25. Jahrestagung der Österreichischen Gesellschaft für Transplantation, Transfusion und Genetik

Graz, 19.–22. Oktober 2011

Tagungspräsident:
Wolfgang Schwinger, Graz

25th Annual Meeting of the Austrian Society of Transplantation, Transfusion and Genetics

Graz, October 19–22, 2011

Guest Editor:
Wolfgang Schwinger, Graz

Clinical Symposia/Special Topics

Viral infections in patients after organ and stem cell transplantation
Fungal infections in patients after organ and stem cell transplantation
Immune tolerance
Quality of survival after organ and stem cell transplantation
CONTENTS

Parallelsitzung I: Knochenmarktransplantation/Stammzellen I (001–009) ........................................ 4
Parallelsitzung II: Basic Research/Immunsuppressio (010–018) ..................................................... 8
Parallelsitzung III: Klinische Transplantation/Arzneimittelstudien (019–026) ................................. 12
Plenarsitzung I: Young Investigators Award
Klinisch (027–030) ................................................................. 15
Experimentell (031–034) ......................................................... 17
Lunchsymposium Virusinfektionen in der Organ- und Stammzelltransplantation (035–037) .......... 18
Parallelsitzung IV: Knochenmarktransplantation/Stammzellen II (038–046) ............................... 20
Parallelsitzung V: Thorakale Transplantation (047–055) ................................................................. 24
Parallelsitzung VI: Transplantation von Abdominalorganen (Leber, Pankreas)/Nierentransplantation/
Composite Tissue Allotransplantation (056–064) ............................................................................ 27
Plenarsitzung III: Immun- und Organtoleranz/Toleranzinduktion I (065–066) ............................. 31
Plenarsitzung IV: Immun- und Organtoleranz/Toleranzinduktion II (067–068) ........................... 32
Lunchsymposium Pilzinfektionen in der Organ- und Stammzelltransplantation (069–071) ........... 33
Plenarsitzung V: Lebensqualität nach Organ- und Stammzelltransplantation (072–074) .............. 34
Poster Präsentationen
Knochenmarktransplantation/Stammzellen (075–080) ............................................................... 35
Basic Research (081–094) ............................................................ 38
Immunsuppression (095–096) ........................................................................................................ 44
Transplantation von Abdominalorganen (Leber, Pankreas)/Nierentransplantation/Composite
Tissue Allotransplantation (097–112) ....................................................................................... 45
Thorakale Transplantation (113–116) ............................................................................................ 52
Lebensqualität (117–118) .............................................................................................................. 54
Author index ................................................................................................................................. 57

Mit freundlicher Unterstützung von
Autologous haematopoietic stem cell transplantation for consolidation of refractory paediatric Crohn’s disease

A. Hauer1, A. Deutschmann1, H. Lackner2, W. Schwinger2, C. Urban2
1Division of General Pediatrics, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; 2Division of Pediatric Hematology/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

Background. Autologous haematopoietic stem cell transplantation (HSCT) has recently been used successfully in the treatment of adults with refractory Crohn’s disease (CD). We investigated safety and efficacy of HSCT with highly purified autologous CD34+ peripheral blood stem cells (PBSCs) in severe refractory CD in the youngest paediatric patient to date.

Methods. HSCT was performed in a 14-year-old boy with active severe CD for 4 years and ileal stenosis of 30 cm (paediatric CD’s activity index (PCDAI) 70 at entry), refractory or intolerant to multiple drugs, including infliximab and adalimumab. PBSCs were collected after mobilisation with cyclophosphamide 2000 mg/m2 and G-CSF and CD34+-selected by immunomagnetic cell sorting yielding a total of 10.67×108 CD34+-cells/kg. Two months later the conditioning regimen included cyclophosphamide 50 mg/kg for 4 days and thymoglobulin 2.5 mg/kg/day for 3 days. Engraftment time was short (28/70 WBC/µl: day 9, 34,000 platelets/µl: day 11). Main outcome measures were toxicity and clinical remission (PCDAI < 10) at 4 months (primary endpoints) and endoscopic/PET-response and operability at 4 months (secondary endpoints).

Results. PBSC-mobilisation with cyclophosphamide led to initial myelodepression with septicama (rapidly resolved by antibiotics) but also to incipient improvement of CD symptoms (PCDAI: 25). 4 months after HSCT and despite withdrawal of all drugs, both primary endpoints (no toxic sequela, clinical remission) were achieved. As for the secondary endpoints, both PET and endoscopy findings showed dramatic improvement with only mild focal disease residues on histology. The ileal stenosis as the only remnant of active disease was then resectively resected and the patient currently remains in continuous remission.

Conclusions. Autologous HSCT (with CD34+-selected PBSCs) was safe and induced complete clinical and subtotal endoscopic and histological remission at 4 months in a paediatric patient with refractory CD, allowing for as minimal an ileal resection as possible. Removal of the autoreactive immune system and re-establishment of a new immune system by transfusion of highly purified autologous CD34+-cells might thus be a further promising option within a multimodality therapeutic approach for refractory paediatric CD.

Stammzelltransplantation bei Kindern mit Parvovirus B19 ausgelöster SAA oder MDS

H. Lackner, P. Sovinz, W. Schwinger, M. Benesch, V. Strenger, S. Schmidt, C. Urban
Klinische Abteilung für Pädiatrische Hämato-/Onkologie, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Graz, Graz, Österreich

Grundlagen. Parvovirus B19 (PVB19) als Ursache einer schweren aplastischen Anämie (SAA) oder eines myelodysplastischen Syndroms (MDS) ist bisher erst selten beschrieben. Es existieren auch kaum Berichte über Stammzell-Transplantationen (SCT) bei diesen Krankheitsbildern.

Methodik. Bei 6 Patienten mit SAA (n = 4) oder MDS (n = 2) wurde bei Diagnosestellung eine frische Infektion mit PVB19 mittels positivem Nachweis von IgM, IgG und PCR nachgewiesen. Alle Patienten erhielten eine SCT unter dem Schutz repetitiver intravenöser Immunglobulin (IVIG)-Gaben. Das virologische Monitoring mittels PCR erfolgte in 5 von 6 Fällen in der Akutphase wöchentlich, danach monatlich bis zur hämatologischen Rekonstitution.

Ergebnisse. Die 4 Patienten mit SAA erhielten Knochenmark eines HLA-identen Geschwister-Spenders (n = 3) oder HLA-idente hochgereinigte, periphere Stammzellen eines unverwandten Spendern (n = 1). Ein Patient entwickelte nach SCT eine chronische, hypoplastische Anämie, die bis zur vollständigen Blutbild-Regeneration am Tag 186 andauerte. Der Posttransplantations-Verlauf der übrigen 3 Patienten war komplikationslos mit einem Leukozyten-Engraftment nach 8–31 Tagen und einer hämatologischen Rekonstitution nach 36–112 Tagen. Die 2 Patienten mit MDS wurden nach Konditionierung mit Thiopeta, Fludarabin und ATG einer SCT mit unverwandten Spendern (1x Knochenmark, 1x periphere hochgereinigte Stammzellen) unterzogen. Nach zögerlichem Leukozyten-Engraftment dauerte es 1260 bzw. 139 Tage bis zur Blutbild-Normalisierung. PVB19 wurde in der PCR bis zum Tag 686 bzw. 139 nachgewiesen.

Schlussfolgerungen. Eine erfolgreiche SCT bei diesen Patienten ist möglich, sofern eine engmaschige Monitorisierung der PVB19-PCR und eine konsequente repetitive IVIG-Therapie erfolgen. Der Transplantationsverlauf kann durch ein zögerliches Engraftment und eine prolongierte „poor graft function“ kompliziert werden.

Retrospective study to test ferritin serum levels as biomarker for graft-versus-host disease-associated non-infectious inflammatory reaction in 117 children after hematopoietic stem cell transplantation

M. Großekathöfer1, E. D. Güçlü1, A. Lawitschka1, S. Matthes-Martin1, G. Mann1, C. Peters1, M. G. Seidel1,2
Background. Myelodysplastic syndromes (MDS) are a heterogeneous group of stem cell disorders characterized by bone marrow dysplasia, peripheral cytopenia, and an enhanced risk to transform to acute myeloid leukemia (AML). In most patients, treatment options are limited to supportive care and palliative cytoreduction. However, in a group of patients, intensive therapy can be offered. The only established curative treatment approach for these patients is haematopoietic stem cell transplantation (SCT).

Methods. In the present study, we retrospectively analyzed a cohort of 60 adult patients (33 males, 27 females) with MDS (n = 28) or MDS transforming into secondary AML (n = 33), who underwent SCT at our institution between 1988 and 2010. Fifty-one patients had an HLA-identical related transplant donor, and 9 had an HLA-matched unrelated donor. The median age at time of SCT was 44 years (range: 18 to 68 years). According to the WHO classification, 4 patients had RA, 1 RARS, 3 RCMD, 1 RCMD-IRS, 6 RAEB-1, 12 RAEB-2, 1 CMMI, and 32 had AML following RAEB at SCT. Conditioning consisted of chemotherapy plus total body irradiation (55/60 patients) or chemotherapy alone (5/60 patients). Graft versus host disease (GvHD) prophylaxis consisted of a combination of low-dose methotrexate and cyclosporine A (37/60 patients) or cyclosporine A plus mycophenolate mofetil (23/60 patients).

Results. Patients were followed up with a median observation time of 16 months (range: 1–218). Currently, 34 patients (57%) are alive. Of the 26 patients who died, post-transplantation relapse occurred in 12 patients, and 14 patients died of treatment-related causes (multi-organ failure, n = 7; sepsis, n = 4; haemorrhage, n = 3). In multivariate analysis we identified pre-transplantation ferritin as a significant adverse prognostic variable for survival in our MDS patients. In contrast, the overall outcome after SCT was independent of IPSS risk categories or the WHO classification.

Conclusions. Based on these data and similar published data we recommend to select patients with MDS or sAML for SCT who are considered candidates for SCT according to the presence of pre-transplantation iron-overload.
data and expert opinion. For both acute as well as aGVHD new definitions were proposed. We performed a prospective study on all consecutive patients undergoing allogeneic hematopoietic stem cell transplantation (HCT) since 2005 to assess the prognostic impact of the new aGVHD staging criteria.

Methods. One hundred seventy-eight patients (85 males, 93 females) with a median age of 40 years alive on day + 100 after HCT with myeloablative (n = 110) or reduced-intensity (n = 68) conditioning and a related (n = 37) or unrelated (n = 141) stem cell donor were enrolled into the study. Starting on day + 100 after HCT all patients were assessed clinically every 3 months in the outpatient clinic for aGVHD activity according to the NIH consensus criteria (Filipovich et al., BBMT 2005;11:945–956).

Results. One hundred twenty-six (71%) patients experienced acute GVHD grades I to IV including 11 with recurrent, 11 with persistent, and 10 with late-onset acute GVHD after a median of 18 (range, 9–120) days after HCT. One hundred-fifteen patients (86%) experienced cGVHD after a median of 151 (range, 82–510) days after HCT. Eighty-nine patients (77%) had classic cGVHD and 26 (23%) overlap syndrome. Probability of overall survival (OS) at 3 years for late-onset aGVHD, chronic classic and overlap cGVHD were 69%, 83%, and 73%. Three-year OS for mild, moderate and severe cGVHD at onset were 93%, 79%, and 62.5% and significantly different between mild and severe (p = 0.007). Patients with progressive onset type of cGVHD had significantly worse three-year survival compared to de novo and quiescent (54.5% vs. 89.5%, 84%, p < 0.01). Three-year OS was also significantly worse in patients with platelet counts below 100 G/l at onset of cGVHD (35% vs. 86%, p < 0.0001).

Conclusions. This prospective analysis supports the importance of distinguishing late-onset aGVHD from cGVHD and indicates a prognostic value of thrombocytopenia and progressive onset type of aGVHD for HCT outcomes.

A single nucleotide polymorphism in the intelectin 1 gene (ITLN1) is associated with acute intestinal graft-vs.-host-disease

H. Hauser, M. Binder, A. Böhm, O. Zach

Stem Cell Transplantation, First Department of Internal Medicine, Elisabethinen Hospital, Linz, Austria

Current concepts suggest a major role for innate immunity in the initiation of acute graft-vs.-host-disease (aGVHD) as well as in Crohn’s disease. Identical single nucleotide polymorphisms (SNP) have been described as risk factors for both diseases. Recently, the noncoding C/T polymorphism rs2274910 in intron 3 of the intelectin 1 (ITLN1) gene (human lactoferrin receptor) has been associated with Crohn’s disease. We prospectively typed this polymorphism in AML patients and their donors. A pilot study of 19 patients in CR1 transplanted from HLA identical sibling donors after myeloablative conditioning was confirmed in a second cohort including 40 other AML patients. A total of 59 consecutive patients (median age 43 yrs (18–63); 25/34 CR1/advanced disease; 40 myeloablative and 19 reduced intensity conditioning; 54 peripheral stem cells) were tested. T-alleles were found at a frequency of 28.8% in recipients and 29.7% in donors. 50.8% of patients had a CC genotype. In the pilot study, 2 out of 12 patients with a CC genotype versus 5 out of 7 patients with a T-allele had acute intestinal aGVHD (p = 0.045). These results were confirmed in a second cohort. Acute intestinal GVHD was found in 3/18 patients (16.7%) with a CC genotype and 12/22 patients (54.5%) with a T-allele (p = 0.014). In a combined analysis (n = 59) we found intestinal aGVHD in 58.6% of patients with a T-allele versus 16.7% of patients with a CC genotype (p < 0.001). The lower incidence of aGVHD grades II-IV in patients with a CC genotype (p = 0.019) was only due to less intestinal aGVHD while no difference was found with regard to skin or liver aGVHD. We did not see any association between donor genotypes and aGVHD. The strong association (RR 3.52; 95% CI 1.5–8.2) between this SNP and the incidence of intestinal aGVHD is in accordance with reports about SNPs in other genes associated with both aGVHD and Crohn’s disease. Our results further support the concept of the importance of the gut associated innate immune system in the initiation of aGVHD.

