. In the low-risk group, 97% of recipients survived whereas only 25% survived in the high-risk group.

Conclusions
FMN allows for excellent risk stratification in liver grafts during HOPE. Categorization in risk groups helps to identify grafts with an especially high risk for higher morbidity, graft loss and even death. The threshold identified in this study enables reliable prediction of patient survival as early as 5 minutes after perfusion start. In addition, FMN levels correlate to increasing rates of complications and higher morbidity underlining the relevance and potential of FMN in hypothermic perfusion viability testing.

References

[1] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.

[2] Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl. 2010;16(8):943-9.

03

Custodiol-N versus Custodiol: Results From A Prospective Randomized Single Blind, Multicenter Phase III Trial In Patients Undergoing Heart Transplantation

Emilio Osorio-Jaramillo[1], Christoph Knosalla[2], Jan Gummert[3], Gabor Szabo[4], Franziska Wittmann[1], Ruhi Yeter[2], René Schramm[3], Johannes Goekler[1], Felix Hennig[2], Michiel Morshuis[3], Andreas Zuckermann[1], Arezu Aliabadi-Zuckermann[1]

[1] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria
[2] Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Berlin, Germany
[3] Clinic for Thoracic and Cardiovascular Surgery, Heart and Diabetes Centre North Rhine-Westphalia, Ruhr-University Bochum, Bad Oeynhausen, Germany
[4] Department of Cardiac Surgery, Middle German Heart Centre, University Hospital Halle (Saale), Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany

Background
Custodiol is a well-established preservation solution in solid-organ-transplantation. Custodiol-N, a novel Custodiol-based solution, includes iron chelators to reduce oxidative injury and L-arginine to improve endothelial cell function. Earlier results in coronary artery bypass-surgery, showed good cardiac protection without any safety concerns. Our aim was to evaluate safety and efficacy of Custodiol-N to preserve donor hearts for cardiac transplantation.

Methods
A prospective randomized, single-blind multicenter non-inferiority trial was conducted at three centers in Austria and Germany. 105 patients were randomized to Custodiol-N (n=53) or Custodiol (n=52). Recipients awaiting their first transplant from ≥18 and ≤65 years were included. Primary endpoint was creatine kinase-myocardial band (CK-MB) peak value from 4-168 hours after opening of the aortic cross-clamp, with a 30% non-inferiority margin. Secondary endpoints included patient and graft-survival, incidence of primary graft failure and ICU length-of-stay. Endpoints were analyzed in as-treated and per-protocol populations. Follow-up for each patient was 12 months.

Results
Donor age (39.4±12.7 vs 45.1±11.6; p=n.s.) and ischemic times (206.3±49.4 vs. 220.6±65.6; p=n.s.) were comparable between Custodiol-N and Custodiol. CK-MB peak values were lower with Custodiol-N vs Custodiol (136.3±70.7 vs 178.2±202.4 U/L; p<0.0001 for non-inferiority of Custodiol-N by 30%, in the per-protocol and as-treated-population). In a parameter estimate calculation the relative CK-MB level of Custodiol-N compared to Custodiol was 0.764 (95%CI [0.627-0.931], p=0.0076) in the as-treated-population, showing superiority of Custodiol-N. Survival was comparable at 30-days and 1-year (Custodiol-N: 100%, 88.7%; Custodiol: 98.1%, 90.4%, p=0.83). Primary graft failure was 11.3% for Custodiol-N vs 21.5% for Custodiol (p=0.19). Median ICU length-of-stay was 8 (IQR 5-11) in Custodiol-N vs 11 days in Custodiol (IQR 6-19; p=0.13). Numbers of possibly related adverse events were similar (Custodiol-N: n=3, Custodiol: n=4).

Conclusions
Custodiol-N is safe and provides similar cardiac protection as the established Custodiol solution. Both solutions were safe to use in clinical heart transplantation. (Funded by Dr. F. Köhler Chemie GmbH; ClinicalTrials.gov number, NCT02869022)

04

6MWD As Predictor For Long Term Survival After Lung Transplantation In Patients With ILD

Panja M. Boehm[1], Elias Kampschulte[1], Sophia Auner[1], Caroline Hillebrand[1], Peter Jaksch[1], Konrad Hoetzenecker[1], Christopher Lambers[1], Alberto Benazzo[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background
The 6-minute walking distance (6MWD) is a well-established predictor for mortality in patients with interstitial lung disease (ILD). In this study, we aimed to investigate the 6MWD as a possible predictor for long-term survival after double lung transplantation (LTx) in patients with ILD.

Methods
A single-center, retrospective data analysis in patients with ILD undergoing LTx was conducted. All ILD patients transplanted between 2013 and 2022 with a pretransplant 6MWD measurement were included. Patients were divided into quintiles according to their 6MWD (QI: 0-10m; QII: ≥10-70m; QIII: 71-230m; QIV: 231-360m; QV: 361-600m) and compared to short- and long-term survival after LTx. Statistical calculations included Kaplan-Meier survival and Cox proportional hazard models.

Results
A total of 196 patients were included (68% males) with a median age of 56 year. The survival probability after 1 year was 78.1% and after 5 years 71.3%, with significant differences between the quintiles (log-rank test p=0.037). The 5-year survival probability for the five groups was: QI: 50.2% (95% CI 29%-71%); QII: 81.8% (95% CI 66%-98%); QIII: 64% (95% CI 44%-84%); QIV: 78.3% (95% CI 61%-95%); QV: 82.4% (95% CI 67%-98%). In contrast, lung function parameters and lung allocation score could not be identified as predictors for survival.

Conclusions
The collected 6MWD of patients with ILD at the time of listing showed a significant association with the survival after LTx. These findings may impact the pre-transplant management of patients with ILD.

05

CD8+CD3- Cells Are Critical For Treg Mediated Humoral Tolerance

Romy Steiner[1,2,3], Anna M. Weijler [3], Moritz Muckenhuber [3], Thomas Wekerle [3], Jonathan Sprent [4], Nina Pilat [2,1,3]

[1] Center for Biomedical Research and Translational Surgery, Medical University of Vienna, Vienna, Austria
[2] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria
[3] Department of General Surgery, Medical University of Vienna, Vienna, Austria
[4] Immunology Division, Garvan Institute of Medical Research, Sydney, Australia

Background
Recently, our group achieved significant extension of allograft survival in a murine model of skin transplantation by selective *in vivo* expansion and activation of Tregs using interleukin-2 (IL-2) coupled to a specific antibody against IL-2 (IL-2cplx). Here, we aimed to investigate the effect of alloreactive CD8+ 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 along with fully mismatched BALB/c skin grafts. Indicated groups were treated with different anti-CD8 mAbs, depleting either all CD8+ populations (anti-CD8a) or specifically CD8+ T cells (antiCD8b). To dissect the mechanisms of allograft rejection in this model, donor-specific antibody (DSA) development, *in vitro* T cell alloreactivity and graft infiltrating leucocytes were assessed.

Results
IL-2cplx therapy in combination with rapamycin and anti-IL-6 mAb significantly prolonged survival of fully mismatched skin grafts. Importantly, IL-2cplx based therapy prevented humoral rejection and development of DSAs. Although, CD8 depletion did extend skin graft survival, CD8a (but not CD8b) depletion prevented humoral tolerance. Furthermore, CD8a depletion resulted in the increase of donor-responsive Th2 cells as well as graft infiltrating recipient CD4+ effector T cells by POD20. In addition, T follicular helper and T follicular regulatory cell levels were increased within the spleen in the absence of CD8 alloreactivity compared with non-depleted/fully mismatched recipients.

Conclusion
IL-2cplx therapy induces humoral tolerance and prevents the development of DSAs. Depletion of pan-CD8 cells using anti-CD8a mAb does not further prolong skin graft survival but leads to donor-specific antibody formation whereas CD8b depletion did not restore humoral alloreactivity, suggesting a critical role of CD8+ non-T cells in the sustained prevention of recipient sensitization. Moreover, proinflammatory processes are thought to be a consequence of CD8a depletion, as increased migration of recipient CD4+ effector cells into skin grafts and elevated donor-responsive Th2 cells were observed.

06

Adoptive Cell Transfer For Allergen Specific Tolerance Induction

Lisa Prickler[1], Anna Marianne Weijler[1], Verena Kainz[1], Romy Steiner[1], Konstantinos Mengrelis[1], Jasmin Mucha[1], Bernhard Kratzer[2], Ulrike Baranyi[3], Nina Pilat[1], Barbara Bohle[4], Winfried Franz Pickl[2], Rudolf Valenta[4,5,6,7], Birgit Linhart[4], Thomas Wekerle[1]

[1] Department of General Surgery, Division of Transplantation, Medical University of Vienna, Vienna, Austria
[2] Department of Cellular Immunology and Immunohematology, Institute of Immunology, Medical University of Vienna, Vienna, Austria
[3] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria
[4] Department of Pathophysiology and Allergy Research, Division of Immunopathology, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, 1090 Vienna, Austria
[5] National Research Centre (NRC), Institute of Immunology Federal Medical-Biological Agency (FMBA) of Russia, 115478 Moscow, Russia
[6] Laboratory for Immunopathology, Department of Clinical Immunology and Allergy, Sechenov First Moscow State Medical University, 119435 Moscow, Russia
[7] Karl Landsteiner University of Health Sciences, 3500 Krems, Austria

Background
Hematopoietic cell transplantation has primarily been investigated as an approach of inducing tolerance in organ transplantation, but this concept could potentially be applied to other immune-mediated disorders. A protocol for allergen-specific tolerance based on the transplantation of bone marrow cells which were retrovirally transduced to express the allergens has recently been established. Transgenic BALB/c mice that express Phl p 5 on the cell surface were developed as cell donors. In this work, we examined whether recipient mice may develop tolerance to Phl p 5 by receiving purified cell populations obtained from Phl p 5+ mice.

Methods
Purified CD19+ B cells, from Phl p 5-transgenic mice, were transplanted to recipient mice (BALB/c, 8–10 weeks), pretreated with anti-CD40L antibody and rapamycin. Flow cytometry was used to track the chimerism levels in blood throughout the experiment. Following three subcutaneous sensitizations with Phl p 5 and a control allergen, Bet v 1, tolerance was evaluated by ELISA in serum samples. To assess the allergen-induced lung inflammation, whole body plethysmography (WBP) was performed.

Results
Chimerism levels were induced in the recipient mice for up to 2-3 months after receiving purified CD19+ B cells. In contrast to untreated but sensitized mice, chimeric mice did not exhibit a Phl p-5-specific IgE and IgG_1 antibody response. Since Bet v 1-specific antibody responses were observed in all mice groups, tolerance induction was specific for Phl p 5. In contrast to sensitized animals, CD19+ B cell-treated mice showed unharmed lung function based on WBP.

Conclusions
We showed that transferring Phl p 5-expressing B cells can result in chimerism induction and allergen-specific tolerance for up to 14 weeks. These results highlight how hematopoietic cell transplantation may be used to treat a variety of immunological conditions by promoting tolerance.

07

Perioperative IL-6 Blockade Promotes Intra-Graft Regulation And Prevents Costimulation-Blockade Resistant Rejection

Moritz Muckenhuber[1], Konstantinos Mengrelis[1], Anna Marianne Weijler[1], Romy Steiner[1], Verena Kainz[1], Heinz Regele[2], Sophia Derdak[3], Anna Kubetz[1] and Thomas Wekerle[1]

[1] Medical University of Vienna, Dept. of General Surgery, Div. of Transplantation
[2] Medical University of Vienna, Dept. of Pathology
[3] Medical University of Vienna, Core Facilities

Background
The use of costimulation blockade (CTLA4Ig/belatacept) in transplantation remains limited by an increased incidence of T cell-mediated rejection, which also persists after induction therapy with anti-thymocyte globulin (ATG). Herein, we investigate why ATG fails to prevent costimulation blockade-resistant rejection and how this barrier can be overcome.

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, cardiac allografts were explanted 2 weeks after transplantation to assess intra-graft regulation via RNA sequencing and flow cytometry of graft infiltrating leukocytes (GIL).

Results
The addition of ATG induction to CTLA4-Ig maintenance significantly extended the median survival time of cardiac allografts (CTLA4-Ig=36 days, ATG/CTLA4-Ig=80 days). Yet, most of these grafts showed early signs of TCMR and half of the grafts were eventually lost during follow up. While ATG induction improved the balance between Tregs and effector T cells in the peripheral compartment, it had no such effect within cardiac allografts but rather induced a pro-inflammatory cytokine environment. Neutralizing IL-6 alleviated intragraft inflammation, increased intragraft Treg frequencies long-term, and enhanced intragraft IL-10 and Th2 cytokine expression. Combining ATG with IL-6 blockade led to 100% long-term heart graft survival under CTLA4Ig therapy with preserved graft histology.

Conclusion
IL-6 blockade prevents costimulation blockade-resistant rejection in combination with ATG, thereby eliminating a major impediment to clinical use of costimulation blockers in transplantation.

Targeting DSA-Secreting Bone Marrow Long-Lived Plasma Cells With CTLA4-Ig

M. Muckenhuber[1], K. Mengrelis[1], AM. Weijler[1], T. Kreuzbauer[1] and T. Wekerle[1]

[1] Medical University of Vienna, Dept. of General Surgery, Div. of Transplantation

Background
The importance of bone marrow resident plasma cells for long-lasting humoral immunity has been highlighted in several models for vaccination and infectious diseases. To which extent this cell population is also responsible for upholding a sustained humoral response against (donor)-HLA antigens in the transplant setting remains unclear. We therefore sought to identify and characterize DSA-secreting plasma cells to provide insight into their underlying biology.

Methods
C57BL/6 were grafted with a fully mismatched balb/c cardiac allograft without any immunosuppression. DSA were assessed via flow crossmatch and MHC-specific ELISA. Spleen and bone marrow cells of cardiac allograft

recipients isolated 20 weeks post transplantation were cultured separately for 48h. DSA within the cell culture supernatants were measured via flow crossmatch. Splenic and bone marrow plasma cells were quantified in transplant recipients and age-matched controls using flow cytometry. Selected groups of cardiac allograft recipients were treated with CTLA4-Ig for 6 weeks (50mg/kg on days 0, 4, 14 and 28) starting 10 weeks after transplantation (i.e. 9 weeks after cardiac allograft rejection).

Results

Serum IgG DSA persisted for up to 15 months after rejection of fully mismatched heart allografts (BALB/c to B6). We found that donor MHC-specific antibodies, in this setting, were exclusively secreted by bone marrow (BM) resident long-lived plasma cells (LLPC; $TACI^+$ $CD19^-$). LLPC were phenotypically distinct from short-lived BM plasma cell populations ($TACI^-$ $CD19^-$ and $TACI^+$ $CD19^+$) and displayed the highest surface expression of CD28. Therefore, starting 10 weeks after transplantation (when DSA levels were stable and depending on LLPC), we treated cardiac allograft recipients with CTLA4-Ig. A 6-week course of CTLA4-Ig significantly lowered DSA levels and specifically decreased BM LLPC compared to an untreated control group conducted in parallel.

Conclusion

Bone marrow resident LLPC represent a crucial source of late DSA that can be targeted with costimulation blockade.

08

The Complex Interplay Of T Cell Depletion With ATG And Adoptive Treg Transfer In Mice

Anna Marianne Weijler[1], Moritz Muckenhuber[1], Lisa Prickler[1], Verena Kainz[1], Anna-Lena Pirker[1], Thomas Wekerle[1]

[1] Medical University of Vienna, Department of General Surgery, Division of Transplantation, Vienna, Austria

Background

In the transplant setting, adoptive cell therapy for induction of a pro-tolerogenic state is on the rise. T cell depletion with the use of ATG before the transfer of regulatory T cells (Tregs) is thought to increase the efficacy of the transferred cell product. Nevertheless, lymphodepletion is followed by increased homeostatic proliferation, release of cytokines and development of antibodies against the ATG compounds itself. Reversely, concomitant immunosuppressants potentially effect these processes. Here we investigated this complex interplay between these simultaneous events which currently is poorly understood.

Methods

C57BL/6 mice were injected once with 18mg/kg ATG and either CTLA4Ig (10mg/kg, d0, 4, 14, 28), rapamycin (1mg/kg, every other day), prednisolone (3mg/kg, d0) or $0.5x10^6$ CD45.1 Tregs (d4). Homeostatic T cell proliferation was determined via Ki-67 using Flow Cytometry. Furthermore, the presence of free ATG in serum was measured via a binding assay to isolated lymphocytes and the production of antibodies against ATG were measured using ELISA.

Results

Free ATG in serum was cleared fast, peaking on day 1 after ATG administration and could not be detected after day 4. Notably**,** no changes were seen in levels of homeostatic proliferation when ATG was combined with either CTLA4Ig, rapamycin or prednisolone. Treg levels were significantly higher when rapamycin was added and led to an increased CD4:CD8 ratio. Transferred CD45.1 Tregs were found in secondary lymphoid organs, but not in blood, 20 days after transfer and showed similar characteristics to recipient CD45.2 Tregs. Interestingly, treatment with CTLA4Ig or rapamycin prevented the production of ATG antibodies.

Conclusion

Administration of ATG together with rapamycin could help to increase the pro-tolerogenic state by increasing Treg levels. The absence of anti-ATG antibodies through additional treatment with CTLA4Ig or Rapamycin might lead to a prolonged presence of free ATG in serum, which must be considered when combined with adoptive cell therapy.

02 - Liver TX

09

Systemic Doxorubicin-Based Chemotherapy In Liver Transplantation For Hepatocellular Cancer: 20-year Outcomes Of A Randomized Controlled Trial

Jakob Mühlbacher[1], Benno Lickefett[1], Klaus Walenta[1], Jarina Fabriova[1], Alexander Kainz[2], Herwig Pokorny[3], Gabriela A. Berlakovich[1]

[1]Department of Surgery, Medical University of Vienna, Vienna, Austria
[2]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[3]Department of Surgery, Franziskus Spital, Vienna, Austria

Background
A prospective, single-center, randomized, controlled, open-label clinical phase II trial to evaluate administration of doxorubicin-based chemotherapy to patients with hepatocellular carcinoma (HCC) undergoing liver transplantation (LT) as treatment showed no improvement in 5-year survival. This study aims to analyse follow-up data from this randomized controlled trial.

Methods
We report the 20-year follow-up of the patients based on the original study population. Data were collected at scheduled outpatient visits and endpoint data were drawn from a national registry, hospital and autopsy reports. Cases were reclassified and compared based on given pathology reports according to current selection criteria. Survival analysis was performed using the Kaplan–Meier method and a Cox regression model was used for multivariable analysis. Causes of death were compared using the chi-square test.

Results
In the original trial, 62 patients were allocated to either receive LT with chemotherapy (n = 34) or LT alone (n = 28). Even after 20 years, overall survival did not significantly differ between the respective groups (4% vs. 17%; p = 0.195). HCC recurrence was an independent predictor of patient survival in Cox regression analysis (hazard ratio 2.95; 95% confidence interval 1.41–6.16; p = 0.004). Complications after LT (p = 0.562) and causes of death did not significantly differ between groups (p = 0.987). HCC recurrence was the most common cause, followed by cardiac causes and occurrence of de novo malignant disease.

Conclusions
Systemic chemotherapy with doxorubicin did not have an impact on survival in the 5-year or 20-year analyses.

10

Von Willebrand Factor Antigen Facilitates Decision Making Prior To Surgical Treatment Of Patients With Hepatocellular Carcinoma

David Pereyra*[1;2], Anna Kern[2], Jule Dingfelder[1], Sertac Kacar[1], Nikolaus Becker[1], Lindsey Gregory[3], Aidan Mullan[3], Jonas Santol[4], Thomas Gruenberger[4], Rory Smoot[3], Sean Cleary[3], Mark Truty[3], Susanne Warner[3], Cornelius Thiels[3], Michael Kendrick[3], Patrick Kamath[5], Gabriela A. Berlakovich[2], Julie Heimbach[6], Georg Gyoeri[2], Patrick Starlinger[1;5]

[1] Medical University of Vienna, Department of General Surgery, Division of TransplantationSurgery, Vienna, Austria
[2] Medical University of Vienna, Department of General Surgery, Division of Visceral Surgery, Vienna, Austria
[3] Mayo Clinic Rochester, Department of Surgery, Division of Hepatobiliary and Pancreas Surgery, Rochester, Minesota, United States
[4] Clinic Favoriten, HPB center Vienna Health Network and Sigmund Freud Private University, Department of Surgery, Vienna, Austria
[5] Mayo Clinic Rochester, Department of Gastroenterology and Hepatology, Rochester, Minnesota, United States
[6] Mayo Clinic Rochester, Department of Transplantation Surgery, Rochester, Minnesota, United States
* Presenting author

Background

Potential treatment modalities for hepatocellular carcinoma (HCC) are widely varied. Current guidelines aim to clarify patient selection for liver resection (LR) or transplantation (LTx). Both modalities carry significant risk of adverse outcomes. We previously reported on von Willebrand factor antigen (vWF-Ag) as predictor of post-hepatectomy liver failure (PHLF) and mortality on the waiting list for LTx. Here, we aim to explore vWF-Ag as a tool for surgical decision-making in patients with HCC.

Methods

Patients with HCC within Milan criteria and undergoing LR or listed for LTx at Medical University of Vienna and Mayo Clinic Rochester between 2004 and 2022 were included. Previously evaluated cut-offs at 182% and 291% vWF-Ag were used to define low- (≤182%), intermediate- (183%-291%) and high-risk (>291%) groups. Clinical course and overall survival (OS) were prospectively documented.

Results

443 patients were included: 106 underwent LR, 337 were listed for LTx, 199 underwent LTx. Intermediate- and high-risk patients undergoing LR developed higher incidences of PHLF (low=4.0%, intermediate=27.5%, high=53.3%, p<0.001). OS after LR was significantly reduced in these cohorts (median [months]: low=95.5, intermediate=46.7, high=13.7, p=0.006; Fig.1A). High levels of vWF-Ag were further associated with reduced survival on the waiting list for LTx (p=0.01; Fig.1B). Yet, post-LTx OS was comparable between the defined risk groups (median [months]: low=not reached, intermediate=130.4, high=116.6, p=0.343; Fig.1C). Similar results were observed for OS from listing (median [months]: low=108.7, intermediate=131.8, high=90.0, p=0.390; Fig.1D).