B. Kircher, P. Schumacher, B. Lindner, D. Nachbaur

Immunologie und Stammzelllabor, Universitätsklinik für Innere Medizin V, Hämatologie und Onkologie, Medizinische Universität Innsbruck, Innsbruck, Österreich

Grundlagen. Klinische Studien zeigen, dass sich Minorthiskompatibilitätsantigenen (mHag)-spezifische Spender T-Zellen positiv in der Therapie eines leukämischen Relapses nach HLA-identer hämatopoetischer Stammzelltransplantation (SZT) auswirken. Der prädiktive Wert der mHag-Typisierung für das Auftreten eines Graft-versus-Leukämie Effektes oder von Komplikationen nach SZT ist jedoch nach wie vor umstritten. Auch Langzeitstudien über den Einfluss von mHag-Mismatches auf das Überleben der Patienten fehlen. Deshalb haben wir in der vorliegenden Studie Unterschiede in zehn verschiedenen mHag in insgesamt 217 Patienten und ihren HLA-identen Familien- oder Fremdspender untersucht und sie mit Überleben und Komplikationen nach allogener SZT korreliert.

Methodik. Die Bestimmung der mHag wurde mittels Allelspezifischer Polymerase-Kettenreaktion mit Hilfe eines kommerziell erhältlichen mHag-Typisierungkits durchgeführt. Die Wahrscheinlichkeit des Überlebens (bis zu 22 Jahre nach SZT) wurde mittels Kaplan-Meier Überlebenseanalyse, die Komplikationen mittels Cumulativer Inzidenz berechnet.

Ergebnisse. Von den 217 Patienten/Spenderkombinationen wiesen 119 keinen mHag-Mismatch, 67 einen mHag-Mismatch und 31 zwei oder mehrere mHag-Mismatches auf. Sämtliche Patienten mit einem HA-1-, HA-2-, HA-8- (HLA-A2-restringiert) oder HA-3- (HLA-A1-restringiert) Mismatch zeigten eine geringere Rezidivrate als Patienten ohne den entsprechenden mHag-Mismatch. Ein HA-2- und ein HA-3-Mismatch waren jedoch mit einer erhöhten Inzidenz an akuter GVHD und daher mit einer geringeren Überlebensrate verbunden. Patienten/Spenderkombinationen mit einem HY-Mismatch profitierten mit einem leichten Überlebensvorteil (48% vs. 40%). Interessanterweise wirkten sich mehrere mHag-Mismatches positiv auf das Langzeitüberleben aus. Vier Jahre nach SZT betrug das Gesamtüberleben von
Patienten ohne Mismatch 44 %, von Patienten mit einem Mismatch 43 %, von Patienten mit 2 Mismatches 55 % und von Patienten mit 3 Mismatches 75 % (allerdings nur 8 Patienten). In Übereinstimmung mit diesem Ergebnis betrug die Inzidenz der Nonrelapse-Mortalität von Patienten ohne Mismatch 50 %, von Patienten mit einem Mismatch 54 % und von Patienten mit zwei bzw. drei Mismatches 36 % bzw. 14 %. Eine Erklärung für dieses Ergebnis könnte der Graft-versus-Leukämie Effekt sein, der durch die erhöhte Anzahl an Spender T-Zellen induziert wird, die verschiedene hämatopoetisch-restringierte mHag auf den residuellen Leukämiezellen des Patienten erkennen und diese zerstören.

Schlussfolgerungen. Die Bestimmung von mHag in Patient und Spender vor der SZT wäre eine sinnvolle Maßnahme zur zusätzlichen Risikobeurteilung von Kolonien, vor allem aber überleben nach SZT.

009

**Tissue specific epigenetic memory: differentiation capacity of mesenchymal stem cell is restricted to their tissue of origin**

A. Reinish1, N. Liechtenstein1, N. A. Hofmann1, A. Orten1, M. Frühwirth1, K. Schallmoser2, C. Beham-Schmid3, D. Strunk4

1Stem Cell Research Unit, Department of Hematology, Medical University of Graz, Graz, Austria; 2Stem Cell Research Unit, University Clinic of Transfusion Medicine and Blood Group Serology, Medical University of Graz, Graz, Austria; 3Institute of Pathology, Medical University of Graz, Graz, Austria

Human mesenchymal stem cell and progenitor cells (MSCPs) are currently evaluated in clinical trials for bone and marrow regeneration and their immune modulation potential. MSCP show a sort of understanding MSCP functionality in vitro. Improvements of limited clinical efficiency are hampered by a lack of understanding MSCP functionality in vitro. Here we demonstrate that the capacity of in vivo endochondral bone formation followed by infiltration of hematopoietic components can be used as a surrogate to determine in vivo MSCP-multipotentality. MSCP from bone marrow (BM), adipose tissue (AT) and umbilical cord (UC) have been isolated. Comparative analysis of immune-phenotype, adipose, chondro- and osteogenic differentiation potential in vitro shows an almost identical immune-phenotype using a MSCP marker profile. Osteo- and adipogenic differentiation potential in vitro were performed. Epigenetic profiling of MSCP was done using methylation array. In vivo differentiation capacity was tested by transplanting MSCP subcutaneously into immune-compromised mice. The developmental sequence of chondrogenic and osteogenic as compared to perivascular mesenchymal tissue formation was analyzed. Formation of a marrow niche with establishment of the complete host hematopoiesis was studied. Secondary transplants of MSCP were performed and analyzed equally. MSCP from all tissues analyzed show an almost identical immune-phenotype using a MSCP marker profile. Osteo- and adipogenic differentiation potential in vitro as well as gene expression can not distinguish tissue-specific MSCP. MSCP from all tissues except BM lack in vitro chondrogenic differentiation potential using stringent 3D-chon-
Harn-Angiotensinogen-Spiegel im Vergleich zu den mit Candesartan behandelten Tieren.

**Schlussfolgerungen.** Der Renin-Blocker Aliskiren vermied das Fortschreiten der chronischen Transplantatdysfunktion nicht. Der fehlende Schutzeffekt hängt wahrscheinlich entweder mit der verminderten Produktion des protektiven Ang(1–7) oder mit einer ineffektiven intrarenalen RAS-Blockierung zusammen.

---

**Parallelsitzung II: Basic Research/Immunosuppression**

**010**

Direkte Renin-Inhibierung in einem experimentellen Modell der chronischer Nierentransplantatdysfunktion

K. Rusai1, C. Schmaderer2, R. Hermans2, J. Lutz2, U. Heemann1, M. Baumann2

1Abteilung für Nephrologie, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Wien, Wien, Österreich; 2Technische Universität München, München, Deutschland

**Grundlagen.** Die Hemmung des Renin-Angiotensin-Systems (RAS) entweder mit ACE-Hemmern oder mit Angiotensin-Rezeptor-Blockern (ARB) verlangsamt die Progression unterschiedlicher chronischer Nierenerkrankungen und der chronischen Transplantatdysfunktion. RAS-Blockierung kann auch durch eine direkte Renin-Inhibierung erreicht werden, die aber infolge einer verminderten Produktion der protektiven Angiotensin II-Spaltprodukte wie z. B. Angiotensin (Ang)(1–7) zusätzliche Effekte haben kann.

**Methodik.** Im Fischer-Lewis Nierentransplantationsmodell der Ratte wurde der Effekt von Aliskiren (10 mg/kg/Tag) auf die Entstehung der chronischen Transplantatdysfunktion im Vergleich zu einer Behandlung mit Vehikel oder mit dem ARB Candesartan als bekannter Hemmer der chronischen Transplantatdysfunktion untersucht. Analyisiert wurden die Histologie der Niere und der Verlauf der Proteinurie, der Serum-Spiegel von Ang(1–7) und der Spiegel von Angiotensinogen im Harn als Indikator für die intrarenale RAS-Aktivität.

**Ergebnisse.** Im Gegensatz zu Candesartan verminderte Aliskiren weder die klinischen (Proteinurie, Kreatinin-Clearance) noch die histologischen Zeichen (Glomerulosclerose, interstielle Fibrose, Makrophagen-Infiltration) der chronischen Transplantatdysfunktion. Candesartan verbesserte im Vergleich zu Vehikel- und Aliskiren-behandelten Gruppen sowohl die Proteinurie als auch den Histologieschaden. Die mit Aliskiren behandelten Ratten zeigten einen verminderten Serum-Spiegel des protektiven Ang(1–7) und einen höheren Harn-Angiotensinogen-Spiegel im Vergleich zu den mit Candesartan behandelten Tieren.

---

**011**

Kein Unterschied im Gehalt an energiereichen Phosphaten in Organen von Lebendspendern, hinzuoben Spendern und „non-heartbeating“ Spendern im Tiermodell

V. Stadlbauer1, P. Stiegler2, P. Täubl1, M. Sereinigg2, A. Puntsch2, A. Bradatsch1, P. Curcic4, T. Seifert-Held3, G. Zmugg4, T. Stojakovic4, B. Leopold2, D. Blatt2, V. Hork2, U. Mayhauser2, I. Wiederstein-Grasser5, B. Leber2, G. Jürgen1, K. H. Tscheliessnigg6, S. Hallström7

1Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Graz, Österreich; 2Abteilung für Transplantationschirurgie, Universitätsklinik für Chirurgie, Medizinische Universität Graz, Graz, Österreich; 3Abteilung für Herzchirurgie, Universitätsklinik für Chirurgie, Medizinische Universität Graz, Graz, Österreich; 4Universitätsklinik für Neurologie, Medizinische Universität Graz, Graz, Österreich; 5Klinisches Institut für Medizinische und Chemische Labordiagnostik, Medizinische Universität Graz, Graz, Österreich; 6Abteilung für Biomedizinische Forschung, Medizinische Universität Graz, Graz, Österreich; 7Institut für Physiologische Chemie, Medizinische Universität Graz, Graz, Österreich

**Grundlagen.** Es ist unklar, ob Organe von Lebendspendern eine bessere Transplantationseignung im Vergleich zu Organen von hinzuoben Spendern oder „non-heartbeating“ Spendern aufweisen. Transplantationserfolge korrelieren mit dem zellulären Gehalt an energiereichen Phosphaten im Spenderorgan.

**Methodik.** Der zelluläre Gehalt an energiereichen Phosphaten von Herz, Leber, Pankreas und Niere von Lebendspendern, hinzuoben Spendern und „non-heartbeating“ Spendern wurde in einem Schweinemodell (n = 6 pro Spenderart) systematisch untersucht. Für das Hirntodmodell wurde der Hirntod mittels eines Ballons im Epiduralraum unter Narkose induziert. Die Organe wurden 10 h nach Bestätigung des Hirntods entnommen. Das „non-heartbeating“ Modell wurde durch 9V Gleichstrom ein Herzstillstand induziert. Nach 10 min Kammerflimmern ohne Herzauwurf wurde mit Reanimationsmaßnahmen begonnen. Diese wurden für 30 min durchgeführt und dann wurde mit der Organeinnahme begonnen. Für das Lebendspendedemodell wurden die Organe sofort unter Narkose entnommen. Mit einer Eiszange wurden Biopsien vor und nach Perfusion mit der verminderten Produktion der protektiven Angiotensin II-Spaltprodukte wie z. B. Angiotensin (Ang)(1–7) zusätzliche Effekte haben kann.

---

**012**

Parallelversuche der biologischen Aktivität von Knochenmark- und Knochenmark-MSPCs (multipotent stem/progenitor cells) — Direkte und indirekte Multifunktionszellen

D. Blatt2, P. Täubl1, M. Sereinigg2, A. Puntsch2, A. Bradatsch1, P. Curcic4, T. Seifert-Held3, G. Zmugg4, T. Stojakovic4, B. Leopold2, D. Blatt2, V. Hork2, U. Mayhauser2, I. Wiederstein-Grasser5, B. Leber2, G. Jürgen1, K. H. Tscheliessnigg6, S. Hallström7

1Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Graz, Österreich; 2Abteilung für Transplantationschirurgie, Universitätsklinik für Chirurgie, Medizinische Universität Graz, Graz, Österreich; 3Abteilung für Herzchirurgie, Universitätsklinik für Chirurgie, Medizinische Universität Graz, Graz, Österreich; 4Universitätsklinik für Neurologie, Medizinische Universität Graz, Graz, Österreich; 5Klinisches Institut für Medizinische und Chemische Labordiagnostik, Medizinische Universität Graz, Graz, Österreich; 6Abteilung für Biomedizinische Forschung, Medizinische Universität Graz, Graz, Österreich; 7Institut für Physiologische Chemie, Medizinische Universität Graz, Graz, Österreich

**Grundlagen.** Es ist unklar, ob Organe von Lebendspendern eine bessere Transplantationseignung im Vergleich zu Organen von hinzuoben Spendern oder „non-heartbeating“ Spendern aufweisen. Transplantationserfolge korrelieren mit dem zellulären Gehalt an energiereichen Phosphaten im Spenderorgan.

**Methodik.** Der zelluläre Gehalt an energiereichen Phosphaten von Herz, Leber, Pankreas und Niere von Lebendspendern, hinzuoben Spendern und „non-heartbeating“ Spendern wurde in einem Schweinemodell (n = 6 pro Spenderart) systematisch untersucht. Für das Hirntodmodell wurde der Hirntod mittels eines Ballons im Epiduralraum unter Narkose induziert. Die Organe wurden 10 h nach Bestätigung des Hirntods entnommen. Das „non-heartbeating“ Modell wurde durch 9V Gleichstrom ein Herzstillstand induziert. Nach 10 min Kammerflimmern ohne Herzauwurf wurde mit Reanimationsmaßnahmen begonnen. Diese wurden für 30 min durchgeführt und dann wurde mit der Organeinnahme begonnen. Für das Lebendspendedemodell wurden die Organe sofort unter Narkose entnommen. Mit einer Eiszange wurden Biopsien vor und nach Perfusion mit der verminderten Produktion der protektiven Angiotensin II-Spaltprodukte wie z. B. Angiotensin (Ang)(1–7) zusätzliche Effekte haben kann.
Eindeutige miRNA Signaturen von akutem ischämisch-organversagen und akuter zellulärer und humoraler Abstoßung in Nierentransplantaten

J. Wilflingseder, H. Regele, P. Perco, A. Kainz, A. Soleman, R. M. Langer, B. Mayer, R. Oberbauer

3. Interne Abteilung für Nieren- und Hochdruckerkrankungen, Transplantationsmedizin, Rheumatologie, Krankenhaus der Elisabethinen Linz, Linz, Österreich; 2Klinische Abteilung für Nephrologie und Dialyse, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Wien, Österreich; 13Klinisches Institut für Pathologie, Medizinische Universität Wien, Wien, Österreich; emergetec biodevelopment GmbH, Wien, Österreich; 2Abteilung für Chirurgie und Transplantation, Semmelweis Universität, Budapest, Ungarn

Grundlagen. miRNAs sind kurze, einzelstrangierte RNA, die auf Transkriptions- und Translationssebene die Genexpression regulieren. Ziel dieser Studie ist die Identifizierung von deregulierten miRNAs in Patienten mit akuter, zellulärer und humoraler Abstoßung und akutem Nierentransplantatversagen (delayed graft function – DGF) nach der Transplantation.