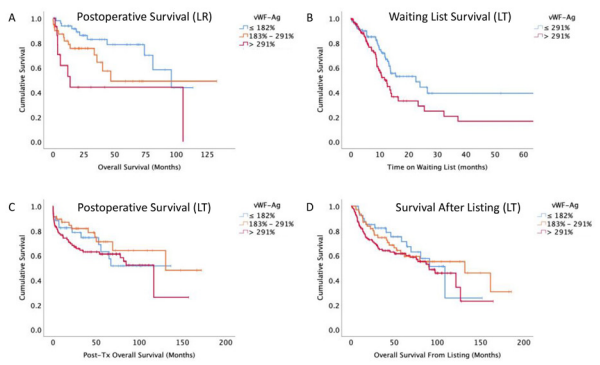

Figure 1

Conclusion

We conclude that vWF-Ag can optimize preoperative decision-making in HCC patients. Patients with HCC displaying high vWF-Ag pare at increased risk for PHLF and reduced OS and might hence not benefit from LR. However, while post-LTx outcome does not differ between vWF-Ag risk groups, high vWF-Ag is connected to early mortality while awaiting LTx. Accordingly, this subgroup of patients may benefit from a vWF-Ag risk adjusted LTx listing process.

11

Influence Of Prophylactic Mesh Implantation In Liver Transplantation On The Occurrence Of Incisional Hernia

Shahdy Al-Sharafy[1], James Waha[1], Thomas Auer[1], Helmut Müller[1], Daniela Kniepeiss[1]

[1]Department of General, Visceral and Transplant Surgery, Transplant Center Graz, Medical University Graz

Background

Incisional hernia is a common complication after liver transplantation (LT). The aim of this study was to evaluate whether the prophylactic implantation of a bioresorbable mesh during LT can reduce the incidence of incisional hernia.

Methods
From January 2018 to February 2022, patients with LT were included in the study. Exclusion criteria were combined transplantations, revision after LT, prior abdominal surgery and existing abdominal wall hernia (except hernia umbilicalis). In patients of the study group, a monofilament, resorbable (12-18 months) synthetic mesh (Phasix) was prophylactically implanted during transplantation in onlay technique. In the control group, the standard abdominal wall closure was performed without mesh plastic. The primary endpoint was the occurrence of an incisional hernia within 1 year after transplantation.

Results
A total of 40 patients were included in the study, 17 (42.5%) in the study group and 23 (57.5%) in the control group. In the study group, one patient (5.8%) had a small (diameter 2 cm) incisional hernia. In the control group there were 4 patients (17.4%) with incisional hernia (diameter 2.5 - 5 cm) within the first postoperative year. In the study group, there was no wound infection or wound healing disorder due to the mesh implantation, one patient had a seroma. In the control group, two patients had a wound infection.

Conclusions
The incidence of incisional hernia was lower in the study group with prophylactic mesh implantation than in the control group without prophylactic mesh implantation. In addition, the diameter of the hernia was larger in the control group than in the study group. The mesh was well tolerated in patients after liver transplantation. In summary, prophylactic mesh implantation in liver transplantation seems to reduce the risk of incisional hernia with a low risk of complications.

03 - Liver TX: Machine Perfusion

12

The Value Of Hyperspectral Imaging During Long-Term Normothermic Machine Perfusion Of The Liver

Magdalena Bordt[1,2], Christina Bogensperger[1,2], Margot Fodor[1,2], Gabriel Putzer[2,3], Simon Mathis[2,3], Judith Martini[2,3], Fabian Scherbauer[1,2], Nikolas Schmidbauer[1,2], Julia Hofmann[2], Andras Meszaros[1,2], Theresa Hautz[2], Franka Messner[1,2], Silvia Gasteiger[1,2], Benno Cardini[1,2], Rupert Oberhuber[1,2], Annemarie Weissenbacher[1,2], Bettina Zelger[4], Martin Herrmann[1,2], Dietmar Öfner[1], Stefan Schneeberger[1,2], Thomas Resch[1,2]

[1]Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria
[2]OrganLife, Organ Regeneration Center of Excellence, Innsbruck, Austria
[3]Department of Anesthesiology and Critical Care Medicine, Medical University Innsbruck, Austria
[4]Institute of Pathology, Neuropathology and Molecular Pathology, Medical University of Innsbruck, Innsbruck, Austria

Background
Hyperspectral imaging (HSI) has been proposed as a real-time tool for the analysis of tissue microcirculation and oxygenation. Whereas HSI seems useful during short-term normothermic perfusion (NMP) of livers, its value for long-term NMP remains elusive.

Methods
Livers were retrieved from ten domestic pigs (70-110 kg) and perfused for seven days under normothermic conditions. Every 12 hours, hyperspectral images of the liver parenchyma were acquired. The near-infrared perfusion index (NIR-PI), tissue oxygen saturation (StO2), tissue haemoglobin index (THI) and tissue water index (TWI) were calculated.

Results
11520 HSI values were generated from 120 images. In eight of ten livers, NMP was uneventful for one week. For such, averaged NIR-PI and StO2 values increased significantly after NMP initiation and remained stable thereafter (NIR 0h vs. 24h: 20.5(42;12) vs.52.5(65;40.3); SpO2: 18%(25;13) vs.39%(50;29); all p<0.0001). Similarly, THI decreased (0h vs. day7: 72(82;61) vs.45(57;33); p<0.0001) and TWI remained stable after 24h until day7 (40(45;34) vs.41(49;31)). In line, perfusate lactate declined (0h vs.24h: 40mmol/Lvs.6mmol/L; p<0.002). In two settings, NMP was altered for technical reasons. In a case of arterial air embolism, immediate low NIR-PI, StO2 and high THI values were registered compared to the eight uneventful livers (NIR-PI:0h: 0vs.20.5; day7: 1vs.19; StO2:24h: 11vs18; day7: 9vs.27; p<0.0001; THI:24h: 77vs.63.6; 48h:77.5vs.57.4; all p<0.001, respectively). Contrarily, levels of ALAT/ASAT/LDH or lactate were elevated with delay (lactate day6: 154mmol/L). Likewise, in a case of partial arterial occlusion, lower NIR-PI, THI and TWI values were observed early (NIR-PI:24h: 41vs.50.5; THI: 51vs.60; TWI: 38vs.40; all p<0.01) combined with low StO2 values from day 3 (StO2:72h: 22%vs.30%; p<0.0001) when altered perfusate parameters were noticeable (lactate: 74mmol/L).

Conclusions
HSI represents a promising novel tool for efficient and feasible surveillance of liver perfusion during long-term liver NMP. Since our observations suggest that HSI can indicate microcircuatory changes earlier than conventional perfusate parameters, these findings require further investigation.

13

Dynamic Changes In Markers Of Coagulation And Fibrinolysis During Normothermic Liver Perfusion Might Reflect On Vascular Integrity And Preservation Injury

Jule Dingfelder, Laurin Rauter, David Pereyra, Sertac Kacar, Gerd Silberhumer, Andreas Salat, Zoltan Mathé, Thomas Soliman, Dagmar Kollmann, Gabriela Berlakovich, Georg Györi

Medical University Vienna, Vienna

Background
During normothermic machine perfusion (NMP), thrombocytes and coagulation factors are exclusively derived from the perfused graft. As some factors are synthesized by the liver and the endothelial cells themselves, these dynamics might reflect on their condition. Further, vascular dysfunction and subsequent microembolisms are known pathomechanisms in IRI and ischemic cholangiopathy. Our aim was to investigate coagulatory factor composition during NMP and their **association with liver function and post-transplant outcomes.**

Methods
During NMP of 27 livers, including 21 from extended criteria donors, D-dimer, thrombocytes, van Willebrand factor activity (vWF), factor V activity (FV) and factor XIII activity (FXIII) in perfusate were assessed. Liver and bile duct biopsies were taken before and after perfusion.

Results
Out of 27 grafts that underwent NMP, 18 livers met viability criteria and were transplanted. Median peak perfusate levels were: D-Dimer 3,39 µg/mL (IQR: 2,83-3,38), vWF 6 % (IQR: 5-8), thrombocytes 14 G/L (IQR: 13-27),

FV 17 % (IQR:6-26), FXIII 32 % (IQR:20-39) and bilirubin 0,85 ng/dL (IQR: 0,66-3,31). Thrombocytes, bilirubin and FV increased steadily, FXIII and D-Dimer peaked and decreased afterwards. Out of 11 cases with irregular coagulation parameters, 6 livers were declined for failure to produce bile or clear lactate. The 5 transplanted livers passed our standard viability criteria. Three recipients had an uneventful follow-up until now. One transplanted DCD liver (5,81µg/mL D-Dimer, 96G/L thrombocytes, bilirubin 5,81 ng/dL, vWF 18 %) performed well on the machine but histology analysis afterwards resulted in fibrotic bile ducts in the back-table biopsy, the recipient later developed a biliary leak and biliary CAST syndrome. Another patient with FXIII of 175 % developed a bile duct necrosis. Median follow-up after transplantation was 12 months (IQR: 12-19).

Conclusions

Vascular integrity and thromboembolic events during preservation might be reflected by composition of pro- and anticoagulatory factors. Further, grafts with pathological biopsies presented with high D-Dimer levels during perfusion. Assessment of dynamic changes in coagulation markers during NMP has the potential to significantly enhance viability testing during NMP. Prospective studies are warranted to validate these initial findings.

14

Endothelial Glycocalyx Damage Marker Syndecan-1 Measured During Hypothermic Oxygenated Machine Perfusion Can Predict Early Allograft Dysfunction After Liver Transplantation

Laurin Rauter[1], Dagmar Kollmann[2], Judith Schiefer[2], Marija Spasic[1], Pierre Raeven[2], Jule Dingfelder[1], David Pereyra[1], David Baron[2], Effimia Pompouridou[1], Thomas Soliman[1], Gabriela Berlakovich[1] and Georg Györi[1]

[1]Department of General Surgery, Division of Transplantation, Medical University of Vienna, Vienna, Austria
[2]Department of Anesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria

Background

During liver transplantation, the graft has to endure an ischemic phase and additional injury after reperfusion (IRI), especially mediated by reactive oxygen species (ROS). The endothelial glycocalyx covers the luminal side of the vascular endothelium and regulates vascular permeability, modulates adhesion of leucocytes onto the vascular wall and transduces mechanical shear stress. It is very sensitive to ROS and therefore degraded during graft preservation and reperfusion. Hypothermic oxygenated machine perfusion (HOPE) is a preservation strategy that can reduce IRI-inflicted graft injury compared to static cold storage (SCS). We aimed to measure glycocalyx degradation after HOPE or SCS alone, to evaluate its viability-assessment potential for liver transplantation.

Methods

We measured glycocalyx degradation via ELISA for its main component Syndecan-1, in samples from 77 liver transplant patients. 37 grafts were directly transplanted

after SCS, 40 grafts additionally underwent HOPE with the Organ Assist® perfusion system, prior to liver transplantation.

Results
Sdc-1 concentrations in the graft effluent are significantly lower after HOPE [466 (350-1073)] compared to SCS alone [4011 (3382-4683] (p<0.001). Further, Sdc-1 concentrations regenerate faster towards baseline levels on postoperative day 1 [HOPE: 362 (232-880) vs. SCS: 1017 (637-1900) p<0.001], indicating a shorter glycocalyx shedding period. Regarding viability assessment, Sd1-concentrations in the perfusate were elevated in EAD patients after 60 minutes of HOPE compared to non-EAD patients [429 (260-556) vs. 896 (419-1681) p=0.018]. Additionally ROC-analysis indicated a significant discriminatory value of Sdc-1 concentration after 60 minutes of HOPE regarding the occurrence of EAD with an AUC of 74% (p=0.018, sensitivity 66.7% and specificity 84.6%).

Conclusions
HOPE reduces the duration of glycocalyx shedding, evident by Sdc-1 release in recipient serum after liver transplantation. Sdc-1 concentration during HOPE can predict early allograft dysfunction. Therefore, Sdcc-1 could be a potential viability assessment marker in liver transplantation.

15

Influence Of Hypothermic Machine Perfusion And Sex Disparity On Patient And Graft Survival In Liver Transplantation

Sertac Kacar, David Pereyra, Jule Dingfelder, Laurin Rauter, Nikolaus Becker, Gerd Silberhumer, Andreas Salat, Thomas Soliman, Gabriela Berlakovich, Georg Györi

Division of Transplantation, Department of General Surgery, Medical University of Vienna, Vienna, Austria

Background
Several factors influence outcome after liver transplantation (LT). Sex disparity and its impact on outcome after LT is an often-overlooked aspect, as disease progress in women tends to be estimated as less severe(1). This investigation aims to describe sex disparity in donors and recipients at our center as well as its influence on outcome after LT.

Methods
233 liver transplantations between 2018 and 2022 were included in this study. Graft and patient survival were compared. HOPE was performed with the LiverAssist device as standard preservation method in 163 cases, static cold storage was used in 62 cases. Median follow-up was 14 months (IQR: 7.4-23.4).

Results
Out of 225 transplanted recipients, 50 were female (22%) and 175 male (78%). The grafts were donated by 99 female (44%) and 126 male donors (56%). Female recipients were younger (mean age 50.1 (SD: 12.8) vs. 56.0 years (SD: 10.3), p=0.002), and both female recipients and donors had a lower BMI (mean 23.9 (SD: 3.4) vs. 27.5 (SD: 5.0) and 23.3 (SD: 5.0) vs. 27.2 (SD: 8.4), both p<0.001). Both donor gGT and donor risk index where higher in male donors but did not reach significance (p=0.170 and p=0.091). Grafts of female recipients were preserved via HOPE in 33/50 (66%) cases, grafts of male recipients in 130/175 (74%) cases. Rate of hepatocellular carcinoma (HCC) was higher in male recipients (64/175 cases, 37% vs. 7/50 cases, 14%). We reported 5 deaths (10%) and 4 graft losses (8%) of female and 31 (18%) and 19 (11%), respectively, of male recipients. One-year-survival of female recipients was 90% while male recipients presented with 79% one-year-survival.

Conclusions
Surprisingly, female recipients presented with higher survival rates despite a higher rate of SCS (34% vs 26%). Recipients of grafts from female donors presented with better survival rates as well. One reason for these results could be the overall better health of the female donors (younger, lower BMI, lower gGT) that were mostly donated to female recipients due to graft size. Further, more male recipients were transplanted due to HCC (35% vs. 13%), further influencing survival differences after LT.

Reference

[1] Sawinski D, Lai JC, Pinney S, Gray AL, Jackson AM, Stewart D, et al. Addressing sex-based disparities in solid organ transplantation in the United States - a conference report. Am J Transplant. 2023;23(3):316-25.

16

Microbiological Swabs Taken During Preservation Of Liver Grafts

Tina Saffarian, Jule Dingfelder, David Pereyra, Laurin Rauter, Gerd Silberhumer, Andreas Salat, Thomas Soliman, Gabriela Berlakovich, Georg Györi

Division of Transplantation, Department of General Surgery, Medical University of Vienna, Vienna, Austria

Background

Hypothermic oxygenated machine perfusion (HOPE) is the standard preservation method at Vienna General Hospital. For extended criteria donor (ECD) grafts, normothermic machine perfusion (NMP) is used, as well as static cold storage (SCS) as a rescue option. Little is known about the impact contaminated preservation fluids have on recipients postoperatively, especially in context of machine perfusion. The aim of this investigation is to achieve better understanding of the microbiological development during preservation.

Methods

Microbiological swabs were taken from the preservation solution during SCS (T1), the perfusion solution before connecting (T2) and after disconnecting the liver (T3). Samples taken from the recipient during surgery include abdominal swabs from ascites or bile ducts. Routine microbiological workups after transplantation (T4) include blood cultures and swabs from catheters, wounds or drains when signs of infection occurred.

Results

Among 236 liver transplants since 2018, 171 donor organs were preserved via HOPE, 65 via SCS.

During SCS, T1 results show microbiological growth in 10 out of 35 (29%) cases. In 3 cases, the same germs that were found in preservation fluid reoccurred during postoperative workups. However, those patients did not have any infection related complications.

During HOPE, 12 out of 79 (15%) T1 samples indicate growth, none of those reoccured within T4. Equally, germs found in T2 swabs were not identified later on. While 9 out of 109 (8%) samples came back positive, results primarily showed cutaneous microorganisms. Among 139 T3 workups, 15 (11%) show bacterial growth. In 1 out of 2 cases of E. faecium, follow up infection (T4) occurred but has been successfully treated with antibiotics.

Conclusion

Most frequently, contamination was documented in T1, predominantly by skin germs. While none of the recipients of HOPE preserved liver grafts presented with bacterial growth of previously detected microorganisms, 3 cases of SCS show postoperative persistence of germs detected during preservation.

This could indicate a protective effect of HOPE on contaminated preservation solution.

For further determination of microbiological development, postoperative follow-ups need to be investigated more thoroughly.

Poster Presentation

17

Robotic-Assisted Kidney Transplantation – First Experience In Austria

Jakob Eichelter[1], Julia Jedamzik[1], Georg Györi[1], Andreas Salat[1], Gabriela Berlakovich[1]

[1]Division of Transplantation Surgery, Department of General Surgery, Medical University of Vienna, Vienna, Austria

Background

Robotic-assisted kidney transplantation (RAKT) has emerged as a groundbreaking surgical technique. Promising outcomes with RAKT include reduced invasiveness, less postoperative pain, decreased blood loss, shorter hospital stays and improved patient recovery compared to open transplantation.

Methods

With assistance of an experienced proctor, the first RAKT in Austria was performed in January 2023. The living donor nephrectomy to retrieve the kidney was also performed using the Da Vinci Si ® (Intuitive Surgical, Inc., 1020 Kifer Road, Sunnyvale, CA 94086). The patient selection for the procedures was focused on absence of comorbidities, regular vascular anatomy and low BMI (body mass index), thus reducing potential risk factor for the first operations. Perioperative data was collected including operation time, complications, postoperative course, graft function, length of hospital stay.

Results

Between 01/2023 and 06/2023 two patients received a RAKT. Both recipients and their related donors (father and brother) were male. BMI was 27 and 24. Side of nephrectomy was left in both cases, side of implantation on the right side. The vascular anatomy was regular, except for the second donor with a short artery and early division into two arteries. Warm ischemia time (WIT) was 2-3 minutes. Operation time including docking was 3:20h and 4:20h. No intraoperative complications occurred, do conversions were necessary. One patient suffered from a neural positioning damage, no other postoperative complications were seen. The hospital stay in both cases was 9 days. Graft function was good and creatinine levels were 1,47 and 1,42 mg/dL in a 4-month follow-up.

Conclusions

RAKT is a complex procedure which needs multidisciplinary and multiprofessional expertise and experience. Proctorship is key during the implementation phase. Sufficient OR capacity and latest equipment is essential for gaining experience, training and patient safety.

18

Viability Assessment During Hypothermic Machine Perfusion With Combined Experimental Biomarkers FMN And Syndecan-1

Laurin Rauter[1], Dagmar Kollmann[2], Judith Schiefer[2], Pierre Raeven[2], Jule Dingfelder[1], David Pereyra[1], David Baron[2], Thomas Soliman[1], Gabriela Berlakovich[1] and Georg Györi[1]

[1]Department of General Surgery, Division of Transplantation, Medical University of Vienna, Vienna, Austria
[2]Department of Anesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria

Background

Novel preservation strategies as hypothermic oxygenated machine perfusion (HOPE) have enabled the use of more extended grafts for liver transplantation. However, biomarkers for viability assessment in HOPE are limited. We recently investigated two experimental biomarkers which, measured during HOPE, could separately predict early allograft function. Flavinmononucleotid (FMN), a mitochondrial respiratory chain complex-1 prosthetic group and Syndecan-1 (Sdc-1), main component of the endothelial glycocalyx, are both released upon oxidative stress and therefore reflect extend of ischemia reperfusion injury in the graft.

Methods
We measured Sdc-1 concentration via ELISA, and FMN via fluorescence spectroscopy in samples collected during HOPE from 40 liver transplant patients. We aimed to improve prediction of transplant outcome by combining the two viability markers in a sequential approach.

Results
With the previously reported cutoff for FMN concentration (10.65 ng/ml) after five minutes of HOPE, we could divide the analyzed patient cohort into a low-risk group (14 of 15 patients no EAD - 93%) and a high-risk group (13 of 21 patients with EAD - 62%). With the previously reported Sdc-1 concentration cutoff (808 ng/ml) measured after 60 minutes of HOPE, 71% of the low-risk group did not develop EAD (17 of 24 patients), whereas 58% of the high-risk group did (7 of 12 patients). The two markers combined further improved the separation into low- and high-risk groups: If both markers were underneath their respective cutoff values all 12 patients (100%) did not develop EAD. If both markers were above their respective cutoffs, six of nine patients (67%) did develop EAD. If only one of the markers cutoff was met, FMN was more reliable as seven of twelve patients (58%) did develop EAD, whereas for Sdc-1 one of three (33%).

Conclusions
Combination of Syn-1 and FMN has significant potential to further improve vialbility testing in hypothermic machine perfusion for liver transplantation. Further prospective studies are warrented to validate these findings.

04 - Kidney TX

Oral Presentation

19

Predictive Validity Of The Basel Assessment Of Adherence To Immunosuppressive Medication Scale (BAASIS©) After Renal Transplantation – A Prospective Cohort Study

Frederik Haupenthal[1], Konstantin Doberer[1], Florian Bauernfeind[1], Luis Naar[1], Habiba Ahmed[1], Bettina Gober[2], Katharina Ebenberger[3], Alexander Kainz[1], Sabina DeGeest[4,5] and Gregor Bond[1]

[1] Division of Nephrology & Dialysis, Department of Medicine III, Medical University of Vienna, Austria
[2] Division of Transplantation, Department of General Surgery, Medical University of Vienna, Austria
[3] Department of Cardiac Surgery, Medical University of Vienna, Austria
[4] Institute of Nursing Science, Department of Public Health, University of Basel, Switzerland
[5] Academic Centre for Nursing and Midwifery, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

Background
While medication adherence to immunosuppressants is crucial for allograft survival after renal transplantation, its assessment in daily clinical practice remains challenging. The BAASIS© is a promising, partially validated self-report instrument yet its predictive validity still needs to be established.

Methods

We used data of the prospective AdTorque-trial (DRKS00026674) including a consecutive sample of 226 adult kidney graft recipients transplanted at the Medical University of Vienna between 01/2018 and 12/2019 and clinically followed up to four years post-transplant. Medication adherence was monitored by a comprehensive, multimodal assessment including the BAASIS© at three-month intervals during the first year and at 24 months during routine follow-up visits. *Implementation and persistence adherence* were assessed three items (i.e. taking, timing and dose-reduction) and one item of the BAASIS©, respectively. Non-adherence was defined by YES on any of these items. The primary clinical outcome was the occurrence of the first biopsy-proven rejection.

Results

Of all 226 recipients (33% female, median age 57 years), 153 remained in the adherence monitoring for two years, resulting in a total of 973 BAASIS©. Non-adherence was reported at least once by 124 (55%) recipients and 67 recipients (30%) revealed non-adherence multiple times. Overall non-adherence increased over time: within the first three months from 11% to 31% and was between 27% to 32% from month 6 to 24 post-transplant. During the clinical follow-up of 34 month (median, IQR 6-44), non-adherent recipients had a significantly higher rate of biopsy-proven rejection than adherent recipients (25% vs. 7%,p<0.001). A time-dependent model showed that self-reported non-adherence predicted an increased risk for rejection (HR 2.43, 95% CI 1.22-4.82,p=0.012).

Conclusion

Our analysis demonstrated predictive validity of the BAASIS©, a self-report instrument which can easily be integrated in daily transplant practice. Frequent adherence assessments might provide a solid basis to identify patients at risk for poor clinical outcomes.

20

BK-Virus-specific IgG Antibodies Identify ABOi Patients At High Risk Of BKPyV DNAemia

Michael Eder[1], Anel Džakmić[1], Sahra Pajenda[1], Haris Omic[1], Günther F. Körmöczi[2], Marlies Schönbacher[2], Robert Strassl[3], Stephan Aberle[4], Nicolas Kozakowski[5], Georg Böhmig[1], Gregor Bond[1], Ludwig Wagner[1], Farsad Eskandary[1]

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[2]Department of Transfusion Medicine and Cell Therapy, Medical University of Vienna, Vienna, Austria
[3]Division of Clinical Virology, Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria
[4]Department of Virology, Medical University of Vienna, Vienna, Austria
[5]Department of Pathology, Medical University of Vienna, Vienna, Austria

Background

ABO blood group-incompatible (ABOi) kidney transplantation is associated with an increased rate of infectious complications caused by BK virus (BKV). With respect to BKV-specific IgG (BKV-IgG) studies reported contradictory results regarding the development of BKV-complications after transplantation. The clinical utility of BKV-IgG quantification in ABOi patients is unclear.

Methods

In this retrospective study BKV-IgG was measured in 117 samples from 32 ABOi-recipients. Samples included day 0 (D0) and months 1 (M1), 2, (M2) and 24 (M24) post-transplantation. BKV-IgG was quantified using an in-house ELISA for BKV-VP1 protein (genotypes 1&4). BKV-IgG was compared between patients with/without the occurrence of the following events within the first 24 months after transplantation: (i) BKPyV-DNAemia, (ii) presumptive BKPyVAN (>10^4 copies/ml) and (iii) biopsy-proven BKPyVAN.

Results

Overall, median BKV-IgG levels were 20.4 BAU/ml at D0 (IQR: 11.1-40.5), 20.7 at M1 (14.8-31.2), 21.7 at M2 (12.7-30.1) and 31.7 at M24 (20.6-48.4). In patients without BKPyV-DNAemia (n=24), BKV-IgG remained stable: D0: 20.0 (11.1-43.8), M1: 21.9 (14.8-31.2), M2: 21.9 (18.7-33.5), whereas a continuous decline was observed in patients

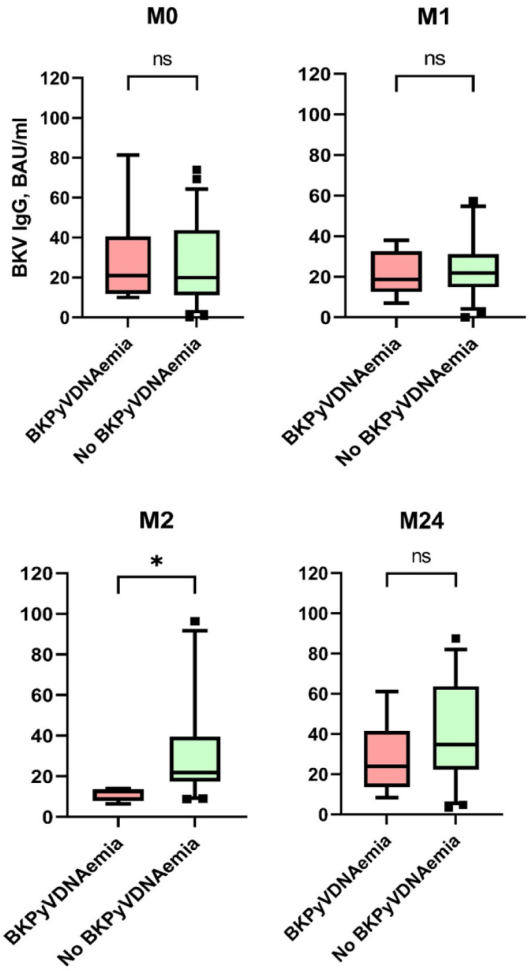

Figure 1

with BKPyV-DNAemia (n=8): D0: 20.9 BAU/ml (11.8-40.5), M1: 18.8 (13.7-28.2), M2: 12.5 (9.4-13.4), showing statistical significance at M2 (p=0.025), but not at D0 (p=0.89) or M1 (p=0.52, Figure1). No significant differences were found for presumptive/definite BKPyVAN. Pre-transplant rituximab (n=21) did not result in lower BKV-IgG: D0 34.0 BAU/ml (11.1-43.8) vs. 18.1 (11.8-34.9, p=0.50), M1: 25.4 (17.6-36.8) vs. 19.1 (14.8-27.5 p=0.25), M2: 20.2 (12.6-71.0) vs. 21.8 (12.7-26.2, p=0.89). Anti-BKV IgG levels at month 24 did not correlate with any clinical endpoint.

Discussion

We observed a significant decline of BKV-IgG in ABOi-patients developing BKV-DNAemia at M2 after transplantation, which may help explain the reported higher incidence of later BKV-complications. However, due to the limited number of outcomes in our small cohort, future studies need to confirm those findings in a larger ABOi-population.

21

The iBox Score As A Predictive Factor In A Retrospective Kidney Retransplant Cohort

Valeria Berchtold[1], Lisa M Grudl[1], Christina Bogensperger[1], Franka Messner[1], Andras Meszaros[1], Schneeberger S[1], Rupert Oberhuber[1], Michael Rudnicki[2], Hannes Neuwirt[2], Annemarie Weissenbacher[1]

[1]Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria.
[2]Department of Internal Medicine IV, Nephrology and Hypertension, Medical University of Innsbruck, Innsbruck, Austria

Background

Predicting kidney allograft survival as precise as possible and within a time frame which is still allowing potential intervention to save the graft and the patient's wellbeing is absolutely desirable. Several factors impacting long-term outcome after kidney transplantation are known, but there are hardly any clinical applicable scores available. The iBox algorithm, developed by the Paris Transplant Group, predicts individual long-term kidney allograft survival for 3, 5 and 7 years.

Methods

The iBox algorithm, including time from transplant, eGFR, proteinuria, anti-HLA donor-specific antibody MFI and biopsy result was applied retrospectively to kidney retransplantations (2nd and 3rd transplants) performed at the Medical University of Innsbruck. The iBox score was calculated with values and parameters on postoperative day 7, 6 and 12 months post-transplant. Donor, recipient and transplant demographics were collated; Cox regression and Kaplan-Meier survival analyses were performed.

Results

Ninety-five retransplants, 75 2nd and 20 3rd, were analysed. Median recipient age was 49 (21-73) and median donor age was 48 (0-73) years. Mean±SD recipient and donor BMI were 22.9±3.2 and 26.3±5.7 kg/m^2. Median panel reactive antibodies were 43 (0-100)%. Mean±SD cold ischemia time was 15.6±4.8 hrs; mean±SD anastomosis time was 28±7 min. Nineteen (20%) kidneys were from

Table 1

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
don_BMI	.054	.037	2.089	1	.148	1.055	.981	1.135
WIT	.129	.052	6.247	1	.012	1.138	1.028	1.259
ECD	.628	.802	.614	1	.433	1.875	.389	9.031
crea_M12	1.290	.822	2.461	1	.117	3.632	.725	18.194
GFR_M12	.063	.029	4.745	1	.029	1.066	1.006	1.128
predi_M12_year7	-6.414	1.769	13.139	1	<.001	.002	.000	.053

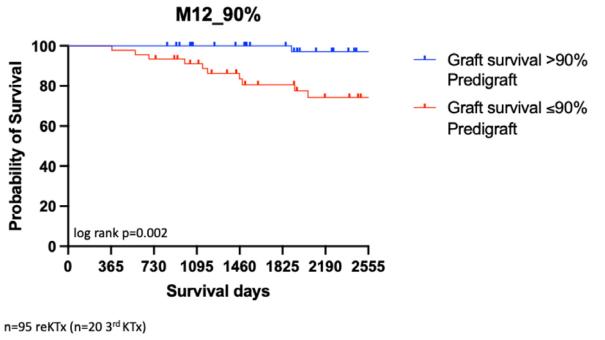

Figure 1 | iBox score evaluated at month 12 after KTx

ECD donors. Thirty-six (37.9%) patients experienced delayed graft function. Mean±SD eGFR at month 12 was 48.4±15.4 ml/min/1.73m^2; mean±SD serum creatinine at month 12 was 1.5±0.8 mg/dl. Overall, 16/95 (17%) patients lost their kidneys; median graft survival was 6 (1-20) years. Univariate analyses revealed month 6 and 12 iBox scores, eGFR and serum creatinine at month 12, donor age, ECD, donor BMI and anastomosis time as significant. Multivariate analyses detected the month-12 iBox score as the most important factor influencing graft survival, besides anastomosis time, and eGFR at month 12 (table 1). Graft survival stratified for an iBox score of more or less than 90% at month 12 was significantly better for the >90% group; log rank p=0.002 (figure 1).

Conclusions

In our cohort, the iBox score significantly predicts graft survival after a 2nd or a 3rd kidney retransplant. These findings have to be validated in a prospective study.

22

Impact Of Natural Killer Cell Functional Genetics On Microvascular Inflammation In The Presence Of Donor-Specific Antibodies

Matthias Diebold[1,2], Hannes Vietzen[3], Laura M. Kühner[3], Sarah M. Berger[3], Andreas Heinzel[1], Carsten T. Herz[1], Katharina Mayer[1], Farsad Eskandary[1], Konstantin Doberer[1], Alexander Kainz[1], Susanne Haindl[1], Nicolas Kozakowski[4], Elisabeth Puchhammer-Stöckl[3], Philip F Halloran[5], Georg A. Böhmig[1]

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[2]Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, University of Basel, Basel, Switzerland
[3]Center for Virology, Medical University of Vienna, Vienna, Austria,
[4]Department of Pathology, Medical University of Vienna, Vienna, Austria
[5]Alberta Transplant Applied Genomics Centre, ATAGC, University of Alberta, Edmonton, AB Canada

Background

Antibody-mediated rejection (ABMR) is a major cause of long-term graft failure. While the exact mechanisms

behind antibody-triggered injury are still unclear, there is emerging evidence for a contribution of natural killer (NK) cells to microvascular inflammation (MVI). To investigate whether genetically determined NK cell functionality affects ABMR activity, we conducted a cohort study to analyze associations of distinct NK cell receptor polymorphisms and the degree of killer immunoglobulin-like Receptor (KIR)-dependent missing self with the development of donor-specific antibody (DSA)-triggered MVI.

Methods

We enrolled 86 DSA-positive kidney transplant recipients in this study, all of whom underwent systematic biopsies during the screening phase of the BORTEJECT trial (NCT01873157). Patients were genotyped for polymorphisms known to determine NK cell activity and phenotypic composition (FCG3A[158-F/V], KLRK1[HNK/LNK], KLRC2[wt/del], rs9916629[C/T]). We also performed KIR typing for the calculation of missing self, defined as the absence of corresponding donor HLA in the presence of educated inhibitory KIR gene.

Results

Forty-four of the 86 patients had ABMR associated with higher levels of MVI and NK cell transcripts. Among tested genetic polymorphisms, only KLRC2$^{wt/wt}$ was associated with a higher MVI score: 2 (median; interquartile range: 0- 3.2) versus 0 (0-1.0); Spearman's rho=0.349, p=0.001. No such association, however, was observed for missing self. NK cell genetics did not impact death-censored graft survival or eGFR slope. In multivariable logistic ordinal regression model, only KLRC2$^{wt/wt}$ was associated with MVI (OR 7.84, 95%CI 2.37-30.47, p=0.001). A risk score combining variants important in univariable analysis (p<0.1) (KLRC2$^{wt/wt}$ and FCG3A[158-F/V]) did not differ from a sum score of all polymorphisms plus missing self.

Conclusion

In this thorough analysis of NK cell genetics only a polymorphism of KLRC2 turned out to be a significant determinant of ABMR activity. No additive effect of other functional NK cell gene polymorphisms and missing self were found.

23

Flavin Mononucleotide As A Possible Prognostic Mitochondrial Biomarker In Renal HMP

Paula van Appeldorn[1], Silvia Gasteiger[1], Julia Hofmann[1], Magdalena Kött[1], Katharina Kinzner[1], Dietmar Öfner[1], Stefan Schneeberger[1], Andras T. Meszaros[1], Annemarie Weissenbacher[1]

[1]Department of Visceral, Transplant and Thoracic Surgery, organLife Laboratory, Medical University of Innsbruck, Innsbruck, Austria

Background

Hypothermic machine perfusion (HMP) of the kidney has become a standard tool in clinical practice. Analysis of the perfusate offers a non-invasive opportunity to assess the perfused organ. However, perfusate markers with robust predictivity are scarce. Flavin-mononucleotide (FMN), a cofactor of the mitochondrial respiratory system, is a surrogate marker for ischemic injury and has already been identified as a predictive tool in MP of the liver. Herein, we investigated the role of FMN during renal HMP and its link to the postoperative outcome.

Methods

Perfusate samples during 51 clinical kidney HMP were collected. The fluorescence intensity (excitation and emission wavelength at 450 and 535nm, respectively) of the samples was determined and the concentration of FMN was then calculated using a standard series with known concentrations. Levels of FMN were then correlated with donor characteristics and postoperative outcome markers such as DGF, serum-creatinine levels.

Results

FMN concentration increased during HMP. Donor BMI correlates with the concentration of FMN at the end of perfusion (linear regression R^2 = 0.13, p = 0.0105). FMN-levels throughout the perfusion differ significantly between kidneys with optimal initial function and those

which develop delayed graft function (p = 0.0024 at 15min, p = 0.0051 at 1h). Higher FMN-levels at the end of perfusion go along with higher serum-creatinine levels 7 days after transplantation (linear regression R^2 = 0.13, p = 0.0155).

Conclusions

We observed a progressive accumulation of FMN during HMP. A higher donor BMI seems to lead to an increased loss of FMN under ischemic conditions. Furthermore, FMN-levels are able to predict the outcome after transplantation. This method could help to discriminate between DGF and initial function already after 15min of perfusion. Therefore, this study adds further information on the renal mitochondrial function upon HMP and FMN appears to be a promising non-invasive assessment tool.

References

[1] Schlegel A, Muller X, Mueller M, Stepanova A, Kron P, de Rougemont O, Muiesan P, Clavien PA, Galkin A, Meierhofer D, Dutkowski P. Hypothermic oxygenated perfusion protects from mitochondrial injury before liver transplantation. EBioMedicine. 2020 Oct;60:103014. doi: 10.1016/j.ebiom.2020.103014. Epub 2020 Sep 24. PMID: 32979838; PMCID: PMC7519249.

[2] Wang L, Thompson E, Bates L, Pither TL, Hosgood SA, Nicholson ML, Watson CJE, Wilson C, Fisher AJ, Ali S, Dark JH. Flavin Mononucleotide as a Biomarker of Organ Quality-A Pilot Study. Transplant Direct. 2020 Aug 21;6(9):e600. doi: 10.1097/TXD.0000000000001046. PMID: 32904032; PMCID: PMC7447496.

[3] Hirst J. Mitochondrial complex I. Annu Rev Biochem. 2013;82:551-75. doi: 10.1146/annurev-biochem-070511-103700. Epub 2013 Mar 18. PMID: 23527692.

24

The Kinetic Of Torque Teno Virus Plasma Load Following Calcineurin Inhibitor Dose Change In Kidney Transplant Recipients

Florina Regele[1], Frederik Haupenthal[1], Luis Naar[1], Habiba Ahmed[1], Stefan Steinringer[1], Sebastian Kaps[1], Konstan tin Doberer[1], Irene Görzer[2], Robert Strassl[3], Elisabeth Puchhammer-Stöckl[2], Gregor Bond[1]

[1] Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria.
[2] Center for Virology, Medical University Vienna, Kinderspitalgasse 15, 1090 Vienna, Austria
[3] Division of Clinical Virology, Department of Laboratory Medicine, Medical University Vienna, Währiger Gürtel 18-20, 1090 Vienna, Austria

Background

The Torque Teno virus (TTV) is non-pathogenic, highly prevalent and reflects the immune status of its host. TTV plasma load is suggested for risk stratification of graft rejection and infection post kidney-transplantation. Currently TTV-guided personalization of immunosuppression post solid organ transplantation is tested in three investigator driven European multicentre interventional randomized controlled trials. For implementation of TTV-guided immunologic monitoring in clinical routine, it is crucial to determine the kinetic of TTV plasma load following adaption of immunosuppression.

Methods

This study was designed to understand the kinetic of TTV load following changes in calcineurin inhibitor (CNI) dosing. Patients were selected from the prospective TTV-POET trial, including all 287 consecutive adult recipients of a kidney-graft transplanted at the Medical University Vienna in 2018 and 2019. We analysed TTV kinetic up to three months following isolated dose adaption of the CNI. TTV was quantified by in-house PCR.

Results

Baseline TTV load was $1.2x10^7$ c/ml ($4.5x10^5$ - $7.8x10^8$) in patients experiencing CNI decrease and $5.9x10^5$ c/ml

($4.2x10^4$ - $1.6x10^7$) in patients with increase. At day 30 TTV was unchanged with $1.7x10^7$ c/ml ($4.0x10^5$ - $1.1x10^9$; p=0.097) following drug decrease and $6.9x10^5$ c/ml ($5.0x10^4$ - $9.3x10^8$; p=0.15) in patients with increase. However, at day 60 TTV was lower in patients with CNI dose reduction $2.6x10^6$ c/ml ($6.5x10^4$ - $2.80x10^8$; p=0.021) and there was a trend towards higher TTV in patients with CNI increase ($5.4x10^6$ c/ml, $5.0x10^4$ - $5.40x10^9$; p=0.064).

Conclusions
Changes in TTV load following adaption of CNI dose in kidney-graft recipients are not expected quickly, but only after two months. Understanding TTV kinetic following changes in CNI dose are crucial for the implementation of TTV-guided immunosuppression in routine clinical care.

25

Modeling Longitudinal Biomarker Assessment To Predict Allograft Rejection In Pediatric Kidney Transplantation: A Computer Simulation For Small Sample Size Cohorts With Rare Events

Fabian Eibensteiner[1], Elias Laurin Meyer[2,3], Krisztina Heindl-Rusai[1], Christoph Aufricht[1], Thomas Mueller-Sacherer[1], Franz Koenig[2]

[1]Division of Pediatric Nephrology and Gastroenterology, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, Austria
[2]Center for Medical Data Science, Medical University of Vienna, Vienna, Austria
[3]Berry Consultants, Vienna, Austria

Background
The complexity of allograft rejection after kidney transplantation (KTX) is incompletely captured by current methods of laboratory testing. Prospective study of non-invasive biomarkers has become increasingly prevalent and frequently utilizes single measurements. Models for complex clinical conditions subject to multiple irregular changes may benefit from biomarker updates at key-points of their trajectories. This is especially relevant for rare events in small cohorts, e.g., pediatric allograft rejection. This study aims to simulate and compare models for prediction of rejection in pediatric KTX using longitudinal biomarker assessments.

Methods
Based on data of our pediatric KTX cohort with plasma TTV measurements (biomarker associated with rejection in adult patients) we conducted extensive clinical trial simulations exploring a broad range of 432 distinct scenarios ranging from no effect to subgroups with larger effects sizes. We used mixed-effects models and permutational rejection sampling to simulate biomarker trajectories and time-to-event data with 5000 replicates per scenario. Accuracy of estimation and statistical power were compared for different models.

Results
We observed increased statistical power across most scenarios and models when sample size and biomarker measurement intervals were increased. Especially for smallest sample sizes (n=100) and low event rates (4%), Cox regression with time-dependent covariates and generalized estimated equations (GEEs) offered highest statistical power. Comparison of case:control patients with parametric (t Test) and non-parametric (Mann Whitney U) methods showed similar results, although markedly decreased power compared to Cox regression and GEEs.

Conclusions
Modeling approaches utilizing longitudinal biomarker assessments generally resulted in higher statistical power, especially for small sample sizes and rare event rates, i.e., rejection in pediatric KTX. Computer simulation and use of the correct model for specific clinical situations is therefore crucial for these patient cohorts to identify non-invasive biomarkers with predictive potential for rejection, and thereby to reduce (repeated) biopsy, which is still needed for diagnosis.

26

Morphologic And Molecular Features Of Late Antibody-Mediated Rejection – Prediction Of Renal Allograft Performance

Carsten T. Herz[1], Matthias Diebold[1,2], Katharina Mayer[1], Alexander Kainz[1], Nicolas Kozakowski[3], Philip F Halloran[4], Georg A. Böhmig[1]

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[2]Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, University of Basel, Basel, Switzerland
[3]Department of Pathology, Medical University of Vienna, Vienna, Austria
[4]Alberta Transplant Applied Genomics Centre, ATAGC, University of Alberta, Edmonton, AB Canada

Background
Late antibody-mediated rejection (ABMR) is a leading cause of graft loss. Innovative morphologic and molecular indices/transcript sets reflecting ABMR activity or acute vs. chronic injury may improve risk stratification where current diagnostic features perform poorly. In the present study, we sought to clarify the independent effects of such variables on the course of renal allograft function (estimated glomerular filtration rate [eGFR] slope) and death-censored graft survival.