Methodik. 65 ausgewählte Nierenbiopsien (30 akute, zelluläre Abstoßung, 11 akute, humorale Abstoßung, 14 DGF) und 10 Protokollbiopsien (Kontrollgruppe) wurden mittels Affymetrix GeneChip mit miRNA Arrays analysiert. Initial wurden experimentell validierte Zielgene (miRTarBase) als Basis für Protein-Protein Interaktionsnetzwerkanalysen und funktioneller Interpretation verwendet. Zusätzliche Target-Gene von Vorhersage-Algorithmus wurden auf der Funktionsebene interpretiert.

Ergebnisse. In der un supervisie ten hierarchischen Klusteranalyse sowie in der Hauptkomponentenanalyse trennten sich die Patienten mit zellulärer und humoraler Abstoßung und DGF von der Kontrollgruppe. Dies lässt den Schluss zu, dass miRNAs bei diesen Hauptkomplikationen eine wesentliche Rolle spielen. Wir konnten zwischen sechs und 20 differenziell regulierte miRNAs zwischen Kontrollgruppe und den Studien gruppen identifizieren. Zellzyklus, Apoptose und Metabolismus waren die Haupteinstiege der Differenzialanalyse. miRNAs, aber auch Immunantwort und Entzündungsprozesse waren von der miRNA-Regulierung betroffen. Mittels Immunohistochemie konnten wir eine Suppression des Dicer Mole küls, ein Schlüsselprotein in der miRNA-Biogenese, in Tubuluszellen von Transplantaten mit zellulärer Abstoßung zeigen.

Schlussfolgerungen. Zusammenfassend sind unterschiedliche miRNA-Signaturen mit zellulärer oder humoraler Abstoßung sowie DGF assoziiert. Die identifizierten miRNAs und Target-Gene werden neue Sichtweisen auf die molekulare Regulation von Transplantatabstoßung und Transplantatversagen erlauben und so den Weg für neue Therapieansätze ebnet. Darüber hinaus könnten die identifizierten miRNAs und Target-Proteine in Zukunft als neue diagnostische Marker eingesetzt werden.

Correlation of recipient factors with the course of lymphocytes after alemtuzumab induction in renal transplantation

A. Weißenbacher, M. Kimelman, T. Hautz, H. Ulmer, C. Bösmüller, M. Maglione, R. Margreiter, R. Öllinger, J. Pratschke, S. Schneeberger

1Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria; 2Section of Medical Statistics and Informatics, Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria

Background. Alemtuzumab, an anti-CD52 T-cell and B-cell depleting monoclonal antibody, used as induction therapy in renal transplantation (KTx). The recovery of lymphocytes after alemtuzumab induction has been investigated in a number of trials, however, the clinical course after KTx has not been correlated with lymphocyte recovery. Herein, we correlate the outcome as well as recipient factors with lymphocyte recovery after induction with alemtuzumab.

Methods. Single center retrospective analysis of 225 patients/consecutive kidney transplantations between 01/2004 and 12/2010 which received alemtuzumab as induction agent (one dose of 30mg). Patients were devided into 4 groups according to lymphocyte recovery at 4 points of time (pre-Tx, 1–3 weeks post-Tx, 3 weeks–3 months post-Tx and 3–6 months after KTx). The relevance of recipient-characteristics was analyzed. Delayed kidney graft function (DGF) was defined as requirement for more than one dialysis within the first week after KTx. Statistical analysis was performed with SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Analysis of variance for repeated measurements with measurement time as within-subject factor and with age, CMV status, DGF status as between subject factors were performed.

Results. Median age of all recipients was 49.63 years, 65.33% were male. Mean lymphocyte counts were 22.8 ± 9.41% pre-Tx, 2.61 ± 3.11% between week 1 and 3, 6.36 ± 6.7% between 3 weeks and 3 months after Tx and 19.20 ± 11.48% at later time points. Among all factors analyzed, DGF, CMV status and age showed a significant correlation with lymphocyte counts. DGF occurred in 27.56% of the recipients. The lymphocyte-counts in the DGF-group were significantly higher, 10.7% vs. 13.13% (p = 0.036) post-Tx. CMV-status of the recipient influences the quantity of lymphocytes pre-Tx significantly (p = 0.009). Age showed a significant influence on the lymphocyte count 3 months post-Tx (p = 0.032).
Conclusions. CMV-status and age have a significant impact on lymphocyte recovery after alemtuzumab induction therapy. Lymphocyte counts early after transplantation represent a prognostic factor for kidney function early after transplantation. A detailed analysis of phenotype and function of lymphocytes after alemtuzumab induction together with a correlation with the clinical course is warranted.

**014**

Belatacept-based immunosuppression in de novo liver transplant recipients: 1-year experience from a phase II study

G. B. Klintmalm^1, S. Feng^2, J. R. Lake^3, H. E. Vargas^4, T. Wekerle^5, S. Meadows-Shropshire^6, M. Agarwal^7, J. C. Garcia-Valdecasas^8

^1Baylor University Medical Center, Dallas, TX, USA; ^2Division of Transplant Surgery, University of California San Francisco, San Francisco, CA, USA; ^3Liver Transplant Program, University of Minnesota, Minneapolis, MN, USA; ^4Division of Transplantation Medicine, Mayo Clinic Arizona, Phoenix, AZ, USA; ^5Division of Transplantation, Medical University of Vienna, Vienna, Austria; ^6Bristol-Myers Squibb, Princeton, NJ, USA; ^7Liver Transplant Unit, Hospital Clinic of Barcelona, Barcelona, Spain

Background. Calcineurin inhibitors contribute to substantial toxicities in liver transplant (LT) patients that can lead to renal dysfunction/failure and cardiovascular (CV) disease. This phase II study evaluated belatacept versus tacrolimus (Tac) in de novo LT recipients.

Methods. 250 LT recipients were randomized to belatacept-based (high dose [HD] or low dose [LD]) or Tac-based regimens. All patients received steroids for the first 3 months.

Results. Demographic characteristics were similar among groups; 46% of patients were HCV positive. The primary endpoint (composite of acute rejection [AR], graft loss [GL], and death by month 6) occurred more frequently in belatacept groups. By year 1, more deaths and GL occurred with belatacept LD vs. other groups. Causes of early (by 6 weeks) death and GL were mostly due to postoperative complications; thereafter causes included sepsis, PTLD, and multi-organ failure. AR was more common with belatacept-based regimens compared to Tac plus MMF. By 1 year, mean cGFR was 15–34 mL/min higher in belatacept vs. Tac groups. Lower blood pressure and less neurotoxicity were observed with belatacept treatment. 2 PTLD cases and 1 PML case (HD group) occurred in the belatacept groups.

Conclusions. Belatacept HD group had comparable efficacy relative to Tac alone but was less effective compared to Tac plus MMF. Belatacept LD group was less effective with more deaths and GL observed compared to both Tac-based groups. Belatacept provided improved renal function with less CV/metabolic and neurotoxicities vs. Tac-based regimens. PTLD and PML were observed with belatacept. The optimal dose/regimen of belatacept in LT is yet to be determined.

**015**

CMV late phase-induced mTOR activation is essential for efficient virus replication in human M2-polarized macrophages

M. Poglitsch^1, T. Weichhart^1, M. Hecking^1, J. Werzowa^1, K. Katholnic^1, M. Antlanger^1, A. Krmptotic^2, S. Jonic^2, E. Puchhammer^3

^1Division of Nephrology and Dialysis, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; ^2Department of Histology and Embryology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia; ^3Department of Internal Virology, Medical University Vienna, Vienna, Austria

Human Cytomegalovirus (CMV) remains one of the most important pathogens following solid-organ transplantation, potentially leading to CMV disease, allograft dysfunction, acute and chronic rejection and opportunistic infections. Mounting evidence indicates that mammalian target of rapamycin (mTOR) inhibitors may decrease the incidence of CMV infection in renal transplant recipients. Here we aimed to elucidate the molecular mechanisms of this effect by employing a human CMV (HCMV) infection model in human macrophages, since myeloid cells are the principal in vivo targets of HCMV and the major viral source during early CMV disease. Here we demonstrate that polarization of macrophages into M1 and M2 macrophages resulted in highly divergent host cell permissiveness for HCMV with optimal infectious susceptibility in M2 versus M1 macrophages. Employing an ultra-high purified HCMV stock (TB-40/E) selective rapamycin-independent induction of IFN-γ transcripts, but no proinflammatory cytokines or early signalling events including MAPK and mTOR signalling could be detected. Assessment of viral gene expression and mTORC1 activity during the course of macrophage infection revealed that rapamycin significantly suppressed CMV replication 3 and 5 days post infection, while CMV proliferation in fibroblasts was largely unaffected by mTOR-blockade. Analysis of mTORC1 activation and late phase viral proteins including pUL-44 and pp65 signified an exquisite mTORC1 dependency of protein synthesis during the late phases of viral replication. Collectively, these data indicate that mTORC1 is essential for virus replication during late phases of the viral cycle in myeloid cells which might explain the potent anti-CMV effects of mTOR inhibitors after organ transplantation.

**016**

CD4/CD25/FoxP3 reg. T-cells counterbalance inflammatory events after brain death

B. Förchinger^1,2, R. Oberhuber^2,3, C. Schmid^1, S. G. Tullius^2

^1Department of Cardiothoracic Surgery, University Hospital Regensburg, Regensburg, Germany; ^2Transplant Surgery Research Laboratory, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; ^3Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria
Background. Brain death (BD) triggers inflammatory signals and graft injury. Clinically, reduced organ quality as a result of brain death contributes to inferior graft and patient survival. Regulatory T-cells are primarily known for their control of the immune response. We analyzed CD25+/FoxP3+ T-cell subpopulations in recipients of either brain dead and native donor hearts. To dissect the role of donor immune competent cells in communic- 
ating inflammatory signals following BD we performed syn- 
geneic cardiac transplants from wildtype and immune deficient donor.

Methods. Hearts from brain dead wild type (BD/WT) C57BL6 mice and Rag2/double knockout (BD/KO) mice were procured 3 hrs following brain death induction and transplanted into WT recipients. Hearts originating from native C57BL6 mice served as controls. By 3 days, T-lymphocyte subpopulations (CD4, CD8, CD4/CD25/FoxP3) were assessed by flow cytometry and graft-specific changes were assessed by IHC and RT-PCR.

Results. Blood pressure remained stable following BD induc- tion and intragraft cell infiltration was comparable in all groups (p = n.s.). Cardiac isografts from BD/WT donors demonstrated pronounced cellular infiltrates; only few cells infiltrated hearts from living WT donors (p = 0.025). Of note, CD4/CD25/FoxP3 regulatory T-cells counts were significantly elevated in recipients of BD/WT grafts (p = 0.04). Recipients of BD/KO heart features reduced CD4+ T-cell infiltrates, but comparable FoxP3 levels (p = n.s.). In contrast, BD/KO heart recipients showed significant- 
ly lower IL-6, IFN-γ, and TNF-α levels (p = 0.03, 0.005, 0.01).

Conclusions. Inflammatory events after brain death are counterbalanced by significantly elevated rates of CD4/CD25/ 
FoxP3 reg. T-cells. Less pronounced consequences of brain death in hearts originating from immune deficient donors suggest a critical role of immune competent cells in communicating inflam- 
matory signals.

Lipocalin-2 as a therapeutic agent in chemotaxis during ischemia and reperfusion injury following solid organ transplantation

P. Schumpp, M. Koller, H. Maier, S. Sickinger, H. Schwebelger, N. Vallant, S. Schneeberger, J. Pratschke, F. Aigner

Department of Visceral, Transplantation and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria

Background. Neutrophil gelatinase-associated lipocalin (NGAL/Lcn-2) expression is associated with ischemia/reperfu- sion injury (IRI) following transplantation and correlates with polymorphonuclear cell infiltration. To get insight into the regulato- ry role of Lcn-2 during IRI the expression of different chemokines and adhesion molecules were analyzed in a murine heart transplantation model.

Methods. The murine heterotopic heart transplant model was also implied exogenous i.p. application of Lcn-2 compared to iron-free Lcn-2.

Results. Significant lower granulocyte infiltration and serum creatinine kinase levels during IRI were observed in the Lcn-2-/ 
transplants correlating with a stable ICAM-1 expression com- pared to the Lcn-2 wt setting (>50% of expression at 2 h of reper- fusion). In the early phase of reperfusion (2 h) MCP-1, KC, LIX and MIP-2 showed a lower expression pattern in the Lcn-2-/ 
transplants with delayed upregulation at 12 h (LIX, MIP-2). After i.p. Lcn-2 application no significant difference in apoptosis was observed. The number of infiltrating granulocytes was reduced after application of the iron-loaded Lcn-2 compared to iron-free Lcn-2.

Conclusions. Our data point to a possible chemotactic role of Lcn-2 which may also affect the expression of particular chem- okines in the early phase of IRI. The role of the iron binding capacity of Lcn-2 in chemotaxis during IRI is still unknown. Understanding these regulatory mechanisms will be crucial to establish treatment strategies for IRI during solid organ trans- plantation.