Methods
Our retrospective cohort study included 75 recipients of an ABO-compatible renal allograft diagnosed with ABMR >180 days post-transplantation. Index biopsies were evaluated following the Banff 2019 scheme whereby sets of single lesions were combined to simplified activity (AI_{3comp}: g+ptc+C4d) and chronicity (CI_{3comp}: cgx2+ct+ci) indices. Transcriptome analysis (MMDx platform) was used to compute molecular transcript sets reflecting tissue injury/repair (IRRAT) and fibrosis (ciprob).

Results
Biopsies (100% donor-specific antibody-positive) were performed 5.17 (median; IQR: 2.41-13.21) years after transplantation. Morphologic phenotypes were active ABMR (20%), chronic active ABMR (62.7%), and chronic (inactive) ABMR (17.3%). Median death-censored graft survival was 7.1 years. In multivariable Cox regression including four selected biopsy-based variables, CI_{3comp} (HR per IQR: 1.98 [95%CI: 0.98-4.02]) and IRRAT (1.95 [0.95-3.97]) were strongest (yet not significantly) associated with graft failure. In a linear mixed model, CI_{3comp} was significantly associated with lower eGFR at baseline (-1.93 [95%CI: -3.00 to -0.87] ml/min/1.73 m^2) per 1 unit increase, with no impact on eGFR slope (-0.08 [-0.64 to 0.48] ml/min/1.73 m^2/year). Conversely, IRRAT associated with a steeper eGFR slope (-0.62 [-1.12 to -0.12]) per 0.1 increase but had no significant association with baseline eGFR (-0.84 [-1.78 to 0.09)]).

Conclusions
Molecular tissue injury/repair reflected by the IRRAT transcript set was the strongest independent predictor of eGFR loss. Our study supports the use of transcriptome analysis to improve outcome prediction and identify patients who could benefit from specific therapeutic interventions.

Poster Presentation

27

Control of Torque Teno Virus Load By Classical Complement Pathway – Results From A First-In-Human Phase I Trial Utilizing Anti-C1s Antibody Sutimlimab

Markus Wahrmann[1], Jakob Mühlbacher[2], Dorian Kulifaj[3], Sophie Courjal[3], Farsad Eskandary[1], Martin Schiemann[1], Bernd Jilma[4], Georg A. Böhmig[1], Gregor Bond[1]

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[2]Department of Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria
[3]bioMérieux SA, Parc Technologique Delta Sud, 09340, Verniolle, France
[4]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria

Background
Torque Teno Virus (TTV) is a highly prevalent, non-pathogenic DNA virus reflecting host immunosuppression. Assessing TTV plasma load is a promising marker for evaluating immunocompetence in transplant patients. However, the immune system compartments regulating TTV load remain poorly understood.

Methods
We analyzed the contribution of the classical complement pathway to the immunological control of TTV load in healthy volunteers and kidney allograft recipients with late ABMR. Participants had previously undergone a phase I study involving sutimlimab, an antibody neutralizing the enzymatic classical pathway subcomponent C1s. Serum samples were analyzed using the qPCR TTV R-GENE® assay for TTV quantification and tested on antibody-endowed HLA microbeads for C3d fixation ability. Treatment protocols included: single infusion of ascending doses (0.3-100 mg/kg) of sutimlimab/ placebo in 48 healthy volunteers, with evaluation on day 0 and 14; four weekly doses of sutimlimab/placebo (30 and 60 mg/kg) in two cohorts of 16 volunteers, with evaluation on day 0, 14, and 35; and four weekly doses of sutimlimab (60 mg/kg) in ten kidney transplant recipients, with evaluation on day 0, 14, 36, and 50.

Results
Only subjects receiving 100 mg/kg anti-C1s in the single-infusion cohorts showed complete complement inhibition on day 14, with a median TTV load increase of 3.46 $\log_{10}$ copies/mL (c/mL; p=0.063 vs. baseline 2.61). Similarly, subjects receiving multiple doses of 30 mg/kg anti-C1s antibody experienced a median TTV load increase to 1.79 $\log_{10}$ c/mL (p=0.054 vs. baseline 1.47). ABMR patients exhibited a median TTV load increase to 4.05 $\log_{10}$ c/mL at day 50 (p=0.018 vs. baseline 3.53). Pearson correlation analysis showed a negative correlation (r=-0.302; p<0.001) between TTV load and C3d fixation ability.

Conclusions
This study provides initial evidence of the complement system's contributing role in controlling TTV. A deeper understanding of the immune response to TTV could optimize its use as an immunological monitoring tool in clinical care for transplant recipients.

28

Double Kidney Transplantation: A Case Report And Review Of The Literature

Manfred Kalteis, Nadina Roth, Matthias Biebl

Department of Surgery, Ordensklinikum Elisabethinen Linz, Austria

Background
Double kidney transplantation (DKT) is a possible strategy to utilize organs from expanded criteria donors which are not suitable for single kidney transplantation (SKT). Thereby the number of kidney transplantations can be increased and organ shortage is reduced.

Methods
We report a case of a two-stage DKT and we provide a review of the literature concerning DKT.

Results
In February 2023, a multi-organ donation took place in our transplant region involving a 50-year-old DBD donor with no comorbidities (Kidney Donor Risk Index was 0.84). One kidney was allocated to a patient at our transplant center and implanted after a cold ischemia time of 6 hours. The second kidney was allocated to a recipient abroad. The results of a kidney biopsy done at the recipient center showed a Remuzzi score of 6, leading to the rejection of the kidney for implantation. Due to its poor organ quality the kidney was also declined by other transplant centers for SKT. Consequently, it was offered to our initial recipient for a DKT. Considering the presumed low quality of the contralateral kidney, we accepted the offer. In a two-stage operation, it was implanted in the contralateral iliac fossa following a cold ischemia period of 24 hours. The subsequent progress was uneventful,

with both kidneys functioning well, and a postoperative creatinine level of 1.1 mg/dl measured 3 months after the surgery. Interestingly, the baseline biopsies from both kidneys done in our institution were scored with a Remuzzi score of 1, indicating a possible misjudgment in the external histological biopsy assessment.

Conclusions
DKT can increase the usage of expanded criteria kidneys, and exceptionally, can be done as a two-stage procedure.

29

HLA Specific Antibodies - Or Rather Not - A Case Report

Daniela Koren, Ingrid Faé, Daniela Kriks, Sabine Wenda, Gottfried Fischer

Department of Transfusion Medicine and Cell Therapy, Medical University of Vienna

Introduction
HLA specific antibodies can be detected with various techniques – current standard tests include the Luminex single-antigen assay and flow cytometry. Both tests correlate usually very well.

We describe a case, where the two tests gave contradictory results.

Case Presentation
The patient was a 59-year-old woman who had been on dialysis since 2018. In 2020, the patient received her first kidney transplant, which had to be explanted already on the second day after the transplantation due to vascular thrombosis.

In April 2023 the patient was offered a second kidney. The virtual crossmatch according to the Luminex results (which have been performed during the quarterly screening) was positive. This required induction therapy (ATG/IAS/Tac/MMF/cortisone).

However, the Luminex test at the day of transplantation showed no DSA. Quite unexpectedly, the flow-cytometric crossmatch from this serum with donor lymphocytes was reproducibly positive. The control, a crossmatch with the patient's own serum, was negative.

Discussion
In search of an explanation we noted that the patient developed very broad reacting antibodies after the explantation of the first kidney – probably due to insufficient immunosuppression. The MFI values of these antibodies however dropped with time to negative values. One explanation for the positive flow crossmatch could be, that the HLA specific antibodies although low in titre when measured on recombinant antigens on beads are of such high affinity to native molecules that they become detectable in the flow crossmatch. Alternatively, the positive flow crossmatch is due to non HLA-antibodies.

30

Diagnostic Accuracy Of Urinary C-X-C Motif Chemokine Ligand (CXCL)9 In Relation To Kidney Allograft Rejection And Injury

Katharina A. Mayer[1], Elisa Merklinger[2,3], Matthias Diebold[4], Stefanie Büsch[2,3], Juliane Rüdiger[2,3], Susanne Haindl[1], Nicolas Kozakowski[5], Andreas Voss[2,3], Nora Karnowski[2,3], Helmut Haslacher[6], Georg A. Böhmig[1]

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria
[2]Clickmer Systems GmbH, Rheinbach, Germany
[3]Apis Assay Technologies Ltd., Manchester, United Kingdom
[4]Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, University of Basel, Basel, Switzerland
[5]Department of Pathology, Medical University of Vienna, Vienna, Austria
[6]Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

Evolving Landscape Of Pediatric Kidney Transplantation: Analysis Of Developments And Outcomes Over The Last 15 Years In Innsbruck

Madita L. Buch[1], Johannes Schauer[1], Fabian Eibensteiner[2], Siegfried Waldegger[3], Hannah Stundner-Ladenhauf[1], Stefan Scheidl[1], Thomas Müller-Sacherer[2], Stefan Schneeberger[1], Katrin Kienzl-Wagner[1]

[1]Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria
[2]Division of Pediatric Nephrology and Gastroenterology, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, Austria
[3]Department of Pediatrics, Medical University of Innsbruck, Innsbruck, Austria

Background
Pediatric kidney transplantation plays a crucial role, offering a life-changing treatment option for children with end-stage renal disease (ESRD).

Methods
A retrospective analysis was conducted on 73 pediatric kidney transplant cases performed between 2007 and 2023 in Innsbruck. Demographic data, surgical techniques, donor data, immunosuppressive regimens administered, and post-transplant outcomes were meticulously assessed.

Results
The analysis reveals significant developments in pediatric kidney transplantation. Since 2019, annual transplant numbers notably increased, with 9 transplants in 2019 and 10 in 2023, compared to fewer than 4 procedures in

Introduction
Measurement of urinary chemokines is considered a valuable marker for detecting and monitoring renal allograft rejection. However, test interpretation could be complicated by rejection-independent graft injury. In this retrospective cohort study, we sought to assess the predictive value of urinary C-X-C motif chemokine ligand (CXCL)9 in relation to biopsy results and factors that could influence urinary chemokine excretion independent of allograft injury.

Methods
We included a "real world" cohort of 100 renal allograft biopsies (42 protocol biopsies; 58 indication biopsies; November 2018 - December 2019). For included biopsies, urine samples were retrospectively analyzed for CXCL9 by ELISA.

Results
Biopsies revealed various types of morphologic injury, among those antibody-mediated rejection (ABMR; n=16), borderline lesions (n=11), T cell-mediated rejection (TCMR; n=7), BK virus nephropathy (n=4). Fifty biopsies showed no specific type of injury. The predictive accuracy of urinary CXCL9 in relation to ABMR, TCMR/borderline lesion, overall rejection or injury of any type was moderate (receiver operating characteristic [ROC] area under the curve [AUC] ≤0.71). The discrimination between normal morphologic and injury of any type was confounded by several factors. Among biopsies with no injury, 27 (54%) were associated with donor-specific antibody (DSA) detection (n=4), leukocyturia (n=12), BK viremia (n=13) and/or C-reactive protein values above 1 mg/dL (n=15). The 23 biopsies without injury and no laboratory abnormalities exhibited a median CXCL9 level of 0 (0-1.5) pg/mg creatinine compared to 27 biopsies without injury but laboratory abnormalities (32.3 [0-146.4] pg/mg) or 50 biopsies with abnormal morphology (82.9; [11.0-202.4] pg/mg). In separate analyses excluding samples associated with laboratory abnormalities the predictive value for ABMR (ROC-AUC: 0.72), TCMR/borderline lesion (0.80) or overall rejection (0.82) increased considerably.

Conclusions
Urinary CXCL9 may be a valuable adjunct diagnostic test that could help guide biopsy management. When interpreting positive test results it is crucial to consider false positive results.

the preceding years. Of the 73 cases analyzed, 25 (34.2%) were female, and the median age was 13. Preemptive kidney transplantation was performed in 24 patients (34,3%). 35 transplants were living donor kidney transplants (47.9%). A significant development was the introduction of ABO incompatible transplantation in 2023. All patients received triple immunosuppressive therapy consisting of a calcineurin inhibitor (Tacrolimus 86.6%), Mycophenolate mofetil (98.6%) and corticosteroids.

Outcomes for patients with available follow-up data showed acute rejection in 6 out of 48 patients (12.5%), delayed graft function in 4 out of 46 cases (8.7%). 9 out of 58 cases (15,5%) experienced graft loss, including 4 patients who died due to infection and cardiovascular-related complications despite having functioning grafts. Reoperation was required in 12 patients (out of 73 16.4%), primarily due to hematoma. CMV reactivation occurred in 10 (21,7%) children and EBV reactivation in 8 (17,4%).

Conclusions

This study provides valuable insights into the developments and outcomes of pediatric kidney transplantation over the past 15 years in Innsbruck. The notable increase in transplant numbers since 2019 and the introduction of ABO incompatible transplantation reflect the evolving landscape of this field. Challenges such as acute rejection, graft failure, and complications requiring reoperation persist. Continued multidisciplinary research is needed to optimize long-term outcomes in pediatric kidney transplantation.

05 - Basic Science

Oral Presentation

32

Impact Of Maintainance Immunosuppressives And BH4 On Macrophages

Katharina Lackner[1], Susanne Ebner[1], Bernhard Texler[1], Ilaria Dorigatti[2], Jakob Troppmair[1], Stefan Schneeberger[1], Katrin Watschinger[2], Manuel Maglione[1]

[1]Medical University of Innsbruck, Visceral, Transplant and Thoracic Surgery, Daniel Swarovski Research Laboratory, Innsbruck, Austria
[2]Medical University of Innsbruck, Institute of Biological Chemistry, Innsbruck, Austria

Background

For successful organ transplantation lifelong immunosuppression is mandatory but current maintenance immunosuppressive protocols do not meet the clinical needs. Therefore, the quest for new molecular targets interfering with the immune system is crucial. There is increasing interest in better understanding the role of macrophages which were identified to make up 60% of infiltrating cells during acute rejection. The effect of maintainance immunosuppressives on macrophages is poorly investigated as the main focus relied on the adaptive immune system. Tetrahydrobiopterin (BH4) has been shown to prevent lethal ischemia reperfusion injury of the graft (IRI) as well as chronic and acute graft rejection. BH4 is an essential cofactor for two enzymes highly present in macrophages. One is the M1 macrophage marker inducible nitric oxide synthase (iNOS). The second, alkylglycerol monooxygenase (AGMO), is expressed in M2 macrophages. Here, we investigated distinct macrophage phenotypes prestent during acute rejection and the effect of immunosuppressives these cells.

Methods
We analyzed gene expression of macrophage markers in allogeneic grafts from a murine heart transplantation model treated with BH4 and CsA using TaqMan technology.

Additionally, we isolated bone marrow-derived macrophages (BMDMs) from C57Bl/6 mice, incubated them with the BH4 precursor sepiapterin as well as cyclosporin A (CsA), prednisolone, tacrolimus, sirolimus or mycophenolate mofetil (MMF) and polarized them to M1 and M2 phenotypes. Immune cells were then characterized for cell viability and gene expression of polarization and activation markers.

Results
Heart allografts treated with BH4 and CsA show different expression of macrophage markers compared to untreated allografts. Treatment of BMDMs with diverse immunosuppressive agents reveal signs of altering the cell viability of macrophage phenotypes and some immunosuppressives also modify macrophage phenotypes indicated by changes of M1 and M2 macrophage markers.

Conclusion
Our experiments show an immunosuppressive effect of BH4 via macrophages and indicate that maintainance immunosuppressives also affect macrophages.

33

Donor-Specific IgE Increases Donor-Specific B Cells And Augments Alloreactive T Cell Proliferation In A CD23-Dependent Manner

Anna Marianne Weijler[1], Moritz Muckenhuber[1], Marlena Buresch[1], Birgit Linhart[2], Thomas Wekerle[1]

[1] Medical University of Vienna, Department of General Surgery, Division of Transplantation, Vienna, Austria
[2] Medical University of Vienna, Center for Pathophysiology, Infectiology and Immunology, Institute of Pathophysiology and Allergy Research, Vienna, Austria

Background
Donor-specific IgE develops in murine and human transplant settings. While the significance of IgE in allergies and other TH2 type disorders is well described, the potential role of this antibody isotype in transplant rejection remains unclear. In allergy research, IgE is connected to increased T cell activation as well as allergen-specific antibody levels via formation of immune complexes that bind to CD23 (FceRII) expressed on B cells. Here we investigate if MHC-specific IgE augments the alloresponse via CD23.

Methods
Serum was isolated from C57BL/6 mice after rejection of a fully mismatched BALB/c cardiac allograft and incubated with donor MHC monomers to form MHC-IgE immune complexes. IgE activity was eliminated in control samples via heat inactivation. Monomer-incubated serum samples were injected into the hindlimb footpads of C57BL/6 mice. After 7 days draining lymph nodes (dLN) were isolated and T and B cell subsets were analysed via Flow Cytometry. Before footpad injection, a group of mice received a systemic administration of a blocking anti-CD23 antibody (clone B3B4), selectively inhibiting IgE binding.

Results
Inhibition of IgE significantly decreased proliferation of CD8+ and CD4+ T cell, measured via Ki-67, and activation of CD4+ and CD8+ T cells, measured via CD44, in draining lymph nodes upon injection of MHC-sensitized serum. Blocking of CD23 in footpad injected mice led to decreased proliferation of CD8+, but not CD4+, and decreased activation of CD4+ as well as CD8+ T cells. Inhibition of IgE as well as blocking of CD23 decreased levels of MHC-specific germinal center B cells.

Conclusion
These findings indicate that donor-specific IgE stimulates alloreactivity, augmenting T cell and B cells activation via formation of MHC-IgE complexes binding via CD23. Donor-specific IgE may thereby contribute to the alloresponse directed against organ transplants.

34

Perturbing the NAD Salvage Pathway As A New Therapeutic Target To Combat Acute Allograft Rejection

Bernhard Texler[1], Fabian Egger[1], Giulio Ciucci[2], Susanne Ebner[1], Katharina Lackner[1], Jakob Troppmair[1], Stefan Schneeberger[1], Serena Zacchigna[2], Manuel Maglione[1]

[1]Medical University of Innsbruck, Visceral, Transplant and Thoracic Surgery, Daniel Swarovski Research Laboratory, Innsbruck, Austria
2Cardiovascular Biology Laboratory, International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy

Background
Acute allograft rejection is closely tied to the metabolism of T cells, which is highly relevant for T cell differentiation and effector function. Suppressing alloreactive and not regulatory T-cells by perturbation of the nicotinamide adenine dinucleotide salvage pathway by specifically blocking Nicotinamide phosphoribosyltransferase (NAMPT), has been described to ameliorate disease severity in inflammatory and malignant diseases.

Methods
We utilized a heterotopic heart transplantation (HTx) model in mice using allogenic (C3H/J donors, C57BL/6 recipients) or syngenic (C57BL/6 donors and recipients) settings. At day 6, we harvested graft tissue, analyzed mRNA expression of inflammatory cytokines, and performed immunohistochemistry to investigate the degree of rejection. Additionally, serum NAMPT levels were quantified via ELISA. $CD4^+$ and $CD8^+$ T cells from human peripheral blood were isolated and treated with a NAMPT inhibitor to assess viability and cytokine expression. Furthermore, we isolated and treated neonatal rat cardiomyocytes and with a NAMPT inhibitor to exclude adverse effects.

Results
We present an ideal model to study allograft rejection resulting in an upregulation of pro-inflammatory markers and a high histological rejection score between the allogenic and syngenic group, which also show an increased serum expression of NAMPT, suggesting an involvement during allograft rejection. We analysed the effect of NAMPT inhibition on neonatal rat cardiomyocytes and can exclude any adverse effects in steady-state and during ischemia/reperfusion. We then isolated different T cells and observed a reduced expression of IFNγ and increased cytotoxicity under NAMPT inhibition, which was more prominent in $CD8^+$ T cells than $CD4^+$ cells and had little effect on regulatory T cells.

Conclusion
We unveiled that NAMPT is upregulated during allograft rejection and that modulating NAMPT is effective in suppressing activation of alloreactive T cells without affecting regulatory T cells. This leads us to the hypothesis that NAMPT is a promising candidate for a novel therapeutic target.

35

Targeting DSA-Secreting Bone Marrow Long-Lived Plasma Cells With CTLA4-Ig

Moritz Muckenhuber[1], Konstantinos Mengrelis[1], Anna Marianne Weijler[1], Teresa Kreuzbauer[1] and Thomas Wekerle[1]

[1] Medical University of Vienna, Dept. of General Surgery, Div. of Transplantation

Background
The importance of bone marrow resident plasma cells for long-lasting humoral immunity has been highlighted in several models for vaccination and infectious diseases. To which extent this cell population is also responsible for upholding a sustained humoral response against (donor)-HLA antigens in the transplant setting remains unclear. We therefore sought to identify and characterize DSA-secreting plasma cells to provide insight into their underlying biology.

Methods

C57BL/6 were grafted with a fully mismatched balb/c cardiac allograft without any immunosuppression. DSA were assessed via flow crossmatch and MHC-specific ELISA. Spleen and bone marrow cells of cardiac allograft recipients isolated 20 weeks post transplantation were cultured separately for 48h. DSA within the cell culture supernatants were measured via flow crossmatch. Splenic and bone marrow plasma cells were quantified in transplant recipients and age-matched controls using flow cytometry. Selected groups of cardiac allograft recipients were treated with CTLA4-Ig for 6 weeks (50mg/kg on days 0, 4, 14 and 28) starting 10 weeks after transplantation (i.e. 9 weeks after cardiac allograft rejection).

Results

Serum IgG DSA persisted for up to 15 months after rejection of fully mismatched heart allografts (BALB/c to B6). We found that donor MHC-specific antibodies, in this setting, were exclusively secreted by bone marrow (BM) resident long-lived plasma cells (LLPC; $TACI^+$ $CD19^-$). LLPC were phenotypically distinct from short-lived BM plasma cell populations ($TACI^-$ $CD19^-$ and $TACI^+$ $CD19^+$) and displayed the highest surface expression of CD28. Therefore, starting 10 weeks after transplantation (when DSA levels were stable and depending on LLPC), we treated cardiac allograft recipients with CTLA4-Ig. A 6-week course of CTLA4-Ig significantly lowered DSA levels and specifically decreased BM LLPC compared to an untreated control group conducted in parallel.

Conclusion

Bone marrow resident LLPC represent a crucial source of late DSA that can be targeted with costimulation blockade.

36

Gene Expression Analysis of B and T Cells in Lung Transplant Patients Receiving mTOR Inhibitor

Hatice Oya Akyildiz[1], **Shahrooz Nasrollahi Shirazi**[1], Sophia Auner[1], Konrad Hötzenecker[1], Peter Jaksch[1], Alberto Benazzo[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background

Understanding the effects of mTOR inhibitors on gene expression profiles in lung transplant patients is of great interest for personalized therapeutic approaches. Investigating dysregulated genes in B and T cells provides valuable insights into the intricate molecular mechanisms of mTOR signaling and immune responses, thereby enhancing the development of targeted therapies.

Methods

Peripheral blood mononuclear cells (PBMCs) were collected from lung transplant recipients both before and 12 months after transplantation. B and T cells were isolated from PBMCs using magnetic beads, followed by RNA extraction and sequencing. Data analysis was performed at the Core Facility Genomics, Medical University of Vienna, utilizing the STAR aligner, DESeq2, and RSEM.

Results

The analysis revealed several genes with significant dysregulation in B and T cells at 12 months post-transplantation compared to the pre-transplantation state. In B cells, the upregulation of PIK3R3 suggests a potential compensatory mechanism in response to mTOR inhibition, while the upregulation of CD244 indicates its influence on autophagy modulation. Additionally, the upregulation of CAMP, S100A4, and SLPI in B cells suggests their involvement in immune activation and cell viability. Notably, previous studies have demonstrated increased SLPI production with mTOR inhibition. In T

cells, the upregulation of PIK3R3 and STAT1, along with the downregulation of ID3, provides insights into their roles in mTOR signaling and immune regulation.

Conclusion
The upregulation of PIK3R3, CD244, CAMP, S100A4, SLPI, STAT1, and the downregulation of ID3, in B and T cells of the lung transplant patients receiving mTOR inhibitor, reveal important insights into compensatory responses, autophagy, immune activation, and cell viability. These findings significantly contribute to our understanding of mTOR pathway dysregulation, facilitating the development of targeted therapies to optimize immune responses and improve outcomes in lung transplant recipients.

Keywords: Lung transplantation, mTOR, Gene expression, B cells, T cells

37

Cytokine Absorption During Ex Vivo Liver Perfusion Potentially Reduces Cytokine Levels And Inflammation

Sabrina Stimmeder[1], Bettina Leber[1], Lisa Rohrhofer[1], Jennifer Weber[1], Kathrin Briendl[1], Ariane Aigelsreiter[2], Robert Sucher[1], Philipp Stiegler[1]

[1]General, Visceral and Transplant Surgery, Department of Surgery, Medical University of Graz, Austria
[2]Diagnostic and Research Institute of Pathology, Medical University of Graz, Austria

Background
Ex vivo machine perfusion methods have emerged as a promising tool for organ preservation, reconditioning and repair. However, the underlying process triggers inflammatory processes. An approach to counteract the release of cytokines and thus mitigate the inflammatory response, is the inclusion of an CytoSorb adsorber into a liver perfusion circuit.

Methods
Porcine livers were subject to 24h of static cold storage and subsequently perfused for 24h in a sub-normothermic oxygenated machine perfusion circuit. A CytoSorb adsorber was connected in parallel to the venous arm and livers were perfused either with (n = 5) or without (n = 3) this device. Throughout perfusion perfusate was collected for analyzing perfusion parameters (pH, glucose, lactate) and snap frozen for post hoc assessment of liver function and inflammation. Tissue biopsies were taken every 3h.

Result
Baseline cytokine levels (IFN-gamma, IL-10, IL-12, IL-18, IL-1alpha, IL-1beta, IL-1ra, IL-2, IL-4, IL-6, IL-8, MMP1, TNF-alpha) were similar in both groups. Pro-inflammatory cytokines IL-6, IL-8 and IL-18 increased over time in both groups, with a numerically greater increase in the control group, reaching statistical significance at 24h. Levels of IL-12 were significantly lower in the CytoSorb group from 6h of perfusion onwards. The anti-inflammatory cytokines IL-10 and IL-1ra increased throughout perfusion in both groups, with the latter plateauing after 12h, and were significantly lower in the CytoSorb group at 12 and 24h. Liver enzymes showed an upward trend in both groups, with a numerically greater increase in the control group.

Conclusions
The inclusion of an adsorption device is feasible in the sub-normothermic setting of ex vivo liver perfusion and has the potential to reduce elevated cytokine levels. This proof-of concept study provided first insights into cytokine adsorption during sub-normothermic machine perfusion and is basis for further experiments to understand the effect of cytokine removal, especially on ECD grafts.

38

Cytokine Profiling In DBD And DCD Livers During Normothermic Machine Perfusion

Julia Hofmann[1], Andras T. Meszaros[1], Madita L. Buch[1], Florian Nardin[1], Verena Hackl[1], Bettina Zelger[2], Margot Fodor[1], Carola J. Strolz[1], Benno Cardini[1], Rupert Oberhuber[1], Annemarie Weissenbacher[1], Thomas Resch[1], Jakob Troppmair[1], Stefan Schneeberger[1], Theresa Hautz[1]

[1]OrganLife Laboratory and Daniel Swarovski Research Laboratory, Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria
[2]Department of Pathology, Medical University of Innsbruck, Innsbruck, Austria

Background
Donation after circulatory death (DCD) organs are increasingly considered for liver transplantation to overcome organ shortage. Such organs may benefit from normothermic machine perfusion (NMP), which allows for evaluation of organ quality and functionality prior to transplantation. For this, reliable biomarkers are required. We herein compared cytokine expression of DBD and DCD organs during NMP, which may be included in the assessment of organ quality.

Methods
DBD (*N*=27) and DCD (*N*=13) livers undergoing NMP (OrganOx Metra) were included in this study, of which 29 (DBD=22, DCD= 7) were found suitable for transplantation. Perfusate samples were collected after start and at the end of NMP. They were analyzed for GM-CSF, IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-12p70, IL-13, IL-18 and TNFα (Invitrogen Th1/Th2 Cytokine 11-Plex Human Procarta-PlexTMPanel). Statistical analysis was performed in the light of the donor type and clinical outcome.

Results
In the early phase of NMP, we did not observe significant differences between DBD and DCD livers for the analyzed cytokines. However, we found specific dynamics in the course of NMP. With prolongation of perfusion, IL-5, IL-6 and IL-1β increased, which resulted in significant differences when comparing DBD and DCD grafts with subsequent transplantation (IL-5: $p<0.0001$, IL-6: $p=0.0145$, IL-1β: $p=0.0173$). In contrast, IL-12p70 decreased in both donor types ((DBD: $p<0.0001$; DCD: $p<0.0001$). Despite a high inter-graft variability in the non-transplanted group, similar courses have been found for some of the discarded livers.

Conclusions
Cytokine quantification may be included in the organ assessment parameters for livers during NMP and help to select the optimal organs for transplantation.

Poster Presentation

39

Innovative Organ Transport Method: Advanced Air Mobility

Robin Karpstein[1,2], Robert Sucher[1], Florian Holzapfel[2], Peter Biberthaler[3], Philipp Stiegler[1]

[1]Clinical Department of General, Visceral, and Transplant Surgery, Medical University Graz, Graz, Austria
[2]Institute of Flight System Dynamics, Technical University of Munich, Munich, Germany
[3]Institute of Trauma Surgery, TUM School of Medicine Klinikum rechts der Isar, Munich, Germany

Background
Solid organ transplantation still is the unique therapy option to cure several end-stage diseases. Organ transplantation requires swift transportation from donors to recipients to improve the recipient's medical outcome as Cold Ishemea Time (CIT) is a critical factor for a successful transplantation. The potential of Advanced Air Mobility (AAM) for organ transplantation in Germany and Austria is assessed in this study. Today, AAM is discussed and tested for transport solutions in healthcare due to potential time savings associated with air transportation. In Europe, AAM is not yet discussed for organ transplantation, also because the technical feasibility is unclear and the required range and payload unknown.

Methods
We applied a Monte Carlo simulation to derive the trip length distributions for organ transplantations in Germany and Austria. Using Eurotransplant data for 2018 - 2021 and ÖBIG data for 2017 to 2021, a weighted Monte Carlo simulation is performed.

Results
We find that 48% of all organ transports within Germany, and 80% of all organ transports within Austria are within a trip length of less than 150km. In Austria, we find that 88% of kidney, 75% of liver, 73% of heart, and 65% of lung transplants are covered within a trip length of 150km.

Conclusion
AAM has the potential to revolutionize organ transports, because a range of 150km is technologically feasible until 2030, with practical ranges of up to 100km available today. Air taxis promise a potential for heart and lung transplantations, because the operating team usually chaperones these two organs, while drone technology presents a great benefit to liver, kidney, and pancreas transports that are usually unchaperoned. AAM improves the transportation time and availability compared to current technology and can be introduced as an additional resource to the current organ transplantation system.

40

The Enhancer Landscape Predetermines The Skeletal Regeneration Capacity Of Stromal Cells

Sarah Hochmann[1]*, Kristy Ou[2]*, Rodolphe Poupardin[1]*, Michaela Mittermeir[1], Martin Textor[3,4], Salaheddine Ali[3,5,6], Martin Wolf[1], Agnes Ellinghaus[3,4], Dorit Jacobi[3,4], Juri A. J. Elmiger[3,4], Samantha Donsante[7], Mara Riminucci[7], Richard Schäfer[8,9], Uwe Kornak[3,5,6,10], Oliver Klein[3], Katharina Schallmoser[11], Katharina Schmidt-Bleek[3,4], Georg N. Duda[3,4,12], Julia K. Polansky[2,13], Sven Geissler[3,4,14#], Dirk Strunk[1#]

[1]Cell Therapy Institute, Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TReCS), Paracelsus Medical University (PMU), 5020 Salzburg, Austria.
[2]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), T Cell Epigenetics, Augustenburger Platz 1, 13353 Berlin, Germany.
[3]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), Augustenburger Platz 1, 13353 Berlin, Germany.
[4]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Julius Wolff Institute (JWI), Augustenburger Platz 1, 13353 Berlin, Germany.
[5]Institute for Medical Genetics and Human Genetics, Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany.
[6]Max Planck Institute for Molecular Genetics, 14195 Berlin, Germany.
[7]Department of Molecular Medicine, Sapienza University of Rome, 00189 Rome, Italy.
[8]Institute for Transfusion Medicine and Immunohematology, Goethe University Hospital, German Red Cross Blood Service Baden-Württemberg— Hessen gGmbH, 60323 Frankfurt am Main, Germany.
[9]Institute for Transfusion Medicine and Gene Therapy, Medical Center – University of Freiburg, 79106 Freiburg, Germany.
[10]Institute of Human Genetics, University Medical Center Göttingen, 37073 Göttingen, Germany.
[11]Institute for Transfusion Medicine, PMU, 5020 Salzburg, Austria.
[12]Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA 02115, USA.
[13]German Rheumatism Research Centre (DRFZ), 10117 Berlin, Germany. 14Berlin Center for Advanced Therapies (BECAT), Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany.
*These authors contributed equally to this work. #These authors contributed equally to this work.

Background
Multipotent stromal cells are considered attractive sources for cell therapy and tissue engineering. Despite

numerous experimental and clinical studies, broad application of stromal cell therapeutics is not yet emerging. A major challenge is the functional diversity of available cell sources.

Methods

Here, we investigated the regenerative potential of clinically relevant human stromal cells from bone marrow (BMSCs), white adipose tissue, and umbilical cord compared with mature chondrocytes and skin fibroblasts in vitro and in vivo.

Results

Although all stromal cell types could express transcription factors related to endochondral ossification, only BMSCs formed cartilage discs in vitro that fully regenerated critical-size femoral defects after transplantation into mice. We identified cell type–specific epigenetic landscapes as the underlying molecular mechanism controlling transcriptional stromal differentiation networks. Binding sites of commonly expressed transcription factors in the enhancer and promoter regions of ossification-related genes, including Runt and bZIP families, were accessible only in BMSCs but not in extraskeletal stromal cells.

Conclusion

This suggests an epigenetically predetermined differentiation potential depending on cell origin that allows common transcription factors to trigger distinct organ-specific transcriptional programs, facilitating forward selection of regeneration-competent cell sources. Last, we demonstrate that viable human BMSCs initiated defect healing through the secretion of osteopontin and contributed to transient mineralized bone hard callus formation after transplantation into immunodeficient mice, which was eventually replaced by murine recipient bone during final tissue remodeling.

Reference

Hochmann et al., Science Translational Medicine. 2023 Mar 22;15(688):eabm7477. doi: 10.1126/scitranslmed.abm7477. PMID: 36947595

41

Moderate LMWH Anticoagulation Improves Success Rate Of Hind Limb Allotransplantation In Mice

Barbara Kern[1,2,3], Muhammad-Imtiaz Ashraf[1], Anja Reutzel-Selke[1], Joerg Mengwasser[1,4], Dietrich Polenz[1], Edward Michaelis[5,6], Johann Pratschke[1], Stefan G. Tullius[7,8], Christian Witzel[2]*, Igor M. Sauer[1]*

[1]Department of Surgery, Campus Charité Mitte | Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany
[2]Department of Plastic Surgery, Campus Charité Mitte | Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany
[3]Berlin Institute of Health, Charité – Universitätsmedizin Berlin, Berlin, Germany
[4]Department of General, Visceral and Transplant Surgery, Regenerative Medicine and Experimental Surgery, Hannover Medical School, Hannover, Germany
[5]Department of Pathology, Charité – Universitätsmedizin Berlin, Berlin, Germany
[6]Institute of Pathology, DRK Kliniken Berlin, Berlin, Germany
[7]Division of Transplant Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
[8]Einstein Berlin Institute of Health Visiting Fellow, Charité – Universitätsmedizin Berlin, Berlin, Germany.
* Denotes joint senior authorship

Background

The mouse hind limb model represents a powerful research tool in vascularized composite tissue allotransplantation, but its applicability is limited due to poor graft survival (62%-83%). Vascular thrombosis and massive hemorrhage are the major causes for these drop-outs. We hypothesize that because of better anticoagulation effect and lower risk of thrombocytopenia, application of low-molecular-weight-heparin (LMWH) will minimize vascular complications and enhance graft and animal survival.

Methods

Fifty allogeneic hind limb transplantations were performed (C57BL/6 to DBA/2 mice) using five different

anticoagulation protocols (Figure 1). Bleeding and thromboembolic events were recorded macroscopically by postoperative hemorrhage and livid discoloration of the graft, respectively. Graft perfusion and survival were monitored daily by capillary-refill-time of graft toes within 2-3 seconds. Vascular congestion and tissue necrosis were examined by histological evaluation of hematoxylin-eosin-stained tissue sections.

Results

All transplantations were technically successful. Increase in thromboembolic events and a concomitant decrease in bleeding events were observed with the decreasing concentration of heparin in the perfusion solution. While treatment of donor and recipient with low dose of LMWH could not reduce thromboembolic events, moderate dose effectively reduced these events. Compared to the poor outcome of graft perfusion with heparin alone, additional treatment of donor and recipient with low dose of LMWH improved graft and animal survival by 18%. Interestingly, animals treated with moderate dose of LMWH demonstrated 100% graft and animal survival (Figure 2).

Conclusion

Treatment of donor and recipient mice with a moderate dose of LMWH prevents vascular complications and improves the outcome of murine hind limb transplants.

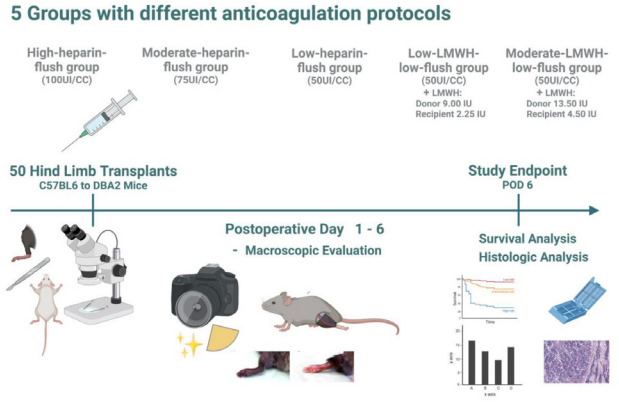

Figure 1

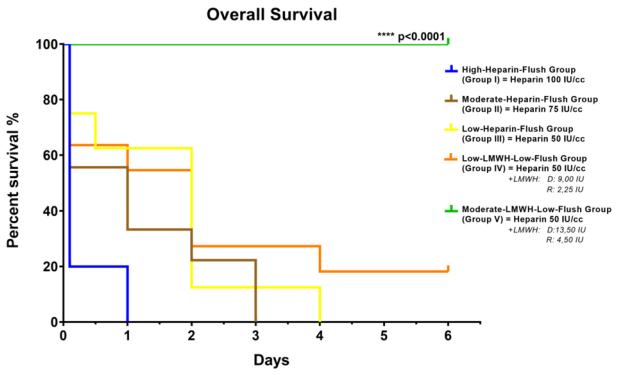

Figure 2

42

Deep Immune Phenotyping Of iPSC-derived HLA-Homozygous Cardiomyocytes

Nicole Maeding[1], Rodolphe Poupardin[1], Anna Steinhuber[1], Nils Kriedemann[2], Robert Zweigerdt[2], Dirk Strunk[1]

[1]Experimental and Clinical Cell Therapy Institute (ExCT), Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TreCS), Paracelsus Medical University, Salzburg, Austria
[2]Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO), Department of Cardiothoracic, Transplantation and Vascular Surgery (HTTG), REBIRTH - Research Center for Translational Regenerative Medicine, Hannover Medical School, Hannover 30625, Germany

Background

Restoration of damaged cardiac tissue poses a challenge as adult cardiomyocytes do not proliferate and thus do not regenerate. Cardiomyocytes generated in vitro from induced pluripotent stem cells (iPS-CM) are a promising approach to replenish lost *cardiomyocytes*. Nonetheless, iPS-CM constitute a graft with a distinct immunephenotype and the risk for rejection. One approach to

reduce this risk and increase matching frequencies is the use of HLA homozygous (HLAho) iPSC strains. Here we performed immune profiling of 3D-differentiated HLA heterozygous (HLAhet) and HLAho iPS-CM to define their immunological phenotypes and aid in investigations into the immune response towards iPS-CMs in different matching scenarios.

Methods

Cardiomyocytes were differentiated from HLAhet and HLAho iPSC aggregates in a 3D culture system using Wnt pathway modulation. On differentiation day 10 aggregates were dissociated and cardiac identity was determined by flow cytometry. Immune profiling was carried out on cardiomyocytes from steady-state and proinflammatory conditions (i.e. stimulation with IFNγ and TNFα) as well as corresponding iPSCs using a flow cytometric screening approach interrogating 354 surface markers. Unsupervised hierarchical clustering and pathway analysis were applied to identify differentially expressed molecules relevant to immune recognition.

Results

We show that iPSCs express low levels of HLA-ABC and β-microglobulin (B2M), however, expression was lower in HLAho iPSCs. While HLA-DR and -DQ were not detected both, HLAhet and HLAho iPSCs, expressed the natural killer (NK) cell ligand MIC-A/B and immunosuppressive CD276. By contrast, iPS-CM downregulated HLA-ABC and MIC-A/B. Proinflammatory stimulation did not affect MIC-A/B levels but it induced expression of HLA-ABC and CD55 (decay accelerating factor, DAF) in iPS-CM.

Conclusions

Downregulation of HLA-ABC and MIC-A/B in iPS-CM suggests these cells may not be recognized by T or NK cells. Yet, microenvironmental stimuli can induce HLA-ABC, CD55, and potentially other relevant molecules which necessitates functional validation in suitable *in vitro* assays.

43

Comprehensive Characterization Of Immune Cell Phenotypes In Lung Transplant Patients Receiving Belatacept

Hatice Oya Akyildiz[1], Shahrooz Nasrollahi Shirazi[1], Sophia Auner[1], Konrad Hötzenecker[1], Peter Jaksch[1], Alberto Benazzo[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background

Lung transplantation is a life-saving procedure for end-stage lung diseases. Belatacept, a selective costimulation blocker, improves transplant outcomes by inhibiting T cell activation. However, the dynamic changes in immune cell phenotypes over time in lung transplant patients receiving belatacept remain poorly understood.

Methods

We characterized immune cell phenotypes in 7 lung transplant patients over time. Whole blood samples were collected weekly for 24 weeks post-treatment with belatacept. Flow cytometry analysis assessed major leukocyte subsets, including T cells, B cells, dendritic cells, and their respective subpopulations.

Results

Lymphocytes remained stable initially, with a slight increase at the second month. The percentage of B cells in lymphocytes gradually rose from 0.2% at baseline to 1% at week 20 and thereafter. Among B cell subsets, IgD+CD27+ increased after week 7, reaching 60% at week 10 and remaining stable until week 24. IgD-CD27+ memory B cells decreased from 50% at baseline to 25% at week 7 and remained stable. IgM+IgD+CD38-CD27- B cells increased after week 10, reaching over 4% at week

24. Within T cell subpopulations, CD8+CM CD27-CD28+ cells slightly increased from 0.5% at baseline to 0.4% at week 20. CD8+ effector CD57+ PD1- and CD8+ EM CD57+ PD1- cells gradually increased to 10% by week 24.

Conclusions
Our study provides a comprehensive characterization of immune cell phenotypes in lung transplant patients receiving belatacept. The observed changes in B and T cell subsets, including increased IgD+CD27+ B cells, decreased IgD-CD27+ memory B cells, and expansion of CD8+CM CD27-CD28+ and CD8+ EM CD27-CD28+ T cells, underscore the immunomodulatory effects of belatacept. These findings further support the understanding of belatacept's impact on immune cell subpopulations, contributing to the development of personalized immunosuppressive strategies for optimizing long-term graft survival.