Supplement 242

Glomeruläre Effekte des mTOR-Inhibitors Rapamycin in der nephrotoxischen Serumnephritis

A. H. Kirsch1, A. Tagwerker2, A. R. Rosenkranz1, K. Eller1

1Klinische Abteilung für Nephrologie, Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Graz, Österreich; 2Universitätsklinik für Innere Medizin IV, Medizinische Universität Innsbruck, Innsbruck, Österreich

Grundlagen. Der mTOR Inhibitor Rapamycin ist ein Immuno- suppressivum, welches klinische Anwendung zur Prävention von Abstoßungsreaktionen bei nierentransplantierten Patienten gefunden hat. Einer der limitierenden Faktoren bei der klinischen Anwendung ist das de novo Auftreten von Proteinurie. Ziel der Arbeit war es, die glomerulären Veränderungen der Rapamycin- induzierten Proteinurie in einem experimentellen Modell der nephrotoxischen Serumnephritis (NTS) näher zu untersuchen.

Methodik. NTS wurde in C57BL/6 Mäusen induziert und die Gabe von Rapamycin in einer Dosis von 0,5 mg/kg 14 Tage nach Induktion begonnen. Die Mäuse wurden am Tag 35 sakrifiiziert und Gernome der Nephrotoxizität durch Geneexpressionssanalyse isoliert. Außerdem wurde mittels Immunhistochemie die glomeruläre Expression von T-Zell- (CD4), Makrophagen- (F4/80, CD68), Podocyten- (Nephrin), sowie Endothelzellenmarker (CD31) untersucht.

Ergebnisse. Mäuse, die mit Rapamycin ab Tag 14 behandelt wurden, entwickelten eine signifikant erhöhte Proteinurie im Vergleich zu den Kontrolltieren. Dies war mit einer verstärkten glomerulären Infiltration von CD4-positiven (mittlere intraglo- 
muläre positive Zellen/50 Glomeruli 4,43 ± 0,68 vs. 2,23 ± 0,57; p < 0,05), F4/80-positiven (8,2 ± 1,58 vs. 3,64 ± 0,74; p < 0,05) und CD68-positiven Zellen (18,80 ± 3,05 vs. 9,15 ± 1,61; p < 0,05; n = 13 Rapamycin, n = 12 Vehikel) assoziiert. Keine Unterschiede fanden sich in der glomerulären Färbung von Nephrin und CD31. Real-time PCR der aus Glomeruli gewonnenen RNA zeigte, dass die Rapamycin-Behandlung zu einer verstärkten Expression der proinflammatorischen Zytokine IL-6 (12,0 ± 5,2 vs. 1,0 ± 0,1; p < 0,05) und TNF-α (3,4 ± 0,6 vs. 1,0 ± 0,1; p < 0,05) führte, während sich hierbei keine Hinweise auf eine Schädigung der Endothelzellen ergaben. Außerdem fand sich eine gesteigerte glo- 
muläre Expression des Transkriptionsfaktors Foxp3.
Schlussfolgerungen. Zusammenfassend zeigen unsere Daten, dass die Rapamycin-induzierte Proteinurie auf einer proinflammatorischen Wirkung auf Makrophagen und nicht auf einer Podozyten- oder Endothelzellschädigung beruht.

Parallelsitzung III: Klinische Transplantation/Arzneimittelstudien

019

Das Spektrum maligner Hauttumoren nach Transplantation

I. H. Wolf
Universitätsklinik für Dermatologie, Medizinische Universität Graz, Graz, Österreich

Organtransplantierte Patienten/innen zeigen in Folge der notwendigen immunsuppressiven Therapien ein erhöhtes Risiko für Hauterkrankungen. Im Vordergrund stehen Infektionen und vor allem maligne Hauttumoren.

Bei TX-Patienten/innen findet man ein bis zu 200-fache Erhöhung der sog. „non-melanoma skin cancer“-Gruppe und eine 5-fache Steigerung der Melanom-Inzidenz im Vergleich zur Normalbevölkerung. Das klinische Bild dieser Neoplasien ist nicht selten atypisch, das Verhalten aggressiv und die Prognose ungünstig. Die Intensität bzw. Dauer der Immunsuppression und die Wahl der immunsuppressiven Medikamente in Verbindung mit der aktuellen und zurückliegenden UV-Exposition korreliert dabei mit der Tumorentstehung. Besonders wichtig sind regelmäßige Nachsorge-Untersuchungen post Transplantation, welche in speziellen dermatologischen Ambulanzen durchgeführt werden sollten. Hierbei stehen heute moderne Hauttumor-Therapieformen („targeted“ therapy und Immunmodulatoren) zur Verfügung.

020

Comparative pharmacokinetic study of two mycophenolate mofetil formulations in stable kidney transplant recipients

G. Sunder-Plassmann1, P. Reinke2, T. Rath3, A. Wieck4, M. Nowicki4, R. Moore5, J. Lutz3, M. Gaggi1, M. Ferk6

1Division of Nephrology and Dialysis, Department of Medicine II, Medical University Vienna, Vienna, Austria; 2Department of Nephrology and Intensive Care Medicine, University Hospital Charité, Berlin, Germany; 3Department of Nephrology and Transplantation, Westpfalz-Klinikum, Kaiserslautern, Germany; 4Department of Nephrology, Endocrinology, and Metabolic Diseases, Silesian University School of Medicine, Katowice, Poland; 5Department of Nephrology, Hypertension, and Transplantation, University of Łódź, Łódź, Poland; 6Nephrology & Transplant, University Hospital Wales, Cardiff, United Kingdom; 7Division of Nephrology, Department of Medicine, University Hospital Rechts der Isar, München, Germany; 8Teva Pharmaceuticals Europe, Harlow, United Kingdom

Background. Belatacept is a co-stimulation blocker which has recently been approved as immunosuppressive therapy in renal transplant recipients. Here we assess the outcome of patients that have been treated with belatacept for 10 years after kidney transplantation.

Methods. In our center, 22 patients were enrolled in the phase II multi-center belatacept trial that started in 2001. Patients were randomly assigned to belatacept- (n = 14) or CyA- (n = 8) based immunosuppression (all patients received basiliximab, MMF and steroids). In the retrospective analysis we report the outcome of the belatacept group as of June 2011. Patient and graft survival, the incidence of acute rejection, kidney function (calculated GFR, MDRD [ml/min/1.73 m²]) and cardiovascular risk profiles (triglycerides and cholesterol) are presented.
Results. At an average of 9.2 (8.5–10.1) years after kidney transplantation, 9 out of 14 belatacept (64%) patients are still on therapy. Five patients discontinued the study: 1 due to lack of efficacy (ATG-resistant rejection), 1 due to PTLD, 1 due to pneumocystis carinii pneumonia and 2 patients withdrew consent (1 and 3.5 years after transplantation with a functioning graft; GFR: 65.4 and 46.05 ml/min/1.73 m²). Three patients died: the patient with PTLD and the patient with pneumocystis carinii pneumonia shortly after discontinuation and the patient with lack of efficacy 6 years later due to cardiac arrest. Two patients developed biopsy-proven acute rejection (2/14; 14.3%) (BANFF IIa, BANFF IIb). In 8 out of 9 patients kidney function remained stable over time: mean GFR 12 months after kidney transplantation 59.64 (SD 10.6), mean eGFR at the time of the last visit: 59.32 (SD 11.2). One patient had an impaired kidney function with a GFR of 45.03 at the last visit (GFR at month 12: 68). Mean serum triglycerides and cholesterol at 12 months after transplantation were 167 (SD 70) and 207 (SD 34) respectively, and changed little over time (mean triglycerides: 159 (SD 44) and cholesterol: 201 (SD 44) at the last visit).

Conclusions. In this selected group of patients enrolled in a phase II trial, continuous use of belatacept therapy for 10 years is associated with stable long-term graft function in a high percentage of patients.

Conclusions. The overall functional outcome and patient satisfaction after bilateral hand, bilateral forearm and unilateral hand transplantation are highly encouraging. All patients are now free of rejection with moderate levels of IS.

Conclusions. Conversion to SRL from CNI therapy resulted in improved renal function in cardiac transplant recipients with renal insufficiency, but was associated with an attendant AR risk and higher discontinuation rate due to AEs.

Results. Range of motion reached up to 70% of normal with a grip strength of 2–10 kg. Hand function correlated well with time after transplant and amputation level. Intrinsically hand muscle function recovery and discriminative sensation were observed in all patients. Complications included CMV infection, fungal infection, hypertension, hyperglycemia, transient creatinine increase and headache. Three, six, four, and one rejection episode were successfully treated with steroids, anti-Ti-CD25, anti-CD52 antibodies and/or intensified maintenance IS. Skin histology at current shows no or mild perivascular lymphocytic infiltrates without signs of progression. Vessels are patent without signs for luminal narrowing or intimal proliferation.

Results. At an average of 9.2 (8.5–10.1) years after kidney transplantation, 9 out of 14 belatacept (64%) patients are still on therapy. Five patients discontinued the study: 1 due to lack of efficacy (ATG-resistant rejection), 1 due to PTLD, 1 due to pneumocystis carinii pneumonia and 2 patients withdrew consent (1 and 3.5 years after transplantation with a functioning graft; GFR: 65.4 and 46.05 ml/min/1.73 m²). Three patients died: the patient with PTLD and the patient with pneumocystis carinii pneumonia shortly after discontinuation and the patient with lack of efficacy 6 years later due to cardiac arrest. Two patients developed biopsy-proven acute rejection (2/14; 14.3%) (BANFF IIa, BANFF IIb). In 8 out of 9 patients kidney function remained stable over time: mean GFR 12 months after kidney transplantation 59.64 (SD 10.6), mean eGFR at the time of the last visit: 59.32 (SD 11.2). One patient had an impaired kidney function with a GFR of 45.03 at the last visit (GFR at month 12: 68). Mean serum triglycerides and cholesterol at 12 months after transplantation were 167 (SD 70) and 207 (SD 34) respectively, and changed little over time (mean triglycerides: 159 (SD 44) and cholesterol: 201 (SD 44) at the last visit).

Conclusions. In this selected group of patients enrolled in a phase II trial, continuous use of belatacept therapy for 10 years is associated with stable long-term graft function in a high percent age of patients.

Conclusions. The overall functional outcome and patient satisfaction after bilateral hand, bilateral forearm and unilateral hand transplantation are highly encouraging. All patients are now free of rejection with moderate levels of IS.

Conclusions. Conversion to SRL from CNI therapy resulted in improved renal function in cardiac transplant recipients with renal insufficiency, but was associated with an attendant AR risk and higher discontinuation rate due to AEs.
Impact of different ATG dosing protocols on long-term outcome after cardiac transplantation

A. Aliabadi, M. Grömm, F. Eskandary, D. Dunkler, T. Haberl, C. Pelanek, S. Mahr, G. Lauffer, A. Zuckermann
Division of Cardiac Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria

Background. ATG-induction therapy after heart transplantation is still controversial and used only by less than 50% of centers. Moreover, there exist no data about the optimal dosage of ATG-induction. The aim of this study is to compare different doses of ATG-induction.

Methods. Between 1996 and 2009 586 cardiac transplants were performed in our center. 523 (89%) patients with full data sets were included in the analysis. The median age was 56 years, 21% (n = 112) were female. The median follow-up time was 98 months. Patients were divided into 3 different groups according to total ATG dose: Group A: 4.5 mg/kg vs. Group B: 4.5–7.5 mg/kg vs. Group C: >7.5 mg/kg. Survival, incidence of rejection, infection, graft vasculopathy and cancer were compared by Kaplan-Meier analyses (log rank test).

Results. There was better early (12 m) and late (150 m) survival in Group B (A: 80%, 43%; B: 90%, 65%; C: 88%, 58%; p = n.s.), however, the difference was not significant. Freedom from treated acute rejection was better in group B (88%) compared to A and C (79%, 80%, p = 0.08). Signs of histological rejection were significantly different between the groups (A: 25%, B: 18%, C: 33%; p = 0.03). Group B had the lowest incidence of severe infection (A: 37%, B: 21%, C: 51%; p = 0.01). CMV infection incidence was higher in group C (35%) compared to groups A, B (20%, 23%; p < 0.01).There was no significant difference in freedom from graft vasculopathy between the groups (A: 91%, B: 85%, C: 79%; p = n.s.). The incidence of cancer was similar in all ATG groups (A: 3%, B: 7%, C: 11%; p = n.s.).

Conclusions. Different doses of ATG-induction seem to have a significant impact on the outcome of heart transplantation. There is a strong need for more studies on optimization of ATG therapy.

Nighttime kidney transplantation – a risk or a need?

K. Kienzl-Wagner, S. Schneiderbauer, C. Bösmüller, J. Pratschke, R. Öllinger
Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria

Background. Kidney transplantation is performed as emergency surgery also as a nighttime procedure to reduce cold ischemia time and therefore improve outcomes after kidney transplantation. However, surgical procedures performed during nighttime in the context of 24 hour shifts and sleep deprivation have been associated with a higher rate of complications than elective surgery. The aim of this retrospective analysis is to determine the impact of nighttime surgery on the outcome after kidney transplantation.

Methods. All kidney transplants from cadaveric donors performed at our center from January 2000 through January 2010 (n = 873) were included in this retrospective study and grouped according to the time of surgery: daytime (from 8 a.m. to 8 p.m., n = 608) versus nighttime (from 8 p.m. to 8 a.m., n = 265). Statistical analysis compared patient and graft survival in the two groups, rate of delayed graft function and acute rejection as well as surgical complications.

Results. 5-year patient survival rates of 87% and 85% and 10-year patient survival rates of 73% and 69% in daytime and nighttime kidney transplantation did not show any significant difference. Also, graft survival at 5 and 10 years did not differ significantly (85% versus 83% and 69% versus 60%) in the two groups. Delayed graft function occurred in 31% of daytime transplants compared to 37% of nighttime procedures (p = 0.06). Acute allograft rejection was observed in 23% of daytime graft recipients compared to 18% of nighttime graft recipients (p = 0.13). Furthermore, nighttime procedures were associated with a 23% risk of surgical complications which was not significantly different from daytime surgery (22%, p = 0.7).

Conclusions. Nighttime kidney transplants are not associated with a higher surgical complication rate than daytime procedures. Nighttime kidney transplant procedures have the same outcome as daytime transplants and are necessary to keep cold ischemia time as short as possible.