Keywords: Lung transplantation, belatacept, immune cell phenotypes, flow cytometry, B cells, T cells

44

Development Of An Easy-to-Use Flow Cytometric Panel For Monitoring B Regulatory Cells In Transplant Recipients

Hatice Oya Akyildiz[1], Shahrooz Nasrollahi Shirazi[1], Sophia Auner[1], Peter Jaksch[1], Konrad Hötzenecker[1], Alberto Benazzo[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background
Monitoring B regulatory cells (Bregs) and their functional properties, including IL-10-induced expression, is vital for understanding their immunomodulatory role in transplant recipients. We developed a user-friendly flow cytometric panel for identifying Breg subpopulations and assessing IL-10-induced expression in whole blood samples and peripheral blood mononuclear cells (PBMCs).

Methods
The flow cytometric panel included antibodies against CD45, CD5, CD38, CD27, CD11b, CD73, CD39, CD19, CD1d, CD71, CD24, and IL-10. Stimulation experiments were performed using various conditions and time points. Whole blood samples (100 µl) or PBMCs (1x10^6 cells/ml) were stimulated with PMA/ionomycin/monensin, LPS, or PMA/ionomycin/Brefeldin A for 30 minutes to 16 hours. Cells were then stained, fixed, permeabilized, and incubated with an IL-10 antibody. Flow cytometry analysis was conducted using the DxFLEX flow cytometer.

Results
Our panel enabled the identification of 27 distinct Breg subpopulations in whole blood and PBMCs of healthy donors and lung transplant patients who received alemtuzumab and blatacept at 12 and 7 months post-transplantation, respectively. Notably, we observed a significant 4-fold increase in IL-10-induced expression upon stimulation with PMA/ionomycin/Brefeldin A, which had the most pronounced effect on IL-10 expression compared to other conditions. Although Breg subpopulations were tested in both healthy donors and lung transplant patients, the validation of IL-10-induced expression in Bregs of transplant patients is currently underway.

Conclusions
Our flow cytometric panel offers a comprehensive approach for monitoring Breg subpopulations and assessing IL-10-induced expression. Further validation studies in different transplant protocols are warranted to establish the clinical significance and utility of IL-10-induced expression in Bregs.

Keywords: B regulatory cells, Bregs, IL-10-induced expression, flow cytometry, transplantation, immunomodulation

45

Nutritional Supplements Effects In Combination With CTx In Treating CRCLM. Rat Model

Beatrice Lukenaite[1,2], Bettina Leber[1], Philipp Stiegler[1], Robert Sucher[1], Kestutis Strupas[2]

[1]General, Visceral and Transplant Surgery, Department of Surgery, Medical University of Graz, 8036 Graz, Austria
[2]Faculty of Medicine, Vilnius University, 01513 Vilnius, Lithuania

Background
Colorectal cancer (CRC) is the third most diagnosed cancer in the world and second in mortality of all cancers. At the time of diagnosis, 20% of the patients have distant liver metastasis (CRCLM), which lowers patient's survival rate and possibility of radical treatment. In these cases, patients undergo chemotherapy (CTx). The aim of this study is to evaluate nutritional supplements effect in combination with probiotics in CRLM treatment with CTx in rat model.

Methods
Six-week-old male Wistar rats received either multispecies probiotic (1.2×10^9 CFU/daily) or placebo mixture in combination with one of the nutritional supplements (glycine, sulforaphane or melatonin). After 14 days, rat CRC cells (CC531) were implanted under the liver capsule. After 1 week of inoculation, rats we treated with FOLFOX CTx. Changes in the tumor were measured in micro computed tomography (micro-CT) scans on 28 and 34 experimental days. Blood samples from every timepoint were analyzed.

Results
Probiotics helped to significantly reduce body weight loss for the rats receiving CTx. Sulforaphane in combination with probiotics was most effective. Sulforaphane alone (without chemotherapy or probiotics) decreased the tumor volume significantly comparing to glycine or melatonin alone. Rats that received probiotic and sulforaphane treatment had significantly less days of diarrhea comparing with other groups. Micro-CT image analysis also shows inhibited tumor growth in rats with nutritional supplements.

Conclusions
Study shows that nutritional supplement in combination with probiotics reduces the side effects of CTx (such as weight loss and diarrhea) and inhibits tumor growth in rat CRCLM model. More research is still needed to conclude the effectiveness of nutritional supplement in treating CRCLM before implementing them into daily practice.

46

Sub-Normothermic Liver Machine Perfusion: Equal Performance Of Custodiol® and Belzer MPS®

Sabrina Stimmeder[1], Bettina Leber[1], Kathrin Briendl[1], Jennifer Weber[1], Lisa Rohrhofer[1], Ariane Aigelsreiter[2], Tobias Niedrist[3], Robert Sucher[1], Philipp Stiegler[1]

[1]General, Visceral and Transplant Surgery, Department of Surgery, Medical University of Graz, Austria
[2]Diagnostic and Research Institute of Pathology, Medical University of Graz, Graz, Austria
[3]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

Background
In the setting of liver transplantation, the only cure for a variety of end-stage liver diseases, machine perfusion (MP) is gaining importance. Different MP protocols are available where reported differences are not limited to perfusion temperature but also perfusion solutions supporting different temperature settings. Herein investigate the performance of Custodiol® in 12h of sub-normothermic MP (SNMP) of non-transplantable human liver grafts and compare it to Belzer MPS®.

Methods
Twenty human livers, rejected for transplantation by all centers, subjected to a 12h period of SNMP at 21°C with either 2L of Custodiol® or Belzer MPS® by means of a LiverAssist® device were included in the study. Perfusate and tissue samples before start, after 6h and at the end of SNMP were analyzed for classic liver parameters, along with perfusate (ELISA) and tissue (qPCR) markers of organ damage. pH-stability and bile production were recorded as extended measures of liver quality and a pathologist determined tissue quality. To minimize confounding factors, propensity score matching was done by means of the R Software. The study was approved by the local ethics review board and conducted according to the guidelines of the Declaration of Helsinki.

Results
After propensity score matching (two-to-one nearest neighbor with replacement) 16 livers were analyzed. Most parameters revealed no differences between Custodiol® and Belzer MPS® except for increased MLKL mRNA expression and impaired pH-stability for SNMP with Custodiol®. None of the other parameters, including pathology, supported this finding with slightly increased bile production in the Custodiol® perfused livers pointing the opposite direction.

Conclusions
Results of this study suggest equal performance of Custodiol® and Belzer MPS® during 12h of liver SNMP.

47

Experimental Static Cold Storage Of The Rat Uterus: Protective Effects Of Relaxin- Or Erythropoietin-Supplemented HTK-N Solutions

Lina Jakubauskiene [1,2], Matas Jakubauskas [1,2], Gintare Razanskiene [2,3], Bettina Leber [1], Diana Ramasauskaite [2], Kestutis Strupas [2] and Philipp Stiegler[1]

[1] General, Visceral and Transplant Surgery, Department of Surgery, Medical University of Graz, Graz, Austria
[2] Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[3] National Centre of Pathology, Affiliate of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

Background
Uterus transplantation (UTx) is the only treatment method for women with absolute uterine factorinfertility. Currently, the number of grafts retrieved from deceased donors is increasing, hence, prolonged cold ischemia time is inevitable. Thus, this study was designed to assess the effect of the novel relaxin (RLX) or erythropoietin (EPO)-supplemented Custodiol-N (HTK-N) solutions in an experimental uterus static cold storage (SCS) model.

Methods
A total of 15 Sprague Dawley rats were used. Uterus horns were randomly assigned into three groups (n = 10/group). SCS was performed by keeping samples at 4 °C in HTK-N solution without or with different additives: 10 IU/mL EPO or 20 nM RLX. Tissue samples were taken after 8 and 24 h of preservation. Uterine tissue histology, and biochemical and immunohistochemical markers were analyzed.

Results
Uterine tissue histology, and biochemical and immunohistochemical markers were analyzed. No significant differences in SCS-induced tissue damage were observed

between groups after 8 h of preservation. Uterine tissue histology, MDA, SOD levels and the TUNEL-positive cell number showed severe damage in HTK-N without additives after 24 h of preservation. This damage was significantly attenuated by adding RLX to the preservation solution. EPO showed no favorable effect.

Conclusions
Our study shows that RLX as an additive to an HTK-N solution can serve as an effective uterine tissue preservative in the uterus SCS setting.

06 - ICU

Oral Presentation

48

Organ Donation In Austria – What Can We Learn From Recent Data?

Theresia Unger, Ulrike Fischer, Marianne Ganahl, Manfred Willinger

The Austrian National Public Health Institute, Gesundheit Österreich GmbH (GÖG), ÖBIG-Transplant, Vienna, Austria

Background
The number of organ donors in Austria is relatively high in international comparison, but no sustainable supra-regional increase succeeds. The aim of this work is to discuss limitations and strategies for improvement based on current data.

Methods
In addition to national and international data provided by Eurotransplant and national transplant centers, the documentation by donor coordinators (LTXB) was used for analysis. The LTXB have been installed within the framework of the national action plan in 30 hospitals so far and one of their duties is to document the reasons why deceased ICU patients with brain damage do not become organ donors.

Results
According to LTXB data for 2022, about 30 percent of the deceased ICU patients with brain damage were identified as potential organ donors, and in about 14 percent of the cases organs were used for transplantation. The number of DCD remained very low, although this was where the greatest potential lied, following the data. Other relevant reasons that prohibited organ donation were family opposition, malignancy, and other aspects of organ quality as well as the fact that intensive care was not initiated or reduced before organ donation could take place.

Conclusions
Constant awareness-building is necessary as organ donation is a rare event in most hospitals, so routine is often lacking, and the benefit for the patients on the waiting lists (and the society) should be communicated to those who oversaw the donor care. Criteria for organ donation should be defined evidence-based and the possibilities for donor examination in regional hospitals should be considered. Doctors and nurses should be prepared for the challenging communication with the donors' families in line with Austria's opt-out-legislation. More special training programs and public campaigns might be helpful for that. And finally, DCD programs should be initiated in transplant centers and donor hospitals that are not yet familiar with the procedure.

49

Early Extubation After Liver Transplantation Has A Low Rate Of Emergent Reintubation

Conrad Lacom[1], Rishi Kothari[1,2], Alessandro Galli[1], Michael Bokoch[1], Dieter Adelmann[1]

[1]Department of Anesthesia, University of California, San Francisco, San Francisco, CA, United States
[2]Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA, United States

Background
Practice of early extubation after liver transplantation (LT) varies due to safety concerns. We aimed to assess early extubation rates and their trend over ten years at a high-volume LT center. We characterize the frequency and causes of reintubation and associated patient and procedural factors.

Methods
We conducted a retrospective analysis of all adult LT performed at UCSF between June 2012 and July 2022. The study population was stratified into (1) patients who were extubated early (i.e. in the operating room or within the first hour of ICU admission) and (2) those in whom extubation was delayed. Early extubated patients were screened for reintubation, i.e. requiring mechanical ventilation within 48 hours after end of procedure. Medical records were reviewed to establish the indication for reintubation. Wilcoxon rank sum tests were performed to assess differences in patient and procedural factors between the two groups.

Results
1660 patients were included, of which 988 (60%) underwent early extubation. Yearly rates of early extubation ranged from 52% to 71% without any clear trend over time. Reintubation within 48 hours occurred in 32 patients (3% of early extubations): 21 patients (2%) remained intubated after a reoperation; Only eleven patients (1%) required emergent reintubation due to respiratory failure or for airway protection. Patients extubated early had significantly lower median estimated blood loss [2L (IQR 1,3.5) vs. 4.5L (IQR 2.3,8.5), p <0,001], received less transfusion of allogeneic blood products [8 (3, 17) units vs. 22 (13, 33) units, p <0.001], had lower median MELD-Na scores [17 (12,28) vs. 33 (21,39), p <0,001] and shorter median ICU lengths of stay [41 (29,61) hours vs. 76 (50,117) hours, p <0,001].

Conclusion
Most liver transplant recipients can undergo successful, early extubation in a high-volume LT center. In correctly selected patients, emergent reintubation is required in one percent of cases.

50

Red Blood Cell Transfusion-Related Dynamics Of Extracellular Vesicles In Intensive Care Patients – A Prospective Subanalysis

Pierre Raeven[1], Katharina Karlhofer[1,2], Jonas Brugger[3], Konrad Hoetzenecker[4], Christoph Domenig[5], Gerda Leitner[6], Martin Posch[3], David M. Baron[1], Andreas Spittler[2]

[1]Medical University of Vienna, Department of Anesthesia, General Intensive Care, and Pain Management, Division of General Anesthesia and Intensive Care, Vienna, Austria
[2]Medical University of Vienna, Department of Surgery, Division of Visceral Surgery and Core Facility Flow Cytometry, Vienna, Austria
[3]Medical University of Vienna, Center for Medical Statistics, Informatics, and Intelligent Systems, Section for Medical Statistics, Vienna, Austria
[4]Medical University of Vienna, Department of Thoracic Surgery, Vienna, Austria [5]Medical University of Vienna, Department of Surgery, Division of Vascular Surgery, Vienna, Austria
[6]Medical University of Vienna, Department of Blood Group Serology and Transfusion Medicine, Vienna, Austria

Background
Extracellular vesicles (EVs) accumulate during packed red blood cell (PRBC) storage and may be relevant for personalised transfusion medicine. To date, the involvement of EVs in transfusion-related immunomodulation (TRIM) has not been prospectively evaluated in intensive care unit (ICU) patients.

Methods
This was a prospective subanalysis of a recent observational feasibility study in postoperative ICU patients after: 1) open aortic surgery (Aorta), 2) bilateral lung transplantation (LuTx), and 3) other types of surgery (Comparison). Patient plasma was collected three times each before and after PRBC transfusion at 30-minute intervals. The total number of EVs and EVs derived from erythrocytes (EryEVs), total platelets (total PEVs), activated platelets,

granulocytes (GEVs), monocytes, and myeloid cells in PRBC samples and patient plasma were analyzed by flow cytometry. Statistical analysis was performed by Spearman's correlation test, linear mixed models and pairwise comparisons by Wilcoxon matched-pairs test. Twenty-three patients (Aorta n=5, LuTx n=9, Comparison n=9) were included in the final analysis.

Results

All EV subgroups analyzed were detectable in all PRBCs samples (n=23), but concentrations did not correlate with storage time. Moreover, all EVs analyzed were detectable in all plasma samples (n=138), and EV counts were consistent before transfusion. Concentrations of total EVs, EryEVs, total PEVs, and GEVs increased after transfusion compared with baseline in the entire cohort but not in specific study groups. Furthermore, the change in plasma EV counts (total EVs and EryEVs) after transfusion correlated with PRBC storage time in the entire cohort.

Conclusions

EVs were detectable in all PRBC and plasma samples. Individual EV subtypes increased after transfusion in the entire cohort, and in part correlated with storage duration. Future clinical studies to investigate the role of EVs in TRIM and personalised transfusion medicine are warranted and should anticipate a larger sample size.

07 - Cell Therapy

Poster Presentation

51

Impact Of The Recipients' Pre-Treatment Blood Lymphocyte Count On Intended And Unintended Effects Of Anti-T-Lymphocyte Globulin In Allogeneic Hematopoietic Stem Cell Transplantation

Alexander Nikoloudis[1,2,*], Veronika Buxhofer-Ausch[1,2], Christoph Aichinger[1], Michaela Binder[1], Petra Hasengruber[1], Emine Kaynak[1], Dagmar Wipplinger[1], Robert Milanov[1], Irene Strassl[1,2], Olga Stiefel[1,2], Sigrid Machherndl-Spandl[1,2], Andreas Petzer[1,2], Ansgar Weltermann[1,2], Johannes Clausen[1,2]

[1]Ordensklinikum Linz – Elisabethinen, Department of Internal Medicine I: Hematology with Stem Cell Transplantation, Hemostaseology and Medical Oncology, Linz, Austria
[2]Johannes Kepler University, Medical Faculty, Linz, Austria
*Correspondence: alexander.nikoloudis@ordensklinikum.at

Background

In allogeneic hematopoietic stem cell transplantation (HSCT), Anti T Lymphocyte Globulin (ATLG) may be used for prevention of severe graft-versus-host disease (GVHD). ATLG is targeting both the recipient's lymphocytes and those transferred with the graft. Assuming an

inverse relation between the recipient's abso-lute lymphocyte count (ALC) and exposure of remaining ATLG to the graft, we aim to evaluate the impact of the recipients' ALC before the first ATLG administration on the benefits (prevention of GVHD and GVHD-associated mortality) and potential risks (increased relapse incidence) associated with ATLG.

Methods

In recipients of HLA-matched, ATLG-based HSCT (n=311), we assessed the incidence of acute GVHD, GVHD-related mortality and relapse, as well as other transplant-related outcomes, in relation to the respective ALC (divided into tertiles) before ATLG.

Results

The top-tertile ALC group had a significantly increased risk of aGVHD (subhazard ratio (sHR) 1.80; [CI 95%; 0.78-1.67]; P=0.01) and aGVHD-associated mortality (sHR 1.85; [CI 95%; 1.04- 3.27]; P=0.03). In the highest ATLG dose level (≥45mg/kg), recipients with lowest-tertile ALC had a trend towards increased relapse in-cidence (sHR 4.19; [CI 95%; 0.99-17.7]; P=0.05, n=32).

Conclusion

ATLG dosing based upon the recipient's ALC may be required for an optimal balance between GVHD suppression and relapse prevention.

52

Systemic Steroid Use And GVHD Adjudication During The First Year After Allogeneic HSCT

Julia Cserna, Hanna Knaus, Agnes Abrahamowicz, Katja Zeiser, Werner Rabitsch, Margit Mitterbauer, Philipp Wohlfarth

Einrichtung für Stammzelltransplantation (KMT), Universitätsklinik für Innere Medizin I, Medizinische Universität Wien

Background

Steroids are the first-line treatment for GVHD but may also be administered for other reasons after allogeneic HSCT. There is limited knowledge about the total burden of steroid treatment and the clinical circumstances leading to their use in cases of suspected GVHD.

Methods

We conducted a retrospective single-center cohort analysis of all patients undergoing allogeneic HSCT at our institution between 01/2015 and 06/2021. The primary endpoints were frequency, timing, and reasons for systemic steroid treatment during the first year after HSCT. Secondary endpoints included diagnostic procedures and findings related to a suspected GVHD diagnosis.

Results

Among 455 patients (median age: 51 [IQR: 39-59] years; 39% female), 57% (n=232) received steroids at least once within the first year after HSCT. Of these patients, 31% (n=73) were given a second course. The reasons for administering steroids were mainly GVHD treatment (71%; n=211), GVHD prophylaxis (8%; n=24), or other causes (21%; n=63). Median initial steroid doses in three groups were 0.96 [0.66-1.14], 0.91 [0.48-1.84], and 0.63 [0.26-1.29] mg prednisone equivalent/kg; median treatment durations were 61 [37-120], 89 [48-164], and 35 [17-78] days, respectively. In patients treated for acute GVHD (n=135), biopsies of involved organs were taken in 63% (n=85), with 66 (78%) confirming the diagnosis and 19 (22%) yielding an equivocal or negative result. In chronic GVHD, biopsy frequency was lower (24%; n=18), and diagnostic uncertainty was higher (39% equivocal/negative; n=7). Systemic steroid utilization was highest during month three after HSCT but never dropped below 20% during the 1-year follow-up (Figure).

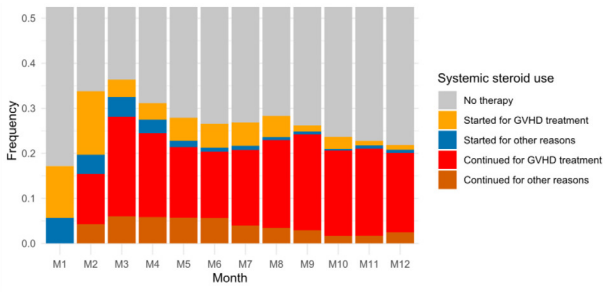

Figure 1

Conclusion
We observed a high rate of systemic steroid treatment throughout the first year after HSCT. About 30% of courses were started for reasons other than GVHD treatment. Given the observed diagnostic uncertainty, only considering confirmed GVHD as a surrogate underestimates the burden of systemic steroid treatment following HSCT.

53

Protein Corona Of EVs Is Essential For Skin Cell Self Organization And Aids Wound Healing

Martin Wolf[1], Rodolphe Pupardint[1], Fausto Gueths Gomes[2], Anna Raninger[1], Patricia Ebner[1], Sarah Hochmannn[1], André Cronemberger Andrade[1], Nicole Maeding[1], Balazs Vari[1], Essi Eminger[1], Astrid Obermayer[3], Thomas Heuser[4], Michaela Öller[2], Hans-Dieter Volk[5], Katharina Schallmoser[2] and Dirk Strunk[1]

[1]Cell Therapy Institute Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TReCS), Paracelsus Medical University (PMU) Salzburg, Austria
[2]Platelet Research Group, Transfusion Medicine Institute, both: Spinal Cord Injury and Tissue Regeneration Center Salzburg (SCI-TReCS), Paracelsus Medical University (PMU) Salzburg, Austria
[3]Department of Biosciences, Paris Lodron University Salzburg, Austria
[4]Vienna Biocenter Core Facilities, Vienna, Austria
[5]Berlin Institute of Health at Charité – Universitätsmedizin, BIH Center for Regenerative Therapies (BCRT), Berlin, Germany

Background
Transport of functional protein cargo via extracellular vesicles (EVs) is an important mechanism in cell communication. We investigated the distribution of active cargo proteins between EV's inside and outside to evaluate their implications for theraputic applications.

Methods
EVs from placenta-derived stromal (PLX) cells conditioned medium or from human platelet lysates were enriched by tangential flow filtration (TFF) optionally followed by ultracentrifugation or size exclusion chromatography (SEC). Following MISEV2018 guidelines EV preparations were characterized using western blot, tunable resistive puls sensing (TRPS), cryo electron microscopy and super-resolution microscopy. Self organization capacity in presence or absence of different EV preparations was analyzed in a highthroghput organoid assay. Contribution of EVs to woundhealing was assessed in an in vivo model transplanting human skin cells on NSG mice.

Results
EV identity could be confirmed for both sources by enriched expression of tetraspanins in EV preparations compared to originating cells. Integrity for platelet and PLX cell derived EVs was verified by cryo electron microscopy and super resolution microscopy. Spheroid formation of human skin derived fibroblasts alone or as whole skin organoids together with endothelial cells and keratinocytes was only succesful in the presence of TFF purified EVs bearing a functional protein corona while soluble factors alone or corona depleted EVs after SEC could not initiate this process. Also in our in vivo mouse model TFF purified EVs were essential for proper organization of the human skin cells in the wound area and providing sufficient vascular suport.

Conclusion
This findings allowed us to develop a self organizing human skin model in mice and shows the important role of corona proteins for EV function. Recent calculations indicating a 'surface-to-bulk partition of EV cargo', for EVs < 180nm, in favor of surface cargo loading support the new concept of a functional EV corona.

54

BendaEAM Versus BEAM As Conditioning Regimen For ASCT In Patients With Relapsed Lymphoma (BEB): A Multicentre, Randomised, Phase II Trial

Felix Keil[1], Antonia M S Müller[2,3], Andrea Berghold[4], Regina Riedl[4], Veronika Buxhofer-Ausch[5,6], Judith Schuster[7], Corinne Vorburger[8], **Alexandra Böhm**[9], Michael Panny[1], Thomas Nösslinger[1], Richard Greil[7,10,11,12], Panagiotis Samaras[13], Celine Bencker[1], Markus Rütti[3], Thomas Pabst[8]

[1] 3rd Medical Department for Haematology and Oncology, Hanusch Hospital, Vienna, Austria
[2] Department of Transfusion Medicine and Cell Therapy, Medical University of Vienna, Vienna, Austria
[3] Department of Medical Oncology and Haematology, University Hospital Zurich, Zurich, Switzerland
[4] Institute for Medical Informatics, Statistics, and Documentation, Medical University Graz, Graz, Austria
[5] Department of Internal Medicine I with Haematology, Stem Cell Transplantation, Haemostaseology and Medical Oncology, Ordensklinikum Linz Elisabethinen, Linz, Austria
[6] Medical Faculty, Johannes Kepler University Linz, Linz, Austria
[7] Austrian Group Medical Tumor Therapy (AGMT), Salzburg, Austria
[8] Department of Medical Oncology, Inselspital, Bern University Hospital, Bern, Switzerland
[9] Haematological Health Care Centre of the ÖGK Mariahilf, Vienna, Austria
[10] Cancer Cluster Salzburg (CCS), Salzburg, Austria
[11] III'rd Medical Department with Haematology and Medical Oncology, Haemostaseology, Rheumatology and Infectious Diseases, Oncologic Centre, Paracelsus Medical University, Salzburg, Austria
[12] Salzburg Cancer Research Institute with Laboratory of Immunological and Molecular Cancer Research and Centre for Clinical Cancer and Immunology Trials (CCCIT), Salzburg, Austria
[13] Clinic for Haematology and Oncology Hirslanden Zurich, Zurich, Switzerland

Background
Replacement of BCNU in the BEAM regimen (BCNU, etoposide, cytarabine, melphalan) with bendamustine (BendaEAM) before autologous stem cell transplantation (ASCT) is feasible in lymphoma. However, randomised trials are lacking. Here, we present the first trial addressing this topic.

Methods
This multicentre, randomised, Austrian-Swiss phase II study (BEB-trial) compares BEAM with BendaEAM in patients with relapsed lymphoma. Both regimens were administered intravenously before ASCT, in BEAM according to the standard protocol (300mg/m^2 BCNU on day -6), in BendaEAM, BCNU was replaced by 200 mg/m^2 bendamustine given on days -7 and -6. Eligible patients were aged 18-75 years and had mantle cell lymphoma, diffuse large B-cell lymphoma, or follicular lymphoma in first or second remission or chemosensitive relapse. Primary endpoint of the study was to evaluate whether replacement of BCNU by bendamustine reduces lung toxicity, defined as a decrease of the diffusion capacity of the lung for carbon monoxide (D_{LCO}) by at least 20% at three months after ASCT. Data analyses were performed on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT02278796, and is closed.

Results
Between April 20, 2015, and November 28, 2018, 108 patients were enrolled; 53 were randomised to BendaEAM (36 male, 67.9%; 17 female, 32.1%), 55 to BEAM (39 male, 70.9%; 16 female, 29.1%). All patients engrafted rapidly. Lung toxicity did not differ between groups (BendaEAM: *N* = 8, 19·5%; BEAM: *N* = 9, 20·9%). Acute toxicities ≥ grade 3 were comparable in both arms (BendaEAM: 35·8%, BEAM: 30·9%). Overall survival (BendaEAM: 92·5%, BEAM: 89·1%) and complete remission (BendaEAM: 76·7%, BEAM: 74·3%) after one year (median: 369 days) were similar. No difference in quality of life was observed.

Conclusions
We observed equivalent survival and response rates in both regimens, with manageable toxicity. BendaEAM may therefore be considered a reasonable alternative to BEAM.

Funding
Mundipharma

55

Plerixafor Vs Placebo For Stem Cell Mobilization In Patients With Multiple Myeloma Optimizes Collection Results In Moderate Mobilizers (Optimize)

Andreas Tanzmann[1], Manuela Branka[1], Vera Kolovratova[1], Martin Kurz[1], Patricija Raijsp[1], Markus Dettke[1], Michaela Horvath[1], Elke Zipperer[2], Rene Geyregger[2], Konrad Rosskopf[3], Hildegard Greinix[4], Nina Worel[1]

[1]Medizinische Universität Wien, Transfusionsmedizin und Zelltherapie, Wien, Österreich
[2]St. Anna Kinderkrebsforschung GmbH, CHILDREN'S CANCER RESEARCH INSTITUTE / CCRI, Wien, Österreich
[3]Medizinische Universität Graz, Blutgruppenserologie und Transfusionsmedizin, Graz, Österreich
[4]Medizinische Universität Graz, Klinische Abteilung für Hämatologie, Graz, Österreich

Background
This study evaluates the safety and efficacy of plerixafor (PLER), a CXCR4 antagonist, in mobilizing hematopoietic progenitor cells for autologous hematopoietic cell transplantation (HCT) in multiple myeloma (MM) patients.

Methods
A phase IV, multicenter, randomized (1:1), double-blind, placebo-controlled study; patients with MM targeting 2 autologous HCTs mobilized with granulocyte colony-stimulating factor (G-CSF; 2x5 µg/kg) s.c. daily for up to 5 days were eligible. On day 4 of GCSF, peripheral blood (PB) CD34+ count was analyzed and patients were enrolled if they had 15-40 CD34+ cells/µL. They received either PLER at a dose of 240 µg/kg or placebo 4-12 hours before start of apheresis. The primary endpoint was to collect 6 x10E6 CD34+ cells/kg in one apheresis. Additionaly CD34+ and lymphocyte subsets, colony forming units (CFU) and engraftment kinetics were analyzed.

Results
The study was designed for 90 patients but was stopped after 21 patients due to approval of daratumumab also for first line therapy in MM, which led to insufficient mobilization (PB <15 CD34+ cells/µl). With PLER preapheresis CD34+ cell counts were significantly higher (median 93,3/µL vs. 29,34; p-Value 1.71E-08). Ten of 21 (48%) patients received PLER and 11 (52%) placebo. All PLER group patients met the primary endpoint (median 7.6 x10E6; range 7.03 to 13.18 CD34+ cells/kg) compared to none in the placebo group (median 2.52 x10E6 CD34+ cells/kg, range 1.40 to 5.27 x106 CD34+ cells/kg). PLER was tolerated well with only rare cases of gastrointestinal disorders.

Conclusion
Compared to G-CSF alone, PLER+G-CSF allowed collection >6x10E6 CD34+ cells/kg for 2 autologous HCTs in only one apheresis session in moderately mobilizing MM patients (i.e. 15-40 CD34+ cells/µl). This not only reduces apheresis procedures and workload for operators and technicians but also improves planning of apheresis and patient"s comfort. Therefore PLER should be considered also in patients with moderate mobilization.

08 - Heart TX

Oral Presentation

56

Immunity Response During Ex-Situ Heart Perfusion In Donation After Circulatory Death In A Porcine Model

Lukas Stastny[1], Stefan Salcher[2], Nina Hofmann[1], Natalie Huemer[1], Alexandra Ampferer[1], Florian Sommerauer[1], Gabriel Putzer[3], Julian Wagner[3], Judith Martini[3], Stefan Schneeberger[4], Michael Grimm[1], Julia Dumfarth[1]

[1] Department of Cardiac Surgery, Medical University of Innsbruck, Austria
[2] Department of Internal Medicine V, Medical University of Innsbruck, Austria
[3] Department of Anesthesiology and Intensiv Care, Medical University of Innsbruck, Austria
[4] Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Austria

Background
Ex-situ heart perfusion (ESHP) enables the resuscitation and assessment of hearts procured after a donation after circulatory death (DCD). However, a gradual functional decline and edema formation are limiting the potential of this technology. The aim of this study was to investigate the cytokine release during ex-situ heart perfusion in two different procurement strategies.

Methods
12 German domestic pigs were used as heart and blood donors. Donation after circulatory death" (DCD) (n=6) and a control group (n=6) were investigated during 6 hours of normothermic ESHP. Analysis were performed in vivo and after 1, 3 and 6 hours of perfusion. To analyse myocardial metabolic changes during ESHP, arterial lactate and oxygen consumption (OC) were investigated. A magnetic luminex assay was performed to analyse different cytokines. Data were compared between the groups with mixed ANOVA.

Results
Arterial lactate levels were significant higher in the DCD group: 1h: DCD 69.33 vs. DBD 17.33mg/dl p=0.003; 3h: DCD 55.17 vs. DBD 12.33 mg/dl, p<0.001, 6h: DCD 46.17 vs. DBD 13.89mg/dl, p<0.001. There was no difference between the groups regarding oxygen consumption, but a significant interaction between the duration of ESHP and OC (F (1,102, 11,02) = 22,48, p=0.0005)).

Assessment of cytokine release in ESHP revealed no significant difference between both groups, but a significant interaction of the timecourse of ESHP and amount of cytokine release (GM-CSF: F (2, 30) = 26,59, p<0.001; INFγ: F (2, 30) = 35,28, p<0.001, TNFα: F (2, 30) = 11,18, p=0.001, IL-4: F (2, 30) = 52,86, p<0.001, IL-6: F (2, 30) = 145,5, p<0.001, IL-8: F (2, 30) = 36,38, p<0.001)

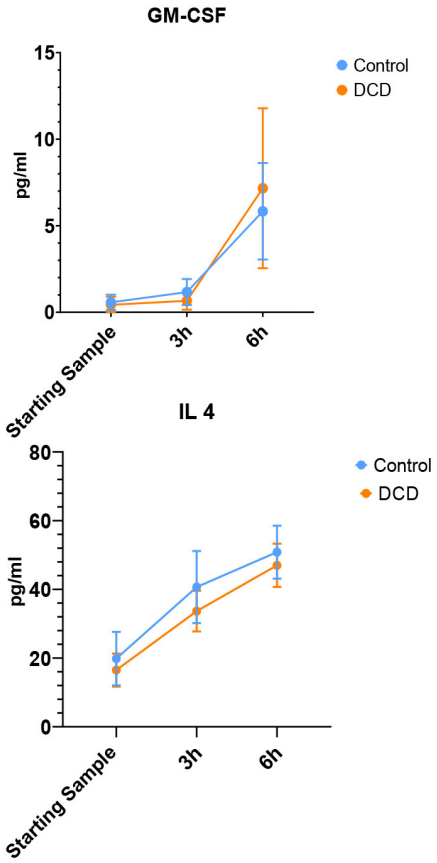

Figure 1

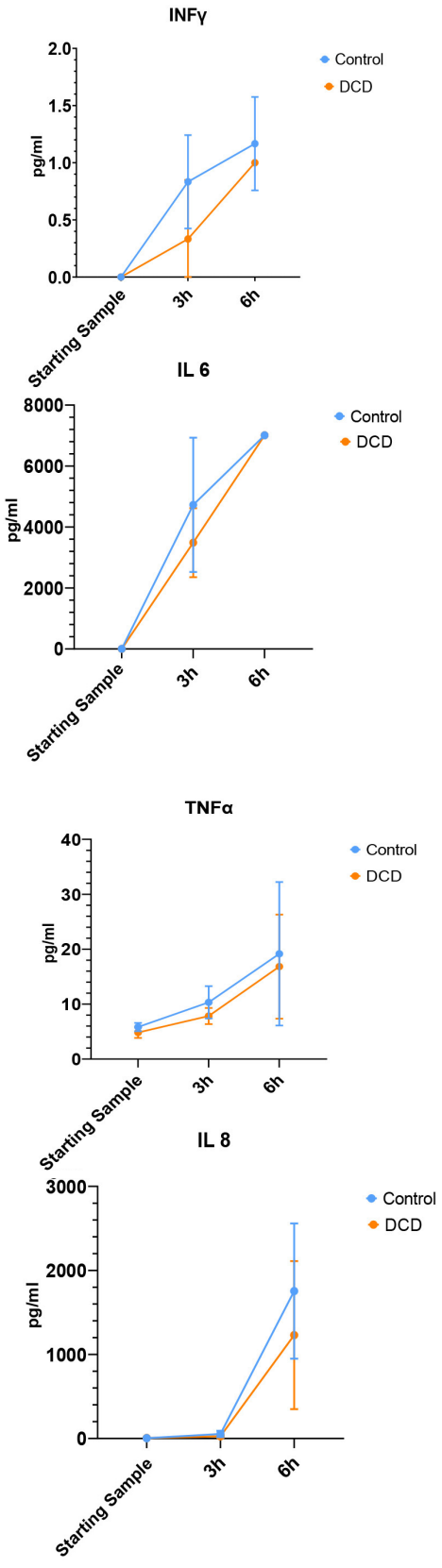

Figure 1 | (Continued)

Conclusions

There was a considerable increase of cytokine levels throughout the entire perfusion time. Interestingly, there was no difference between control group and DCD group regarding cytokine levels. These findings emphasize the impact of ex-situ heart perfusion itself on activation of immune response.

57

10 Minutes Hands-Off Time In Donation After Circulatory Death (DCD) Heart Transplantation

Johannes Gökler, Andreas Zuckermann, Johann Horvat, Roxana Moayedifar, Emilio Osorio, Juliana Coti, Thomas Putz, Franziska Wittmann, Keziban-Uyanik-Ünal, Günther Laufer, Arezu Aliabadi-Zuckermann

Medical University Vienna, Austria

Background

To address the increasing demand for heart transplantation, a clinical program of heart transplantation from donation after circulatory-determined death (DCD) donors was established at the Medical University of Vienna in 2019. However, Austria has a longer observation (hands-off) period compared to other countries, potentially harming the heart that has only limited tolerance to warm ischemia. We report our first DCD transplants performed with 10 minutes hands-off time.

Methods

A retrospective analysis of DCD heart transplantations between 2019 and July 2023 with Direct Procurement and ex-vivo normothermic machine Perfusion (DPP) with Organ Care System (OCS, Transmedics) was performed. All donors were Maastricht category III. Explantation times and postoperative outcomes including PGD, ICU stay and survival, were described.

Results
Seven organs were resuscitated on OCS but two of them were rejected for transplantation (late administration of heparin at procurement and dilated heart in one and therapy-resistant high potassium leading to bradycardia in the other organ). Three donors (60%) and 4 (80%) recipients were male. Recipient age was 61.5, 68, 33.8, 57, 62 years and donor age 42, 30, 37, 18 and 31 years, respectively. Length of agonal phase (withdrawal of treatment to cardiac arrest) was 10 minutes (IQR: 9-14) and surgical warm ischemic time (skin incision to start of cardioplegia) was 4 minutes (3 – 5). Perfusion times on OCS were 223, 236, 316, 373 and 300 minutes. Lactate levels (arterial/venous) were decreasing in all patients with levels at the beginning of perfusion of 6.19 (5.72-6.64)/ 6.20 (5.62-6.37) and at the end of perfusion of 3.64 (2.58-4.34)/ 3.37 (2.72-4.26). All but one patient (ECMO due to PGD with successfully weaning on POD4) were weaned from heart lung machine with moderate inotropic support and normal cardiac function. One patient had moderate to severe tricuspid insufficiency intraoperatively that resolved completely during ICU stay. Length of intensive care unit stay was 8 (7-11) days. All patients had excellent postoperative recovery with good biventricular function and all were discharged from hospital in good clinical condition. One patient died 2 years after transplantation due to a severe infection, all others are still alive 1271, 943, 212 and 175 days after transplantation with normal ejection fraction.

Conclusion
DCD heart transplantation with 10 minutes hands-off time is feasible and with good clinical outcome in our setting of DCD procurement.

58

Heart Transplantation With Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) Therapy

Thomas Putz[1], Andreas Zuckermann[1], Johannes *Gökler*[1], Thomas Haberl[1], Roxana Moayedifar[1], Keziban Uyanik-Ünal, Günther Laufer, Arezu Aliabadi-Zuckermann[1]

[1]Department of Cardiac Surgery, Medical University Vienna, Vienna General Hospital, Austria

Background
Patients on the waiting list for HTx need an optimal anticoagulation strategy in order to prevent stroke or systemic embolic events. Due to the estimated elevated risk of perioperative bleeding in patients on NOAC, they are switched to Vitamin K antagonists while awaiting transplantation. In this case series we report 4 patients with NOAC therapy undergoing HTx.

Methods
We retrospectively reviewed patients with active NOAC therapy undergoing heart transplantation at the Department of Cardiac Surgery at the Vienna General Hospital using QS2. Patients records were investigated including surgical reports for bleeding events, intraoperative admission of blood products and need of surgical revision.

Results
Our patients (n=4, all male) where anticoagulated with either Rivaroxaban (n=2) or Dabigatran (n=2) until the day of HTx. The first patient on Rivaroxaban therapy received a total of 14 RBC concentrates, 16 bags of fresh frozen plasma (FFP) and four platelet concentrates intraoperatively. Due to postoperative diffuse bleeding, surgical revision was necessary. One patient was on Rivaroxaban and had an uneventful perioperative course. A CytoSorb®-Filter was used intraoperatively, 2 RBC concentrates, 5 platelet concentrates and 5 bags of FFP where administered. The third patient was on Dabigatran therapy. Intraoperative course was uneventful, the patient

received 3 RBC concentrates, 5 bags of FFP and 2 bags of platelet concentrates. Due to pericardial tamponade, the patient had to undergo bleeding revision on the first postoperative day. The fourth patient was transplanted with active therapy of Dabigatran and received 2 platelet concentrates (using CytoSorb®-Filter) intraoperatively. In the postoperative course this patient had cardial decompensation followed by implantation of VA-ECMO.

Conclusions
In our small single-center cohort, perioperative bleeding complications were high. In order to optimize patient outcome, the feasibility of the procedure with patients under NOAC therapy should undergo interdisciplinary discussion.

59

Diagnostic Yield Of Routine Biopsies In A Pediatric Heart Transplant Collective

Julian Heno[1], Sabine Greil[1], Doris Luckner[1], Ina Michel-Behnke[1]

[1]Pediatric Heart Center, Medical University of Vienna, Vienna, Austria

Background
Routine endomyocardial biopsies are part of the standard of care in pediatric heart transplantation, although the set intervals vary between transplant centers. In patients beyond infancy, routine biopsies are usually carried out four weeks, one year and every five years after transplantation at our center. As possible less invasive alternatives begin to arise, we set out to evaluate the results of routine versus clinically indicated biopsies.

Methods
Biopsies carried out over the course of 6.5 years at the Viennese pediatric heart transplant center of were retrospectively analyzed with regard to indication and therapeutic consequence.

Results
122 biopsies were done in 48 organ recipients. Of 17/122 (14%) biopsies indicated by clinical presentation of acute rejection, 47% showed histopathological signs of rejection and 30% had therapeutic consequences (number needed to treat = 3.4), 13% had incipient histopathological transplant vasculopathy. 105/122 were routine biopsies, 46 of which were carried out after recent transplantation (<6 weeks) or as follow-up after recent rejection and had a diagnostic yield of 54%, with therapeutic consequences in 17% and vasculopathy in 2%. Of the remaining routine biopsies (n = 61), 87% showed no rejection and in the residual 13% only mild cellular or humoral rejection was detected (1R, AMRI); signs of vasculopathy were found in 3%.

Conclusions
In our pediatric heart transplantation center, indication biopsies as well as biopsies after recent transplantation or rejection had a high diagnostic yield during the observation period, corresponding to a number needed to treat of 3.4 and 5.8, respectively. Routine biopsies detected mild rejection or incipient histopathological transplant vasculopathy leading to intensified risk management in a fraction of cases and did not have grave therapeutic consequences, emphasizing the need to further the quality of non-invasive post-transplant diagnostic in this patient population.

60

Short-term Postoperative BMI Changes In Cardiac Transplant Patients

Anja Langer, Tandis Aref, Thomas Putz, Iuliana Coti, Katharina Ebbenberger, Keziban Uyanik-Ünal, Johannes Gökler, Günther Laufer, Arezu Aliabadi-Zuckermann, Andreas Zuckermann

Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

Background

The presence of obesity or BMI increase is well known to have a detrimental and negative impact on the post-operative outcome of heart transplant recipients. This increase, however, can be caused and influenced by the standard operating medical treatment scheme for immunosuppressive therapy which is required after heart transplantation. The aim of this retrospective analysis is to evaluate the changes in BMI of our study population within the first post-transplant year to develop strategies and obviate weight gain and its long-term consequences in the future.

Methods

66 patients were included in this single-center, retrospective cohort study who underwent heart transplantation at the General Hospital Vienna, Department of Cardiac Surgery from January 2020 until December 2021. All available data were retrieved from the documentation system of the hospital for statistical analyses. Descriptive methods were used to describe the changes in BMI and weight classes in our study group over a follow-up period of one year.

Results

The study population consisted of 50 male (75.8%) and 16 female patients (24.2%). The mean weight at baseline was 78.3kg (95% CI: 74.9-81.6) which resulted in a mean BMI of 25.7 kg/m^2 (95% CI: 24.9-26.6) pre-transplant. 1 patient had a BMI below 18.5 (1.5%) and 6 patients reported a BMI of 30 kg/m^2 and higher. The mean weight at 1-year FUP was 76.5kg (95% CI: 70.0-83.1) with a mean BMI of 25.2 (95% CI: 23.1-27.2). No patient had a BMI of above 30 kg/m^2 at 1-year follow-up.