Ursolic acid a constituent of Dwarf Elder (Sambucus ebulus) inhibits surface expression of endothelial adhesion molecules and prevents intimal hyperplasia in an in vivo model for bypass surgery

D. Wiedemann1, I. Zeller1, S. Schwaiger2, M. Stelzmüller1, S. Kreutmayer2, O. Leberfing2, G. Lauffer1, D. Bernhard1
1Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria; 2Institute of Pharmacy/Pharmacognosy, Medical University of Innsbruck, Innsbruck, Austria; 3Division of Experimental Pathophysiology and Immunology, Innsbruck Biocenter, Medical University of Innsbruck, Innsbruck, Austria; 4Department of Cardiac Surgery, Medical University of Innsbruck, Innsbruck, Austria

Background. In a recent study for the identification of compounds capable of inhibiting VCAM-1 expression we isolated ursolic acid (UA) from extracts of Dwarf Elder. Herein, we analyse the mechanism of action and the in vivo applicability of the compound in a setting for venous bypass graft intimal hyperplasia.

Methods and Results. Our analyses indicate that UA does not interfere with the adhesion molecule expression pathway at or upstream of NFK-B, as NFK-B translocation and NFK-B mediated transcription were not affected by UA. However, UA inhibited adhesion molecule protein synthesis suggesting
acetylated by the presence of only one activating KIR gene) displayed a stable early postoperative kidney function, compared to patients with a KIR haplotype B/x (more than one activating receptor) \( (p = 0.025, \text{ odds ratio } 2.3, \text{ CI } 1.3–3.9) \). Moreover, the absence of KIR2DL2/DS2 genes significantly influenced the risk of ARF \( (p = 0.05) \). A multivariate regression model of clinical and genomic risk factors for ARI/ARF confirmed a link between the KIR haplotype A/A and post-LT acute renal failure \( (p = 0.04) \). In summary, we observed a higher percentage of NK cells prior to LT in patients with impaired renal function and identified the KIR haplotype A/A as an independent genetic risk factor for ARF within the first postoperative week. Our data provide new aspects of an innate immune response within the setting of post-LT kidney injury and failure.
Clinical relevance of preformed complement- and non-complement-fixing HLA alloreactivity in cardiac transplantation

S. Mahr¹, M. Wahrmann², A. Zuckermann¹, G. Böhmig²

¹Division of Cardiac Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria; ²Division of Nephrology and Dialysis, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

Background. There is increasing evidence for a role of alloantibody-mediated rejection in organ transplantation. Solid phase HLA antibody detection using bead array technology may help identify patients at risk of rejection and graft loss.

Methods. In this retrospective monocentric cohort study we evaluated 229 consecutive heart transplant recipients (transplantation between 2000 and 2006; immunosuppression: ATG induction and calcineurin inhibitor-based maintenance therapy) for the presence of preformed (complement- and non-complement-fixing) HLA alloantibodies. Sera obtained immediately before transplantation were screened by FlowPRA, and test-positive sera were subjected to Lumines-based single antigen testing including a test modification for detection of in vitro C4d deposition.

Results. Seventeen recipients (7.3%) were found to have performed IgG type donor-specific alloantibodies (DSA), five of them with C4d-fixing capability. The presence of DSA was related to retransplantation and previous pregnancies, but not associated with prior implantation of a ventricular assist device. Evaluating clinical endpoints, we found an association between DSA and acute rejection (≥grade 1A according to the ISHLT 1998 grading system; no DSA: 17%; [IgG/DSA: 33%; [IgG/C4d] DSA: 60%). However, in our study cohort, sensitization had no effect on long-term survival rates (5-year transplant survival: 72% vs. 92% vs. 80%) or rates of chronic transplant vasculopathy (20% vs. 18% vs. 20%). Moreover, none of the DSA-positive patients was in need of extracorporeal membrane oxygenation, and the duration of post-transplant intensive care did not differ between groups.

Conclusions. In conclusion, our data point to a relationship between preformed donor-specific alloreactivity and acute rejection. However, possibly as a result of our local immunosuppressive regimen, which also includes induction therapy with a depleting anti-lymphocyte antibody, such reactivity did not influence long-term allograft outcomes.

Efficacy and safety of immunosuppression with everolimus in pediatric heart transplantation

M. Schweiger¹, M. Dandel², N. Hiemann³, Y. Weng², M. Hübner², M. Pasic², S. Schubert², O. Grauhan², C. Knosalla², F. Berger³, R. Hetzer⁴, H. Lehmkuhl²

¹Division of Cardiac Surgery, Department of Surgery, Medical University of Graz, Graz, Austria; ²Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany

Background. So far, no data is available on the use of everolimus in pediatric cardiac transplantation. We present the first results of everolimus in pediatric heart transplantation.

Methods. From 2000 to 2008, HTx was performed in 86 children aged below 17 years. 52 of these children received continuously either mycophenolat mofetil (MMF) (Group A, n = 28) with standard cyclosporine A (CsA) exposure or were randomized to receive everolimus (EVE) (Group B, n = 24) with reduced CsA exposure in combination with steroids. During a follow-up period of 24 months, efficacy with regard to acute rejection, allograft vasculopathy and survival as well as safety with regard to myelosuppression, infection, tumors, lipids and body growth was studied.

Results. Mean post Htx CsA exposure was significantly lower in EVE treated children compared to MMF at month 6 (167 ng/ml versus 284 ng/ml), month 12 (mean 134 ng/ml versus 235 ng/ml) and month 24 (79 ng/ml versus 76 ng/ml). Mean daily dose of EVE was 1.16 ± 0.56 mg/m² body surface area resulting in trough levels of 4.8 ± 1.3 ng/ml by 24 months of follow-up. Two cases in each group encountered biopsy-proven acute rejection ≥grade 2R (7% versus 8%; p = 0.043). Cardiac allograft vasculopathy at month 12 was detected in 4 children (16%) with EVE compared to 18% in MMF. Kidney function deteriorated in both groups during the first month, recovering after 24 months to a glomerular filtration rate of 59.1 ± 0.3 ml/min/sqm for EVE versus 88.9 ± 5.2 ml/min/sqm for MMF. Rates of myelosuppressive disorders (anaemia, leukopenia, thrombocytopenia), infections and hyperlipidaemia was low and comparable in both groups. Children with EVE did not encounter inferiority in body growth. 1 child with EVE died following intractable ventricular fibrillation during myocardial biopsy compared to 5 children with MMF (2 deaths due to allograft rejection).

Conclusions. Everolimus with reduced CsA combined with steroids in paediatric cardiac transplant recipients enables high efficacy and is comparatively safe to immunosuppression with MMF and standard exposure of CsA.
031

Transplantation of a minor-mismatched skin graft elicits a rapid humoral response including the induction of antigen-specific IgE

A. Farkas1, U. Baranyi1, R. Valentä, T. Wekerle1

1Division of Transplantation, Department of Surgery, Medical University of Vienna, Vienna, Austria; 2Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center of Physiology and Pathophysiology, Medical University of Vienna, Vienna, Austria

Background. Sensitization to major and minor antigens is a critical problem in transplantation medicine with antibodies of IgM, IgA and IgG isotypes have been demonstrated towards major (i.e. MHC) and minor (i.e. non-MHC) antigens. In a new transgenic mouse model we investigated humoral antigen-specific responses towards a highly immunogenic non-MHC antigen. A transgenic mouse expressing the well-characterized major grass pollen allergen Phl p 5 ubiquitously on the cell surface was generated.

Methods. A Phl p 5-transgenic Balb/c mouse was generated by pronuclear injection integrating Phl p 5 (and GFP) fused to a leader peptide and a transmembrane domain. Splenocytes by pronuclear injection integrating Phl p 5 (and GFP) fused to a leader peptide and a transmembrane domain. Splenocytes were isolated by dextran sedimentation. Phl p 5-specific IgG was determined in sera by ELISAs and T-cell proliferation assays were assessed.

Results. Surprisingly, a prompt rejection of Phl p 5-transgenic skin was elicited (within 8–10 days), accompanied by a strong humoral immune response against major antigens. Additionally to the skin grafted group, mice receiving splenocytes showed Phl p 5-specific IgG isotypes, IgA and IgM were induced. Besides splenocyte-proliferation assays showed Phl p 5-specific T-cell responses in all groups of mice that showed strong humoral responses.

Conclusions. The high immunogenicity of tissue-bound Phl p 5 may represent a new stringent model for studying humoral responses towards non-MHC antigens. Notably, the immune reaction included a rapid IgE response in this model.

032

The influence of recipient age on chimerism-based tolerance induction

K. Hock1, R. Oberhuber2,3, Y.-L. Lee4, T. Wekerle1, S. G. Tullius2

1Division of Transplantation, Department of Surgery, Medical University of Vienna, Vienna, Austria; 2Division of Transplant Surgery and Transplant Surgery Research Lab, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA; 3Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria

Background. Immune senescence substantially alters alloreactivity. Higher frequencies of memory T cells (Tmem) found in older recipients are considered a substantial barrier to tolerance induction. Tolerance induction through mixed chimerism holds promise for clinical translation but has only been investigated in young recipients so far. As the average recipient age has increased substantially in clinical organ transplantation, we investigated the consequences of recipient age on the outcome of costimulation blockade based allogeneic bone marrow transplantation (BMT) for the purpose of mixed chimerism and tolerance induction.

Methods. Young (2 months; weighing approx. 20 grams) and old (12 months; 25 g) recipients (C57BL/6) were treated with 3 or 1 Gy total body irradiation (TBI, d-1) and received adjusted to the body weight 20x10^6 and 25x10^6 un-separated Balb/c BM cells (d0) and co-stimulatory blockade with anti-CD154 mAb (d0) and CTLA4Ig (d + 2) was administered. Lymphocyte subsets and cytokine production were compared between young and old naive mice and multilineage chimerism was followed by flow cytometry.

Results. Old mice contain significantly more CD4 (p < 0.05) and CD8 (p < 0.001) memory T cells (CD44highCD62Llow), early activated CD4 T cells (CD4+CD69+; p = 0.01), less CD4 and CD8 T cells and comparable amounts of regulatory T cells (Tregs; CD4+CD25+FoxP3+; p = n.s. vs. young animals). Moreover, older CD4 and CD8 T cells release more IFN-γ than CD4 (p < 0.05), II-2 (not CD8 T cells), IL-6 (CD4; p < 0.05), II-10 and TNF-α. Chimerism developed earlier in old recipients; within one week most older recipients became chimeric following an irradiation with 3 Gy TBI and co-stimulatory blockade (17/18 vs. 9/18 chimeras, d+7 and 16/17 vs. 12/17, d + 14). Old recipients became even chimeric with a reduction of the total body irradiation to 1 Gy. In sharp contrast, none of the young recipients became chimeric under those conditions (4/8 vs. 0/8 chimeras in young recipient, p < 0.05, d + 30).

Conclusions. Recipient age is linked to a faster donor BM engraftment and chimerism. Moreover, chimerism is attainable with a lower dose of irradiation. Those results support the clinical relevance of the chimerism strategy for tolerance induction.
Rapamycin and anti-LFA-1 overcome the barrier of T cell sensitization in a bone marrow transplantation-based tolerance model

L. Unger, N. Pilat, H. Ramsey, C. Schwarz, K. Hock, A. Forkas, U. Baranyi, T. Wekerle

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

Background. Mixed chimerism is an effective strategy for the induction of transplantation tolerance, however, translation from murine models to the clinical setting is challenging. One hurdle is the high frequency of alloreactive memory T-cells (Tmem) found in the (pre)clinical setting, which is not present to a similar degree in mouse models. To better model this clinical reality, we have developed a murine model in which the transfer of $3 \times 10^6$ T-cells from sensitized mice induces the production of chimerism and tolerance in a well-characterized chimerism model. The trend that elimination of Tmem is lower in the rapamycin-treated group and central deletion is more pronounced over time, but less so in the rapamycin-treated group. IFNgamma-production was reduced by rapamycin or anti-LFA-1 treatment.

Methods. Recipients (C57BL/6) were treated with 3 Gy TBI (d-1) and received approximately $20 \times 10^6$ unseparated Balb/c BM cells (d0) and costimulation blockers anti-CD154 mAb (d0) and CTLA4Ig (d$+2$). 30 $\times 10^6$ Balb/c, CB6F1 (Balb/c x B6), irradiated Balb/c or C3H CD4 T cells (isolated by MACS) were co-transplanted in addition. Groups either received anti-IL-6, anti-IFN-gamma, anti-LFA1 mAb or rapamycin. Multilineage chimerism was followed by flow cytometry and cytokine release was analyzed.

Results. Co-transplantation of $30 \times 10^6$ CD4 T cells but not CD8 T cells triggered rapid BM rejection of donor BM under costimulation blockade within one week in an otherwise successful protocol (0/13 vs. 17/20 chimeras, $p < 0.001$). The levels of IL-6, IFN-gamma, IL-17A ($p < 0.05$) and TGF-beta were found to be higher in mice treated with additional donor T cells. The neutralization of IL-6, but not of IFN-gamma resulted in a significantly higher rate of chimerism induction compared to controls (5/7 vs. 0/5 chimeras; $p < 0.005$). The injection of CB6F1 or irradiated Balb/c CD4 T cells did not abrogate chimerism (5/6 and 4/5 vs. 0/4 chimeras with Balb/c T cells; $p < 0.05$), whereas C3H CD4 T cells induced BM rejection (0/5 vs. 9/9 chimeras BMT, $p < 0.001$). The additional treatment with rapamycin or anti-LFA1 overcome the negative effect of donor T cell injection (5/5 and 6/6 vs. 0/4 chimeras; $p < 0.001$).

Conclusions. The abrogation of BM engraftment through co-transplantation of donor CD4 T cells involves IL-6, requires proliferative capacity of the co-transplanted T cells and needs to recognize the recipient as allogeneic. Neutralisation of IL-6, rapamycin and anti-LFA1 overcome the effect of co-transplanted donor CD4 T cells and offer potential targets for therapeutic intervention in costimulation blockade-resistant rejection.

Lunchsymposium Virusinfektionen in der Organ- und Stammzelltransplantation

Diagnostik von Virusinfektionen in Transplantationspatienten

E. Puchhammer-Stöckl

Department für Virologie, Medizinische Universität Wien, Wien, Österreich

Patienten nach Organ- oder Knochenmarkstransplantationen werden immunsuppressiv behandelt und weisen daher ein anderes Spektrum von potentiell gefährlichen Virusinfektionen auf als immunkompetente Personen. Vor allem Viren, die im normalen Wirt nur leichte oder asymptomatische Infektionen verursachen und latent im Organismus verbleiben, wie Herpesviren (Zytomegalievirus, Epstein-Barr Virus etc.) oder auch Polioviren (BK-, JC-Virus), können unter Immunsuppression hoch replizieren und zu schweren und potentiell tödlichen Infektionen führen.

Um schwere Infektionen oder Reaktivierungen durch verschiedene Viren zu verhindern, wird heute routinemäßig in regelmäßigen Abständen im Verlauf nach Transplantation der direkte und quantitative Nachweis verschiedener Viren (vor allem von Zytomegalievirus) mittels PCR im Blut, aber auch in verschiedenen anderen Patientenmaterialien durchgeführt. Ziel der Diagnostik ist es hier nicht so sehr eine klinisch relevante Virusinfektion nachzuweisen, sondern vielmehr das Vorhanden-
sein einer signifikanten Virusreplikation frühzeitig, noch vor Krankheitsbeginn zu erkennen. Das ist dann auch die Basis für die „präemptive“ antivirale Therapie, die gegeben wird, wenn die Viruslast eine bestimmte Höhe überschreitet, aber noch bevor klinische Symptome auftreten.

Die Festsetzung der virologischen Grenzwerte für den Einsatz der präemptiven Therapie ist aber eine große Herausforderung, da vor allem Herpesviren wie Zytomegalievirus (CMV) oder Epstein-Barr Virus (EBV), aber auch Polyomaviren auch ohne jede Krankheitsrelevanz im Organismus nachgewiesen werden können. Neben den quantitativen PCR Ergebnissen hängt der Einsatz einer präemptiven Therapie auch von be-stimmten weiteren Aspekten ab, wie vom Donor/Recipient Virus-serostatus, dem transplantierten Organ oder vom Material in dem man die Virusnukleinsäure nachweist. Daher ist ein enges Zusammenspiel von virologischer Befunderstellung, Interpretation und der Kenntnis der klinischen Aspekte notwendig, um eine optimale virologische Kontrolle der einzelnen Patienten zu erreichen.

**Antivirale Therapie bei Patienten nach Organ- oder hämatopoetischer Stammzelltransplantation**

V. Strenger

Klinische Abteilung für Pädiatrische Hämat.-/Onkologie, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Graz, Graz, Österreich

Tab. 1: (abstract 036)

| Wirkstoff       | Handelsname          | DNA-Viren | RNA-Viren |
|------------------|----------------------|-----------|-----------|
|                  | HSV 1/2 | EBV | CMV | HHV-6 | ADV | HBV19 | Polyomaviren | Peckenviren | HAV | EV | HCV | Influenza A | Influenza B | Rhinoviren |
| Aciclovir        | Zovirax u.a.         | +   | +   | ?    |      |       |          |            |      |     |     |         |         |           |
| Famciclovir      | Famvir              | +   | +   |      |      |       |          |            |      |     |     |         |         |           |
| Ganciclovir      | Cymevene            | ?   | ?   | +    | +    | +     |          |            |      |     |     |         |         |           |
| Foscarnet        | Foscavir            | +   | +   | +    | +    | +     |          |            |      |     |     |         |         |           |
| Cidofovir        | Vistide             | +   | +   | +    | +    | +     |          |            |      |     |     |         |         |           |
| Adefovir         | Hepsera             | +   | +   | +    | +    | ?     |          |            |      |     |     |         |         |           |
| Lamivudin        | Epivir u.a.         | +   | +   |      |      |       |          |            |      |     |     |         |         |           |
| Ribavirin        | Rebetol u.a.        | +   | +   |      |      |       |          |            |      |     |     |         |         |           |
| Zanamivir/Oseltamivir | Referenz/Tamiflu |      |      |       |      |       |          |            |      |     |     |         |         |           |
| Amantadin        | Amant               | +   | +   |      |      |       |          |            |      |     |     |         |         |           |
| Pleconaril*      | –                   |      |      |       |      |       |          |            |      |     |     |         |         |           |
| CMX001*          | –                   |      |      |       |      |       |          |            |      |     |     |         |         |           |
| Ciprofloxacin**  | Ciproxin            |      |      |       |      |       |          |            |      |     |     |         |         |           |

*(in vitro) Wirksspektrum ausgewählter Viren (ohne anti-retrovirale Substanzen)
Wirksamkeit entspricht nicht den zugelassenen Indikationen
* experimentell, nicht verfügbar ** experimentell
Adoptiver Immuntransfer
virus spezifischer T-Zellen nach Transplantation

T. Feuchtinger
Universitätsklinik für Kinderheilkunde und Jugendmedizin
Tübingen, Tübingen, Deutschland

Reaktivierungen von persistierenden Virusinfektionen sind häufige Komplikationen nach Transplantation. Je nach Risikokonstellation reicht das klinische Spektrum von einem harmlosen Infekt bis zu einem lebensbedrohlichen Infektionsverlauf. Die häufigsten Pathogene sind Cytomegalievirus (CMV), Epstein-Barr Virus (EBV) und Adenoviren (ADV). Die Möglichkeiten der virostatischen Pharmakotherapie sind meist limitiert. Alle drei Virusinfektionen haben gemeinsam, dass für eine Elimination eine suffiziente T-Zellimmunität notwendig ist. Darauf baut die Rationale eines adoptiven Immuntransfers auf, bei dem Ag-specifiche T-Zellen von einem gesunden Spender in einen erkrankten Empfänger infundiert werden. Hierbei ist das Therapieziel eine adaptive Immunität im Empfänger zu induzieren. Im Rahmen einer risikoadaptierten Therapie wurde bei refraktären Virusreaktivierungen nach Transplantation dieses Therapieverfahren angewendet. Eine Ag-spezifische T-Zellantwort konnte im Empfänger gegen immundominante Epitope (pp65 für CMV, Hexonprotein für ADV und EBNA1 für EBV) induziert werden um den Empfänger vor Virus-assoziierten Komplikationen zu schützen.

Parallelsitzung IV:
Knochenmarktransplantation/
Stammzellen II

Transplantation of haploidentical CD3/CD19 depleted stem cells in pediatric patients: current results of the Tübingen trial and additional immunotherapeutic approaches

P. Lang, H.-M. Teiltchik, T. Feuchtinger, M. Pfeiffer, C. Urban, W. Schwinger, B. Gruhn, C. Mauz-Kührholz, A. Schrauder, R. Handgretinger

1University Children’s Hospital Tuebingen, Tuebingen, Germany; 2Division of Pediatric Hemato/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; 3Department of Pediatrics, University of Jena, Jena, Germany; 4Department of Pediatrics, Martin-Luther University of Halle-Wittenberg, Halle, Germany; 5Department of General Pediatrics, University Medical Center Schleswig-Holstein, Kiel, Germany

Background. We investigated the safety and efficacy of T and B cell depleted peripheral stem cells from full haplotype mismatched parental donors in pediatric patients.

Methods. Use of the Clinimacs system and CD3/CD19 coated magnetic microbeads resulted in a 4 log depletion of T cells and allowed to cotransfuse high numbers of donor NK cells (median: 10^7 x 10^9/kg). TBI or busulfan based myeloablative regimens or a melphalan based intensity reduced regimen were used. All patients underwent intensive pretreatment according to current study protocols: 41/106 already received previous allogeneic transplants. The diagnoses were: acute leukemias and MDS (n=60), solid tumors (n=32) and nonmalignant diseases (n=14).

Results. Primary engraftment occurred in 89% of patients. After TLI based reconditioning and second haploidentical stem cell donation, final engraftment was achieved in 100%. Median time to reach >500 neutrophiles/μl and independence from platelet substitution was 10 (8–15) and 9 (5–59) days respectively. 35% of patients had no GVHD, 36% had grade I, 23% had grade II and 4% had grade III. Chronic limited and extensive GVHD was observed in 8 and 11%. Transplant related mortality was 0% at day 100 and 8% at one year. Event free survival at 3 years was 66% for patients with leukemias in any CR and 80% for patients with nonmalignant diseases. Overall survival at 2 years was 20% for patients with solid tumors. Relapse or progression were the major causes of death. Thus, pilot studies with IL-15 stimulated grafts and posttransplant donor-NK cell infusions were initiated and are currently ongoing.

Conclusions. Transplantation of CD3/CD19 depleted haploidentical stem cells resulted in a fast recovery of neutrophiles and platelets. Engraftment rates similar to that of patients with myeloablative standard conditioning and positive selected stem cells could be achieved, possibly due to a graft facilitating effect of cotransfused NK cells. The regimen helped to minimize TRM,
despite intensive pretreatment (including previous transplantation). However, relapse remains a major problem and further immunotherapeutic elements have to be evaluated.

**039**

Antibody based immunotherapy combined with haploidentical stem cell transplantation for high risk neuroblastoma

P. Lang¹, M. Pfeiffer¹, H.-M. Teltschik¹, T. Feuchtinger¹, R. Ladenstein², H. Lode³, C. Urban⁴, W. Schwerzer⁵, R. Handgretinger¹

¹University Children’s Hospital Tuebingen, Tuebingen, Germany; ²St. Anna Children’s Hospital Vienna, Vienna, Austria; ³University Children’s Hospital, University of Greifswald, Greifswald, Germany; ⁴Division of Pediatric Hemato/Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

**Background.** Pediatric patients with relapsed metastatic neuroblastomas have a poor prognosis and additional therapeutic strategies are warranted. We present preliminary results with haploidentical stem cell transplantation and posttransplant immunotherapy with an anti-GD2 monoclonal antibody (CH14.18 CHO).

**Methods.** T and B cell depleted haploidentical stem cells in combination with a toxicity reduced conditioning regime (melphalan, thiotepa, fludarabine and OKT3, now substituted by muromonab-CD3 or anti-thymocyte globulin (ATG) in 7/7, thiotepa (THT) in 6/7, fludarabine (FLU) in 5/7 and total lymphoid irradiation in 2/7 patients. Grafts were either CD34+ selected and/or CD3/19 depleted using the Miltenyi CliniMACS device. Median yield of purified CD34+ cells was 10,17×10⁶/kg (7.85–24.3) and median CD3+ number was 5.5×10⁶/kg (0.84–10). All patients had WBC-engraftment on median day 10 (8–12). There was no GVHD prophylaxis in 2 patients and either cyclosporine-A or mycophenolate mofetil up to day 60 in 5 patients. 1 MUD- HSC recipient who had 6 IS courses and the longest interval to HSCT (13 yrs) and who received the highest CD 3+ dose (10×10⁶/kg) developed GVHD (grade II) on day 60 in 5 patients.

**Conclusions.** Preliminary results of our ongoing study suggest an anti-tumor effect of the donor derived immune system in vitro and in vivo.

**040**

Unrelated donor stem cell transplantation (SCT) in severe aplastic anemia (SAA) refractory to immunosuppression – prevention of rejection and graft-versus-host disease (GVHD)

C. Urban, W. Schwinger, P. Sovinz, M. Benesch, V. Strenger, S. Schmidt, H. Lackner

Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

SCT from a matched sibling donor (MSD) is the treatment of choice for children with SAA, however limited by donor availability. Immunosuppression (IS) as the other option has the disadvantage of high treatment failures. 7 patients with SAA without a MSD and refractory to previous IS, median age 11 years (5–16), median interval from diagnosis to SCT 12 months (3–155) and median number of transplants before SCT 35 (18–116) underwent alternative donor SCT. Donors were matched unrelated (MUD) (n = 4), mismatched unrelated (n = 2) and haploidentical (n = 1). Conditioning regimens contained cyclophosphamide and either muromonab-CD3 or anti-thymocyte globulin (ATG) in 7/7, thiotepa (THT) in 6/7, fludarabine (FLU) in 5/7 and total lymphoid irradiation in 2/7 patients. Grafts were either CD34+ selected and/or CD3/19 depleted using the Miltenyi CliniMACS device. Median yield of purified CD34+ cells was 10×10⁶/kg (7.85–24.3) and median CD3+ number was 5.5×10⁶/kg (0.84–10). All patients had WBC-engraftment on median day 10 (8–12).

**Conclusions.** Long interval to transplant, multiple transfusions and long term immunosuppression before SCT are associated with poor alternative donor SCT-outcomes in SAA. Cyclophosphamide conditioning including FLU, THT and ATG but without TLI, high doses of purified CD34+ cells and/or CD3/19 depletion may prevent graft rejection and GVHD and hasten engraftment. This may facilitate the decision for the earlier use of unrelated stem cells preventing complications from prolonged and multiple immunosuppressive therapies and presumably increasing the survival of patients with SAA without a matched sibling donor.

**041**

Extracorporeal photopheresis in patients with high bleeding risks

N. Worel¹, G. Leitner¹, W. Rabitsch², M. Mitterbauer², P. Kalhs³, Z. Kuzmina², R. Knobler³, U. Just³, H. T. Greinix²

¹Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; ²Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria; ³Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

SCT from a matched sibling donor (MSD) is the treatment of choice for children with SAA, however limited by donor availability. Immunosuppression (IS) as the other option has the disadvantage of high treatment failures. 7 patients with SAA without a MSD and refractory to previous IS, median age 11 years (5–16), median interval from diagnosis to SCT 12 months (3–155) and median number of transplants before SCT 35 (18–116) underwent alternative donor SCT. Donors were matched unrelated (MUD) (n = 4), mismatched unrelated (n = 2) and haploidentical (n = 1). Conditioning regimens contained cyclophosphamide and either muromonab-CD3 or anti-thymocyte globulin (ATG) in 7/7, thiotepa (THT) in 6/7, fludarabine (FLU) in 5/7 and total lymphoid irradiation in 2/7 patients. Grafts were either CD34+ selected and/or CD3/19 depleted using the Miltenyi CliniMACS device. Median yield of purified CD34+ cells was 10×10⁶/kg (7.85–24.3) and median CD3+ number was 5.5×10⁶/kg (0.84–10). All patients had WBC-engraftment on median day 10 (8–12). There was no GVHD prophylaxis in 2 patients and either cyclosporine-A or mycophenolate mofetil up to day 60 in 5 patients. 1 MUD- HSC recipient who had 6 IS courses and the longest interval to HSCT (13 yrs) and who received the highest CD 3+ dose (10×10⁶/kg) developed GVHD (grade II) on day 125 with progressive kidney failure due to microangiopathic hemolytic anemia. All children are alive with a median follow up of 20 months (8–149) with stable complete engraftment and stable chimerism of median 98.5% (90.65–100).