Conclusion

BMI increase poses a challenge in the medical treatment and management of cardiac transplant patients. Further studies will be necessary to investigate whether new treatment options such as SGLT2 inhibitors, incretin mimetics and/or GLP-1 receptor agonist will positively impact the outcome in terms of diabetes control and reduce all-cause mortality through maintaining normal body mass references.

Poster Presentation

61

Outcomes And 3-Years Of Experience With CD38 Antibody Daratumumab In Sensitized Heart Transplantation Recipients

Clemens Atteneder[1], Roxana Moayedifar[1], Maja Nackenhorst[2], Daniela Koren[3], Gottfried Fischer[3], Georg Böhmig[4], Keziban Uyanik-Ünal[1], Arezu Aliabadi-Zuckermann[1], Günther Laufer[1], Andreas Zuckermann[1]

[1] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria
[2] Department of Pathology, Medical University of Vienna, Vienna, Austria
[3] Department of Department for Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria
[4] Division of Nephrology and Dialysis, Medical University of Vienna, Vienna, Austria

Background

CD38 antibody Daratumumab slowly becomes a tool of interest in heart transplantation (HTx), especially in highly sensitized recipients. A cohort which is constantly increasing in number and degree of sensitization. Primarily approved for multiple myeloma therapy its mechanisms on the immune system also show effect in solid organ transplantation.

Methods

Recipients received 10 cycles of 1800mg Daratumumab within six months. Before the antibody therapy 7-10 cycles of immunoadsorption (IAS) was used, whereas the first cycle was performed directly prior HTx. If Daratumumab was used for desensitization three cycles were administered pre-HTx, followed by seven cycles post-HTx. In this case no IAS was used.

Results
In 3 years four highly sensitized HTx-recipients (median calculated panel reactive antibody: 84.5%) were treated with daratumumab. Complement-dependent cytotoxicity assay (CDC) was positive in three patients and median donor specific antibody (DSA) level shortly after HTx was 81.3*10^3 mean fluorescent intensity (MFI). CDC was only negative after desensitization protocol, although no decrease of alloantibodies was recognizable pre-HTx. However, after HTx titer decreased to less than 2000 MFI after 49 days. Similar reduction was observed in two other cases, when administered only after HTx. Endomyocardial biopsies have shown in three recipients pathologic antibody-mediated rejection 2, but patients never have presented clinical signs or reduction of heart function and were never in need of additional immunosuppression (IS). In two patients in hospital treatment was needed due to a fungal meningitis and a post-transplant lymphoproliferative disease after one year of transplantation. All recipients are alive and median follow up period is 705 days (458-1122 days).

Conclusions
This is the first mid-term report of daratumumab-usage in HTx-recipients, showing the ability of daratumumab to minimize cytotoxic antibody-production, to interfere with immune response and to prevent clinical relevant pAMRs. However additional IS always increases the risk of associated adverse events like server infection and PTLD.

62

Psoas Muscle Area: An Independent Predictor For Mortality In Patients Undergoing Heart Transplantation?

Tandis Aref, **Anja Langer**, Thomas Putz, Iuliana Coti, Katharina Ebbenberger, Keziban Uyanik-Ünal, Johannes Gökler, Günther Laufer, Arezu Aliabadi-Zuckermann, Andreas Zuckermann

Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

Background
A plethora of clinical trials already demonstrated a significant association between frailty in patients with heart disease and all-cause mortality. Frailty is defined as a multifactorial geriatric syndrome that describes an age-related decline in muscle mass and strength, also known as sarcopenia. The psoas muscle poses a potentially validated surrogate to delineate sarcopenia after cardiac surgery. The aim of this study is to hypothesize whether there is an association between small psoas muscle area (PMA), transverse psoas muscle thickness (TPMT) and total psoas muscle volume (TPV) with all-cause, 30-day and 1-year mortality in cardiac transplant recipients.

Methods
106 patients who received heart transplantation at the General Hospital Vienna between 2015 and 2018 were included in this single-center, retrospective data analysis. Preoperative CT-scans were used to measure PMA, TMPT and TPV at the superior endplate of L3 and L4 via Osirix and Impax EE. Groups were stratified by lower tertile, listing status (high-urgent, VAD-bridge-to-candidacy, elective) and indexed by body surface area.

Results
The population consisted of 81 male (76.4%) and 25 female (23.3%) patients with a median age of 58 years (IQR 14). The median PMA was 1651.0 mm2/m2 (IQR 608.0) on L3, respectively 2318.5 mm2/m2 (IQR 742.5) on L4. 34 patients (32.1%) were attributed to the small PMA group on L3, 33 (31.1%) on L4. In total, 12 patients (11.3%) died, 8 (7.5%) during the first year. 30-day-mortality was 2.8% (n=3). There were no significant associations between mortality rates and small psoas muscle.

Conclusion
Small PMA did not prove to be an independent predictor in this patient cohort group. Limitations may lie within the low mortality rate, variety of patient characteristics and timepoint of CT-scan. Furthermore, the question arises whether paraspinal muscle and skeletal muscle index may be a more viable tool to measure frailty in cardiac transplant recipients.

09 - Lung TX

Oral Presentation

63

First Report of CD38 Antibody Daratumumab In Clinical Lung Transplantation

Caroline Hillebrand[1], Sophia Auner[1], Daniela Koren[2], Gottfried Fischer[2], Konrad Hoetzenecker[1], Peter Jaksch[1], Alberto Benazzo[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria
[2]Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria

Background
Antibody-mediated rejection (AMR) following lung transplantation (LTx) poses a major threat to allograft function. Current treatment approaches primarily focus on the depletion of circulating antibodies and suppression of B-cell activity, but they often fail to reduce donor-specific antibodies (DSAs) adequately. Daratumumab, a monoclonal antibody targeting CD38, shows promise in reducing DSAs by depleting antibody-producing plasma cells and NK cells, thereby potentially improving the outcomes of AMR. Here we report the first use of daratumumab in the setting of lung transplantation.

Methods
We conducted a retrospective single-center analysis, including all lung transplant recipients who received daratumumab as an add-on rescue therapy for AMR or as part of desensitization therapy pre-/post-transplant. Baseline demographics, immunological characteristics and long-term transplant outcomes were analyzed. All DSAs were detected by Luminex bead assay.

Results
17 patients received subcutaneous doses of 1800mg of daratumumab due to the following indications: 14 patients with de novo DSAs and AMR and 3 patients with pre-transplant DSAs without clinical AMR. Daratumumab was safely administered in all cases. The most frequent complications were infections (52.9%) and neutropenia (58.8%). Among the AMR group, 10 (71.4%) patients showed a significant decrease in their DSAs, with median mean fluorescence intensity (MFI) values dropping to less than 50% of the baseline within 6-9 weeks after the start of daratumumab. Five of these patients, who primarily showed a reduction in DSAs, developed chronic allograft dysfunction (CLAD), three of which required retransplantation. Among the desensitization group, mean MFI values of all three patients decreased to 50.6%, 48.0% and 29.7% of the baseline and none of these patients developed AMR.

Conclusions
Targeting CD38 might represent an effective and promising addition to the AMR treatment panel. Our findings may encourage the conduction of future prospective studies to further elucidate the therapeutic potential of this novel treatment approach in LTx.

64

Women As Lung Transplant Patients - An Immunological Risk?

Daniela Koren, Ingrid Faé, Daniela Kriks, Sabine Wenda, Gottfried Fischer

Department of Transfusion Medicine and Cell Therapy, Medical University of Vienna

It is known that organ transplant candidates who have been exposed to allogeneic cells can develop HLA antibodies, which are considered a risk factor for organ rejection. Even if these patients can be transplanted by temporarily removing the antibodies, they still have a higher risk of complications. If patients do not have

donor-specific antibodies at the time of transplantation, this is usually regarded as a low risk.

A special group of patients are women who have given birth. In a significant proportion of these women, HLA antibodies can be detected by single-antigen testing just a few days after transplantation. Typing of the children shows that these antibodies are directed against paternal HLA antigens. Often these immune responses are not allele specific, but show a broad reactivity. If an HLA antigen of the children happens to be the same as that of the transplanted person, this antigen could be considered a repeat mismatch.

In conclusion, patients who are considered unimmunised prior to transplantation because of negative antibody screening tests should not necessarily be considered immunologically risk-free. Transplantation may stimulate the patient's immunological memory. Previously undetected HLA-specific antibodies may become visible a few days after transplantation and the post-transplant course of the graft may be more complicated than expected.

65

De Novo Donor-Specific Antibodies And Early-Onset Chronic Lung Allograft Dysfunction In Lung Transplantation

Sophia Auner[1], Zsofia Kovacs[1], Jannik Böcker[1], Caroline Hillebrand[1], Panja Böhm[1], Daniela Koren[2], Gottfried Fischer[2], Konrad Hoetzenecker[1], Peter Jaksch[1], Alberto Benazzo[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria
[2]Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria

Background
Chronic lung allograft dysfunction (CLAD) remains an obstacle to long-term survival. In particular early-onset CLAD is a critical factor in early mortality after transplantation. Recent research has highlighted the potential role of de novo donor-specific antibodies (dnDSA) in the development of CLAD, but their precise temporal relationship remains less defined.

Methods
This retrospective study included adult lung transplant recipients with dnDSA (mean fluorescence intensity >1000) from 2016 to 2021. Persistent and transient DSAs were defined as lasting > 6 months and < 6 months, respectively. Early CLAD was defined as CLAD occurring within the first year after transplantation and late CLAD occurring thereafter. The main objective of this study was to analyze dnDSAs as a potential risk factor for early-onset CLAD.

Results
Of 251 lung transplant recipients who developed dnDSA, 41 subsequently developed CLAD. Of these, 46% (n=19) developed early CLAD, while 54% (n=22) developed late CLAD. The early CLAD patients had significantly worse overall survival than the late CLAD cohort (p= 0.009). DSA classes I and II, persistent versus transient dnDSAs, and MFI classes showed no differences between the early and late CLAD cohorts. DSA against HLA class B was more frequent in the early CLAD cohort (p= 0.045). Preformed DSAs were more prominent in the late CLAD group. Although not statistically significant, antibody-mediated rejection (AMR) was more common in patients with early CLAD (37% vs. 14%, p=0.08).

Conclusion
This study highlights the potential role of dnDSA in the development of early-onset CLAD. Further studies are needed to identify risk factors and fully understand the mechanisms leading to early-onset CLAD.

66

TTV Guided Belatacept Conversion After Lungtransplantation: Report Of 7 Cases

Peter Jaksch, Zsovia Kovacs, Gabriella Muraközy, Elisabeth Hielle-Wittmann, Konrad Hötzenecker, Alberto Benazzo

Dept. of Thoracic Surgery, Medical University Vienna, Austria

Background
Calcineurin inhibitor (CNI) based protocols are still the standard immunosuppressive regimen (IS) after lung transplantation (LuTx), although CNI-related toxic effects may occur.

Belatacept, a novel immunosuppressant that blocks a T-cell co-stimulation pathway, is a non- nephrotoxic drug indicated as an alternative to CNIs in kidney Tx.

In most of the published reports on the use of Belatacept after lung TX in combination with CNI sparing protocols, the incidence of acute rejection episodes and early CLAD was unacceptable high.

This study investigated the use of TTV-guided Belatacept dosing to overcome this problem.

Methods
We reviewed a series of 7 LuTx recipients with conversion to a CNI-sparing Belatacept IS regimen within the first 3 years post-LuTx (n = 7). Belatacept dosing was started according to the protocol used in kidney TX recipients and adapted thereafter based on TTV PCR levels (therapeutic range log7 –log9 TTV –PCR copies)

Results
Use of Belatacept was triggered by severe renal failure in all patients. Time to Belatacept after LuTX was 445±300 days (mean 401 days). Mean estimated glomerular filtration rate after starting Belatacept had significantly improved 6 months after initiation (GFR mL/min/1.73m2 before start was 29.5±6.1 and GFR after 6mo 41.0±4.7 , p=0.039).

Tacrolimus dosage was reduced in all patients but not stopped (reduction of target through level to 1.5-2.5ng/ml). There were no episodes of acute cellular (ACR) or humoral rejection (AMR) and none of the patients developed CLAD. One pat died due to pulmonary embolism 101 days after Belatacept start. In 3 patients Belatacept dose had to be adapted according TTV levels (in 2 cases dose had to be increased, in 1 case dose had to be reduced).

Conclusion
Conversion to CNI-reduced Belatacept-based IS with TTV guided Belatacept dosing improved renal function without increasing risk of ACR, AMR or CLAD.

Further studies are needed to prove the safety and efficacy of this therapeutic regimen.

67

First Clinical Experience With Tixagevimab And Cilgavimab In Lung Transplant Recipients During Omicron Wave

Zsofia Kovacs[1], Peter Jaksch[1], Gabriella Murakoezy[1] Konrad Hoetzenecker[1]

Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background
Evusheld™ (tixagevimab and cilgavimab, formerly AZD7442), a long-acting antibody combination is an approved prevention therapy for COVID-19 apart from vaccines. The efficiency of Evusheld in lung transplant recipients and the in vivo neutralization potency against Omicron variant strains is not yet known.

Methods

We analyzed lung transplant recipients who underwent Evusheld immunization between 04/2022-10/2022. All consecutive patients receiving a primary lung transplantation and consented to the injection were included in this retrospective single-center analysis. The dose for prevention of symptomatic disease caused by SARS-CoV-2 was 150mg of tixagevimab and 150mg of cilgavimab, administrated as separate sequential intramuscular injections.

Results

Of the 203 LTRs (53% males and 47% females, with a median age of 57 years) who received prophylactic injections of Evusheld™, 30 (14.7%) developed COVID-19 infection (median of 58,5 days after vaccine). With the exception of four patients, all LTRs were symptomatic. Hospitalization with oxygen support was necessary in two cases, admission to an intensive care unit was not required, respectively. Fifteen patients developed mild, nine patients moderate symptoms including fever, cough and headaches. Two patients reported long-COVID symptoms. The development of symptoms was not in correlation with the COVID-19 antibody status, with the immunosuppressive regimen (including induction therapy) or with the transplant date or diagnosis. The Torque Teno Virus load of infected patients were with a median of 2.39log09 in the upper threshold of the norm.

Conclusion

Evusheld was generally well-tolerated in our cohort. The results validate the original PROVENT phase III study regarding the clinical effectiveness of Evusheld prophylaxis for immunocompromised patients (lung transplant recipients), notably demonstrating effectiveness during the Omicron wave as an appropriate option to prevent COVID-19.

Poster Presentation

68

Lung Transplant In Patients With Suspicious Lung Nodules: A Single-Center Retrospective Data Analysis

Merjem Begic[1], Stefan Schwarz [1], Panja Böhm[1], Alberto Benazzo[1], Zsofia Kovacs[1], Gabriella Muraközy[1], Peter Jaksch[1], Konrad Hoetzenecker[1]

[1]Department of Thoracic Surgery, Medical University of Vienna

Background

Patients with lung cancer or suspicious pulmonary nodules are traditionally rejected for lung transplantation (LTx), despite conflicting studies on the prognostic impact of early stage lung cancer in the LTx setting. In addition, there is a lack of evidence on how often suspicious nodules are found in LTx candidates and how often these nodules turn out to be lung cancer after transplantation.

Methods

As suspicious nodules are not considered a contraindication for LTx by the Lung Transplant Program Vienna, we performed a retrospective analysis of all patients with suspicious lung nodules, who underwent lung transplantation between 01/2012 and 09/2022.

Results

1169 patients received a LTx, at a mean age of 63.3±3 at the time of transplant. Prior to LTx, lung nodules were found in 80 (6.8%) patients. None of the patients was delisted. COPD was the most frequent indication for LTx (67/80; 83.8%) in patients with suspicious nodules. Pathology reports confirmed lung cancer in native lungs

in only 12 (1.5%) of these patients. Most common malignancy in histology was adenocarcinoma in 8/12 cases. Seven (58.3%) patients with carcinoma in the native lung are alive today. Death due to tumor recurrence was documented in 3 patients at 1-, 6-, and 10-months post-transplant. Five-year survival for LTx patients without suspicious lung nodules compared to patients with verified cancer was 73.1% vs 59.2% (Log-Rank p=0.101).

Conclusions
Patients with suspicious lung nodules should not be excluded from LTx. Only a small proportion of these nodules are malignant and even if the explanted lung harbors an early-stage lung cancer, long-term survival is acceptable.

69

Lung Transplantation For Patients With A High-Risk Profile

Panja M. Boehm[1], Sophia Auner[1], Anna Elisabeth Frick[1], Alberto Benazzo[1], Stefan Schwarz[1], Zsofia Kovacs[1], Gabriella Murakoezy[1], Peter Jaksch[1], Konrad Hoetzenecker[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background
Selection of transplant recipients remains one of the major challenges in lung transplantation (LTx). Based on the most recent ISHLT consensus statement, the terms 'absolute' and 'relative' contraindications for LTx were replaced by a system of 'risk factors'. Searching the literature, there is, however, only very limited evidence supporting this concept. The aim of this study was to evaluate the benefit of LTx for patients with a risk profile according to the ISHLT definition.

Methods
In this retrospective cohort study patients with fibrosis, COPD or cystic fibrosis undergoing primary bilateral lung transplantation between 2015 and 2020 were included (n=479). Comorbidities were assessed at time of listing, and scored as high (1 point) or moderate (0.5 points) risk factors according to the latest ISHLT consensus statement. The study cohort was categorized into three groups based on their scores (score 0/1-2/>2). Post-transplant survival probabilities at 3, 12 and 60 months were compared between the groups with Kaplan-Meier survival analysis and log-rank tests.

Results
479 patients (272 males) were included in the study with a median age of 56 years. 133 (27.8%) patients had no relevant comorbidities, 281 (58.7%) scored between 1-2, and 65 (13.6%) had 2 and more risk factors. In Kaplan-Meier analysis there were no significant differences in survival after 3 months (p=0.407), 12 (p=0.551) or 60 months (p=0.457) between the three groups. In uni- and multivariate analysis, only chest wall deformity was a prognostic parameter for impaired survival after the first year after LTx.

Conclusions
LTx for well-selected recipients with substantial comorbidities is safe and associated with similar short- and long-term survival, if performed at experienced transplant centers. In the light of limited organ availability, careful recipient selection remains an ethical and medical challenge and should take an individualized risk-benefit assessment into account.

70

Lung Transplantation For COVID-19-Related Respiratory Failure: 1-Year Outcome Of 29 Patients

Zsofia Kovacs[1], Peter Jaksch[1], Gabriella Murakoezy[1], Konrad Hoetzenecker[1]

[1]Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background
Transplantation offered for selected COVID-19 patients with irreversible lung disease an excellent midterm outcome, however the impact of long-term outcome is not known.

Methods
We analyzed lung transplantations performed between 05/2020-04/2022 due to COVID-19 ARDS. All consecutive patients receiving a primary lung transplantation were included in this retrospective analysis.

Results
A total of 29 patients were transplanted at the medical university of Vienna. 25 (86%) males and 4 (14%) females, with a median age of 54 years, and median lung allocation score of 89,6. No induction therapy was used, except one highly-presensitized female recipient. We used Torque-Teno-Virus (TTV) for tailoring the immunosuppressive therapy. Eleven patients (37,9%) died in the first postoperative year, 9 from secondary sclerosing cholangitis. Two patients received liver transplantation. We identified 2 patients with acute humoral, and 5 with acute cellular rejection, 7 patients have persistent donor specific antibodies. None of the patients developed an early CLAD. Eight patients were treated with multiresistent bacteria, and thirteen with fungal infections, one with CMV viremia. Nine patients needed a Vacuum-assisted closure (VAC) for a wound dehiscence.

Conclusion
Despite prolonged postoperative stay and frequent complicated postoperative course lung transplantation was an effective life-saving treatment for critically ill patients. The health-related quality of life (SF-36) benefit was after a year similar to those with other organ transplantation.

71

Persistent De Novo DSA Are Associated With Shorter CLAD-Free Survival

Sophia Auner, Jannik Böcker, Panja M. Böhm, Caroline Hildebrand, Konrad Hötzenecker, Peter Jaksch, Alberto Benazzo

Department of Thoracic surgery, Medical University of Vienna, Vienna, Austria

Background
De novo donor-specific HLA antibodies (dnDSAs) in lung transplant recipients are linked with chronic lung allograft dysfunction (CLAD) and less favorable outcomes.This study aimed to assess the frequency of transient and persistent dnDSAs and examine the possible impact of persistent dnDSA on patient outcome.

Methods
We conducted a retrospective study of all lung transplant patients at the University Hospital of Vienna between 2016 and 2021 who had de novo DSA. All retransplants and multiorgan transplants were excluded. DnDSAs were defined as persistent if the MFI was >1000 for at least 6 months, and as transient if the MFI was >1000 for less than 6 months, followed by at least one MFI <1000. Additionally, recipients were divided into four groups according to the highest measured dnDSA MFI value: I= 1000-5000; II= 5000-10000; III= 10000-15000; IV= >15000.

Results
We identified 209 lung transplant recipients with dnDSAs. Of these, 36 (17%) had persistent, 117 (56%) had transient dnDSAs. The classification of MFI values into the groups I-IV according to transient and persistent dnDSA is 96 (82%), 14 (12%), 6 (5%), 1 (1%), and 7 (19%), 12 (33%), 6 (17%), 11 (30%) ($p<0.001$). Overall survival was comparable between the two groups ($p=0.950$) with survival rates at 1, 3 and 5 years were 89%, 79% and 76% for recipients with transient dnDSAs and 97%, 81% and 72% for recipients with persistent dnDSAs. CLAD-free survival was shorter in patients with persistent dnDSAs ($p=0.031$). CLAD free survival rates at 1, 3 and 5 years were 93%, 80%, and 79% in recipients with transient dnDSAs and 94%, 61%, and 56% in recipients with persistent dnDSAs.

Conclusion
Our results show a significantly shorter CLAD-free survival in patients with persistent dnDSAs. However, overall survival seem to be comparable among the groups.

Transplant International is the official journal of the European Society for Organ Transplantation (ESOT).

Transplant International aims to be the premier journal publishing the key basic science and clinical developments in organ replacement medicine, including all aspects of transplantation, organ reconditioning, cell therapy, regenerative medicine, bioengineering and artificial organs.

Discover more about the journal

See more →

fro.ntiers.in/TI
publishingpartnerships.frontiersin.org

Contact
TI@frontiersin.org

frontiers