**Conclusions.** Long interval to transplant, multiple transfusions and long term immunosuppression before SCT are associated with poor alternative donor SCT-outcomes in SAA. Cyclophosphamide conditioning including FLU, THT and ATG but without TLI, high doses of purified CD34+ cells and/or CD3/19 depletion may prevent graft rejection and GVHD and hasten engraftment. This may facilitate the decision for the earlier use of unrelated stem cells preventing complications from prolonged and multiple immunosuppressive therapies and presumably increasing the survival of patients with SAA without a matched sibling donor.
Allogeneic stem cell transplantation with reduced intensity conditioning in patients with therapy-related myeloid neoplasms

W. Zinke-Cerwenka1, A. Rohn1, U. Posch2, C. Beham-Schmid2, W. Linkesch1, A. Wöfler1, H. Sill1

1Division of Haematology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; 2Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria

Background. Therapy-related myeloid neoplasms (t-MNs) occur as late complication after cytotoxic therapy for malignant and non-malignant disorders. In most patients with t-MNs, allogeneic haematopoietic stem cell transplantation (HSCT) is the only potentially curative approach. Performed with myeloablative conditioning this option is associated with a high transplant-related mortality (TRM). Here we report our results in using reduced intensity conditioning (RIC) in these patients.

Methods. Between July 2000 and February 2011, 18 patients (male: 5; female: 13; median age: 48.5 years; range: 28–66) with t-MNs underwent RIC HSCT either from a matched sibling (n = 8) or a matched unrelated (n = 7) or one antigen mismatched unrelated donor (n = 3). Primary disorders were solid tumors and haematologic malignancies in 9 patients each. Patients presented with t-MDS (n = 4), t-AML (n = 13) and t-MDS/MPN (n = 1). Cytogenetic analysis revealed clonal aberrations in 15/18 patients. Nine patients were transplanted in 1st CR, one in 2nd CR, five in PR and three in relapsed/refractory disease. Furthermore, five patients showed persistant primary disease. Conditioning regimen consisted of fludarabine/melphalan (n = 15) or fludarabine/low-dose TBI (n = 3). GVHD prophylaxis consisted of cyclosporine and mycophenolate mofetil and additionally anti-thymocyte globulin in unrelated transplantations.

Results. After a median follow-up of 31 months (range: 3–97) 9 patients are alive and in CR. Causes of death were: relapse (n = 4), sepsis/multiorgan failure (n = 4) and GVHD (n = 1). Acute and chronic GVHD was observed in 6 and 5 patients, respectively. The estimated OS is 53.8% at one and 47.9% at three years; the DFS is 48.1% at one and three years, respectively. Of 5 patients transplanted with active primary neoplasms, 2 are alive at 1 year showing CR of both primary and secondary neoplasms which was associated with the development of chronic GVHD.

Conclusions. The results of RIC HSCT in these patients with poor risk disease are encouraging with respect to TRM, relapse rate and overall survival. Our data show a more favourable outcome compared with previous reports using a myeloablative conditioning. Furthermore, allogeneic HSCT should be considered as a potentially curative strategy for patients with t-MNs and persistant primary malignancy.

The bone component of CTA gives rise to donor HSCs which migrate to recipient thymus and differentiate to mature T cells

R. Sucher1,2, C.-H. Lin1,2, D. Zhang3, W. Zhang3, W. P. A. Lee4, F. Lakki5, G. Brandacher1,2,3, J. Pratschke1, X. X. Zheng3

1Department of Visceral, Transplant and Thoracic Surgery, Daniel Swarovski Research Laboratory, Medical University of Innsbruck, Innsbruck, Austria; 2Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 3Department of Plastic and Reconstructive Surgery, University of Pittsburgh, Pittsburgh, PA, USA; 4Both authors contributed equally to this work.

Background. Composite Tissue Allotransplantation (CTA) is immunologically unique in that it represents the only type of graft to include a vascularized functional bone marrow component. Here we studied if the bone component of a composite tissue graft represents the source of HSCs that differentiate in the thymus and thereby reconstitute a functional immune system (CD3+/T cells in peripheral blood/lymphoid organs) in immuno-
Deficient B6/SCID recipients rather than originate from donor mature passenger T cells that expand in the host.

**Methods.** B6 (WT/nude) murine composite tissue grafts (osteomyocutaneous or myocutaneous) were transplanted heterotopically to B6 (WT/scid) recipients using a non-suture cuff technique for revascularization. Flow cytometry of peripheral blood (CD3+, CD19+) was performed at pod 7, 14, 21, 28, 56. In addition, histopathology (H&E) and immunohistochemistry of tissues was performed at indicated time points. To assess immuno-competence, allogeneic skin grafts (Balb/c) were transplanted to either naïve B6/nude, naïve B6/scid or B6/scid mice that prior received a B6/nude CTA.

**Results.** The surgical success rate was 85% in all groups. As expected no CD3+ cells and no rejection of skin allografts were detected in B6/nude and B6/scid controls. B6/scid mice that received B6/nude osteomyocutaneous flaps demonstrated B and T cell immunity from pod 7 and 21 respectively. The percentage of CD3+ and CD19+ cells within peripheral blood mononuclear cells steadily increased to 57.7% and 17.1% respectively at pod 56. Allogeneic skin allografts were rejected 2 weeks after transplantation. However, no B and T cell reconstitution was observed in B6/scid mice receiving B6/nude myocutaneous flaps (without bone component).

**Conclusions.** The vascularized bone marrow component of CTA provides an effective source of HSCs to restore immuno-competence in T- and B-cell deficient mice. This might also contribute to chimerism induction and maintenance after CTA and facilitate the clinically observed immunoprivilege of CTAs.

---

044

**Early in vivo signaling events involved in neo-vasculogenesis via stem cell transplantation using proteomic profiling**

R. Rohban1, A. Reinisch1, N. A. Hofmann1, C. Urfs, N. Etchart2, E. Rohde3, K. Schallmoser4, D. Strunk1

1Stem Cell Research Unit, Department of Hematology, Medical University of Graz, Graz, Austria; 2Department of Blood Transfusion and Serology, Medical University of Graz, Graz, Austria; 3Department of Blood Transfusion and Serology, Paracelsus Medical University Salzburg, Salzburg, Austria

**Background.** The precise mechanisms regulating human neo-vasculogenesis and organ regeneration are still unclear. It has been shown that neo-vasculogenesis can be induced in immunocompromised NOD/scid/IL-2-receptor gamma-knockout (NSG) mice in vivo by transplantation of human bone marrow-derived mesenchymal stem and progenitor cells (hMSCs) and umbilical cord-derived endothelial colony-forming progenitor cells (hECFCs), whereas transplantation of pure hMSC or hECFC cells lack the capacity to form stable functional vessels (Reinisch et al., Blood, 2009). Understanding the activity of the mediators of neo-vasculogenesis would provide us with tools to develop strategies for therapeutic intervention as well as angiogenesis and regenerative applications.

**Methods.** Autologous pairs of hMSCs and hECFCs were transplanted subcutaneously in Matrigel plugs at a ratio of 20:80 into NSG mice and implants were harvested 1 day post transplantation to investigate proteomic profiling using KINEX (www.kinexus.ca), testing over 800 signaling and phospho-proteins. The state of vessel formation and stability of the transplants were verified by immunohistochemistry of the explants 2 and 8 weeks post transplantation.

**Results.** Protein microarray data analysis revealed significant alteration in the expression and activity of components 1) regulating apoptosis, mitotic check point control, and centrosome structure; 2) modulating glycolysis and the coordinated expression of cyto-protective genes; and 3) mediating cell adhesion, migration and tissue invasion. Selected targets are currently being validated by Western blotting to allow for the development of novel therapeutic intervention strategies. A detailed expression and interactive network analysis of targets will be presented and discussed.

**Conclusions.** Our data confirm that more than one purified cell type is needed for tissue engineering in vivo and suggest that composite cellular transplantation may be useful for future therapeutic strategies. Proteomic profiling unraveled at least three distinct but partially overlapping signaling networks involved in the complex process of vascular regeneration. Understanding the origin and activity of the mediators of vessel formation and repair would provide us with tools to develop and further optimize novel cell transplantation strategies.

---

045

**Oxygen sensing of mesenchymal stem and progenitor cells promotes neo-vasculogenesis in vivo**

N. A. Hofmann1, A. Ortner1, R. O. Jacamo2, A. Reinisch1,2, K. Schallmoser1,2, M. Frühwirth1,3, C. Beham-Schmid1, M. Andreff1, D. Strunk1,3

1Stem Cell Research Unit, Department of Hematology, Medical University of Graz, Graz, Austria; 2Department of Leukemia, M.D. Anderson Cancer Center, University of Texas, Houston, Texas, USA; 3Department of Hematology and Stem Cell Transplantation, Department of Internal Medicine, Medical University of Graz, Graz, Austria; 4University Clinic of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria; 5Institute of Pathology, Medical University of Graz, Graz, Austria

**Background.** Vascular regeneration requires a stringent interaction of somatic endothelial colony-forming progenitor cells (ECFCs) with mesenchymal stem and progenitor cells (MSCPs). Hypoxia in ischemic tissue is a key factor driving the revascularization machinery. Because ECFCs, despite hypoxic stimulation, only form patent vessels in vivo in the presence of MSCPcs, we hypothesized that MSCPcs play a decisive role in oxygen sensing during vasculogenesis.

**Methods.** Adult human ECFCs were isolated directly from whole venous blood and MSCPcs from human bone marrow aspirates. Pooled human platelet lysate entirely replaced fetal bovine serum during cell culture. Progenitor cell phenotype, long-term proliferation, molecular cellular response, wound repair as well as migratory and vasculogenic functions were monitored under reduced oxygen levels (5% O2), severe hypoxia (1% O2) and standard culture conditions (20% O2). ECFC and MSCP interaction in vivo and the influence of protein synthesis were studied in immune-deficient NSG mice after subcutaneous injection with matrigel. Immune histochemistry and TUNEL assays were performed on explants in the time course after transplantation.

---

046

**Microarray-based proteomic profiling of aortic endothelial progenitor cells in aortic injury in vivo**

A. Reinisch1, M. Andreeff1,2, M. Frühwirth1,3, K. Schallmoser1,2, A. Ortner1,3, C. Beham-Schmid1,3, K. Leidenius1,3, A. Ortner1,3, D. Strunk1,3

1Stem Cell Research Unit, Department of Hematology, Medical University of Graz, Graz, Austria; 2Department of Leukemia, M.D. Anderson Cancer Center, University of Texas, Houston, Texas, USA; 3Department of Hematology and Stem Cell Transplantation, Department of Internal Medicine, Medical University of Graz, Graz, Austria; 4University Clinics of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria

**Background.** Aortic injury results in inflammation, inactivation of endothelial progenitor cells (EPCs), and neo-intimal formation. Vascular endothelial growth factor (VEGF) is an angiogenic protein that is known to be overexpressed at the site of acute aortic injury in vivo. VEGF is a critical mediator of atherogenesis, maintains the integrity of the injured coronary arteries and activates cutaneous microvascular endothelial cells. Whether local overexpression of VEGF in the aortic injury model contributes to angiogenesis during aortic repair or to atherosclerosis is unknown. A first hint to the regulatory role of the VEGF system in the context of aortic injury is that overexpression of VEGF in the aortic injury model results in a more efficient healing process of the injured aorta and in a decrease in neointima formation.

**Methods.** To address the complexity of protein expression in aortic injury and to identify novel proteins that regulate angiogenesis, aortic injury was induced in mice by balloon catheter-induced injury. At days 3, 7, and 14 post injury, aortic segments were harvested and the protein content was analyzed by means of a mass spectrometry-based approach using a commercial antibody microarray (www.kinexus.ca). This antibody microarray contains a total of 800 antibodies, covering signaling pathways involved in angiogenesis, cell adhesion, migration and proliferation.

**Results.** The microarray-based proteomic analysis revealed a number of changes in protein expression associated with aortic injury. A large number of proteins were upregulated or downregulated following injury, indicating a complex interplay of signaling pathways. Notably, several proteins involved in angiogenesis, inflammation, and cell adhesion were significantly altered. These findings provide insight into the molecular mechanisms underlying aortic injury and suggest potential targets for therapeutic intervention.
Results. In vitro ECFC and MSPC proliferation was reduced with declining oxygen levels, while the absolute colony number remained unchanged. ECFC vascular wound repair and vascular-like network formation in vitro improved with escalating oxygen supply. ECFCs stabilize hypoxia-inducing factor-1α (HIF-1α) only under 1% O₂, while MSPCs stabilize HIF-1α under 1% O₂ as well as 5% O₂ conditions. In a mouse model, injected ECFCs underwent apoptosis after 1 day and attracted mouse leucocytes. In vivo co-cultured ECFCs and MSPCs formed perfused human vessels 7 days after transplantation. Perivascular cells, but not ECFCs, in vivo were positive for HIF-1α. Inhibition of MSPC, but not ECFC, protein synthesis and HIF-1α stabilization prior to co-implantation blocked vessel formation.

Conclusions. These data indicate that hypoxic ECFCs alone are not able to function in vitro and form patent vessels in vivo. MSPCs react to the low oxygen environment and promote ECFCs to form vessels at least in part by rescuing ECFCs from hypoxia-induced apoptosis. This suggests that oxygen sensing MSPCs are a key factor in stem cell transplantation and regenerative medicine.

Accuracy of percutaneous lung biopsy for invasive pulmonary mycosis in children with cancer and hematopoetic stem cell transplantation

R. Crazzolara¹, A. Kneer¹, C. Lass-Flörl², M. Freund³, B. Meister¹, G. Krophofer³
¹Department of Paediatrics, Medical University of Innsbruck, Innsbruck, Austria; ²Department of Hygiene, Microbiology and Social Medicine, Medical University of Innsbruck, Innsbruck, Austria; ³Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria

Background. Low sensitivity and specificity rates for the detection of invasive pulmonary mycosis result in a major cause of mortality among immunosuppressed children. We sought to determine the accuracy of percutaneous computed tomography-guided biopsy in children with cancer and hematopoetic stem cell transplantation.

Methods. We retrospectively reviewed 17 imaging-guided percutaneous biopsies of 17 children for suspicious lesions detected by computed tomography. Thirteen were being treated for hematologic malignancies, three for solid tumors, one for immunodeficiency; 47% had received allogeneic bone marrow or peripheral stem cell transplants. The accuracy of the percutaneous lung biopsy was determined by subsequent surgical resection, autopsy, or clinical course.

Results. Histopathological studies showed 11 biopsy specimens with septate hyphae, indicating a mold, including 6 with Aspergillus, 4 with Mycoraceae, 1 with Aspergillus and Mycoraceae colonies in culture; 2 specimens revealed Candida, 1 Saccharomyces. The remaining 3 biopsies revealed bronchiolitis obliterans pneumoniae. Invasive pulmonary mycosis was detected by percutaneous biopsy with 100% sensitivity and 100% (14/14) specificity. Percutaneous biopsy results influenced the surgical decision in 21% (3 of 14) and changed the treatment option in 78% of the cases. Pneumothorax complicated the biopsy in one patient.

Conclusions. Percutaneous computed tomography-guided biopsy is an accurate technique for the diagnosis of invasive pulmonary mycosis in children. It reveals the local epidemiology, correctly determines the therapeutic anti-mycotic agent and influences the choice of prophylaxis for invasive mycosis.

Modified implantation technique of the HeartWare continuous flow pump as biventricular support system for bridge-to-transplant

N. Reiss¹, L. Arusoglu², U. Schulz²
¹Department of Cardiac Surgery Heidelberg, Universitätsklinikum Heidelberg, Germany; ²Heart Center North Rhine-Westphalia, Ruhr-University of Bochum, Bad Oeynhausen, Germany

Background. The number of patients requiring circulatory support increases steadily because of donor organ shortage and demographic changes. In about 30% of this patient group there is a need for biventricular support. Rotary blood pump technology has led to significant improvement of results in left ventricular failure. Nevertheless, patients with concomitant right ventricular failure have not benefited from this technology so far.

Methods. We now report for the first time a modified implantation technique by cannulating the right atrium in order to reach better hemodynamics for right side support. To place the HeartWare system in the area of the right atrium we have created a cavity (8×8 cm) in the right-sided pericardium using a PTFE membrane.

Results. The design of the HeartWare device enables a quick and less invasive implantation. The small size of the pump allows for intrapericardial placement even in biventricular support. To prevent compromise of the right atrium it is necessary to build a cavity in the pericardium for pump placement.

Conclusions. Adequate pump flow was observed during total support time. The presented implantation technique allows a safe and elegant bridging-to-transplant in Htx candidates representing biventricular failure.

Use of cardiopulmonary bypass for lung transplantation: institutional experience

K. Stüttler, H. Hängler, J. Kilo, S. Semroth, J. Nagiller, M. Grimm, L. Müller
Department of Heart Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria
Background. The use of cardiopulmonary bypass (CPB) for lung transplantation is still judged controversial. However, in 30% of lung transplantations CPB support during the surgical procedure is required for hemodynamic and/or respiratory instability or for repair of intracardiac pathologies. This study aimed to determine if the use of CPB has an effect on survival.

Methods. A retrospective review of 190 lung transplantations in 180 patients (mean age: 59 years [16–67]) with different lung pathologies who underwent bilateral or single lung transplantation between November 1993 and June 2011 was performed. 75 patients (39.4%) in whom elective as well as emergent CPB was necessary were compared with 115 cases (60.6%) without CPB.

Results. The indications for lung transplantation were chronic obstructive pulmonary disease (COPD, \( n = 111 \)), fibrosis (\( n = 32 \)), alpha-1 antitrypsin deficiency emphysema (\( n = 13 \)) and others (\( n = 34 \)). The follow up period ranged from 2 days to 14 years. Total mean survival was 980 days (range 0 to 5276 days). There was no significant difference in mortality between the CPB and the control group (\( p = 0.723 \)). The comparison between COPD patients and other indications for lung transplantation also revealed no significant difference in survival (\( p = 0.11 \)). There was also no difference between COPD patients in whom surgery was performed with CPB or without (\( p = 0.676 \)). Survival rates in patients over 60 years were similar to patients under 60 independent from the use of CPB (\( p = 0.676 \)). There was also no significant difference in the usage of CPB between single versus bilateral lung transplantation (\( p = 0.44 \)).

Conclusions. This study revealed no increase in mortality after lung transplantation when cardiopulmonary bypass was required. When CPB appears necessary it should be employed right away to avoid hemodynamic compromise or severe reperfusion edema due to unacceptable pulmonary arterial pressures.

Successful bridging to heart transplantation using the Levitronix CentriMag system and DuraHeart LVAD in a patient with resuscitation related liver injury

N. Reiss\(^1\), L. Kizner\(^2\), U. Schulz\(^2\)

\(^1\)Department of Cardiac Surgery Heidelberg, Universitätsklinikum Heidelberg, Germany; \(^2\)Heart Center North Rhine-Westphalia, Ruhr-University of Bochum, Bad Oeynhausen, Germany

Background. Mortality rates from cardiogenic shock after acute myocardial infarction remain extremely high. Efforts have been made to develop ventricular assist devices capable of providing complete hemodynamic support in this situation. Mechanical circulatory assistance represents an evident problem when bleeding complications occur. We report a very rare case of successful bridging to heart transplantation despite severe resuscitation related liver injury.

Methods. A 54-year-old male patient underwent failed percutaneous coronary intervention of LAD with consecutive prolonged resuscitation. A Levitronix CentriMag system was implanted via femoral vessels for rapid hemodynamic stabilization. An acute laparotomy was necessary because of severe injury of the left lobe of the liver. During laparotomy the abdominal cavity was tamponaded by multiple compresses. Three times re-laparotomy was necessary to achieve final hemostasis. After four weeks of Levitronix CentriMag support the system was switched to DuraHeart LVAD for long-term assistance as a bridge-to-transplant.

Results. Successful heart transplantation was performed after complete recovery and mobilization of the patient 320 days after the disastrous and hopeless initial situation.

Conclusions. The present case demonstrates that successful bridging to heart transplantation is possible even in cases of severe bleeding complications. Special attention is given to the thin line between bleeding complication and necessary anticoagulation because of mechanical circulatory assist.
Evaluation of efficacy and safety of de novo Advagraf in cardiac transplant patients: early results of an observational study

F. Eskandary, A. Aliabadi, S. Mahr, M. Grömmer, D. Zimpfer, S. Sandner, G. Laufer, A. Zuckermann

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

Background. Advagraf (tacrolimus extended-release capsules) has been tested in de-novo liver and renal transplant recipients. In cardiac transplantation there exists only data on conversion of tacrolimus to advagraf. The aim of this analysis was to evaluate efficacy and safety of de novo use of advagraf in cardiac transplant patients.

Methods. 10 patients received advagraf after ATG induction therapy, 8.1 ± 3.3 days after cardiac transplantation. Mean patient age was 40.1 ± 16.4 years. All patients received also mycophenolate and steroids. Follow-up was 4.4 ± 1.7 months. Dosages, tacrolimus drug levels (tac) and creatinine (crea) levels were recorded 1, 2 weeks and 1 to six months post transplant. Clinical events were defined as acute rejection, infection type, new onset diabetes mellitus (NODM) and renal dysfunction.

Results. Six-month survival was 100%. Two patients were converted to cyclosporine due to NODM 1 and 3 months post transplant. No rejection episodes were recorded during follow-up. Two infections were documented 6 months after transplant (bacterial pneumonia and CMV infection). Advagraf starting dose was 6.2 ± 1.9 mg/d. Crea before start was 1.14 ± 0.34 mg/dl. First measured tac levels at steady state (5 days post drug start) were 7.8 ± 3.7 ng/ml. Until the end of the first month advagraf was slowly decreased to 10.1 ± 1.9 mg/d with tac levels of 10.7 ± 2.8 ng/ml and crea of 1.22 ± 0.31 mg/dl. Three and six month drug doses were 9.3 ± 2.11 and 8.2 ± 0.8 mg with corresponding tac levels of 11.2 ± 2.9 and 11.2 ± 1.3 ng/ml. Crea was 1.47 ± 0.22 and 1.49 ± 0.32 mg/dl. There were no events of renal failure.

Conclusions. Advagraf de-novo therapy shows acceptable efficacy and safety early after cardiac transplantation. ATG induction therapy might be responsible for a low risk of acute rejection despite lower tac levels.

Comparison between referral and explant diagnoses in lung transplant recipients: discrepancies and additional findings

P. Jaksch¹, A. Scheed¹, M.-B. Ernst¹, W. Klepetko¹, G. Dekan², S. Geleff⁰

¹Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria; ²Department of Pathology, Medical University of Vienna, Vienna, Austria

Background. Lung transplantation is a widely accepted therapeutic option for a range of pulmonary conditions in which the diagnosis is often based on clinical data or on limited biopsy material. Posttransplantation complications and recurrence of underlying disease may be related to the primary disease, and an accurate diagnosis is therefore essential.

Methods. A pathologic review was performed on 1056 primary lung transplantations over a period of 22 years (1998 to 2010). Diagnoses of native lungs were compared with referral diagnoses to assess the presence of discrepancies or expanded results like malignancies or infections.

Results. 73 (7%) cases presented a different or expanded diagnosis. Discrepancies between referral diagnosis and histopathology were found in 34 of 1054 cases (3%). The highest percentage of discordance was depicted in chronic obstructive lung diseases (12 of 344), with the final diagnosis of UIP (n = 4), chronic interstitial fibrosis (n = 4), silicosis (n = 2), LAM (n = 1) and sarcoidosis (n = 1). 16 patients who were referred with the diagnosis of an influx and spontaneous depolarization and hereby decreases the heart rate. To improve myocardial oxygenation by extending diastolic time, reducing the heart rate is an important goal for these patients. Objective of the current study is to show the efficacy of the If-inhibitor ivabradine (Procoralan) on the transplanted heart.

Methods. This is a single-center retrospective study including 143 patients, who underwent heart transplantation from 1985 to 2011 at our center in Vienna and who were in need of a heart rate regulating therapy after transplantation. Only patients in stable conditions and with sinus rhythm were treated with ivabradine. An average dose of 10 mg per day was used to control the heart rate. Analyzed data were collected during routine check-ups in our long-term outpatient-clinic and during ergometry examination by periodical measurements of heart-rate, blood-pressure and ECG.

Results. Mean age at the time of transplantation was 51.3 ± 11.9 years, 117 patients (81.8%) were male (age 16–71 years) and 26 patients (18.2%) were female (age 14–68 years). Before establishing the Procoralan therapy, patients had an average heart rate of 96.2 ± 11.9 bpm. With the Procoralan therapy, patients had an average heart rate of 83.1 ± 9.5 bpm. After an average time of 1.8 ± 1.4 years, usage of ivabradine has reduced the heart rate by 14.9 ± 9.4%. In 7 cases (4.8%) we had to terminate therapy because of gastro-intestinal side effects and in 4 cases (2.7%) even under lowest ivabradine dosage patient developed bradycardia.

Conclusions. Using ivabradine after heart transplantation is a safe way to lower heart rate and could become a new indication for If-inhibitors. The individual dosage for each patient has to be found in augmenting the initial daily dosage of 5 mg slowly to the optimum dosage of 10 mg per day.
interstitial lung disease had predominantly emphysema (n = 12), bronchiectasis (n = 2) and histiocytosis X (n = 2). Expanded results included Aspergillus (n = 11) and mycobacterial (n = 16) infections, carcinomas (n = 10), cystic adenomatoid dysplasia (n = 1) and carcinoid (n = 1). However, short- and long-term survival was not different in patients with different diagnoses, malignancies or implanted infections. Interestingly all mycobacterial infections and all malignancies occurred in patients with COPD.

Conclusions. On account of this high rate of discrepancies and its possible influence on survival, frequently repeated clinicopathologic investigations should be performed during the waiting list period.

054
Alemutzumab induction in lung transplantation: efficacy and safety
P. Jaksch, P. Nierlich, A. Scheed, M.-B. Ernst, V. Augustin, C. Aigner, G. Lang, S. Taghavi, W. Klepetko
Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria

Background. Induction therapy with alemtuzumab, followed by lower than conventional intensity post-transplant immunosuppression, has been associated with reduced morbidity and mortality in abdominal and heart transplantation. We performed a prospective randomized trial in lung recipients receiving alemtuzumab in conjunction with reduced immunosuppression compared with patients receiving thymoglobulin in association with routinely dosed immunosuppression.

Methods. 60 lung TX recipients were prospectively randomized in two groups: group A received alemtuzumab in conjunction with early lower-dose tacrolimus, lower-dose steroids, and half-dose mycophenolate mofetil, compared with group B receiving thymoglobulin in association with routinely dosed immunosuppression. Survival analyses examined patient and graft survival, freedom from acute cellular rejection (ACR), lymphocytic bronchiolitis, bronchiolitis obliterans syndrome (BOS), kidney function, infectious complications and post-transplant lymphoproliferative disorder (PTLD).

Results. There were no significant differences in 6- and 12-month survival (alemtuzumab 96% vs. ATG 93% and 93% vs. 96%, respectively, p = NS). Acute cellular rejection episodes = A2 within the first TX year were significant lower in group A (alemtuzumab 0 vs. ATG 0.33, p = 0.019), lymphocytic bronchiolitis was not different between the groups (cumulative B scores group A 2.9 ± 2.7 vs. group B 3.2 ± 2.3 per patient, p = 0.74). There were no significant differences in bacterial (group A 2.1 ± 2.3 per patient vs. group B 2.3 ± 2.0, p = 0.95), CMV (group A 0.43 ± 0.5 per patient vs. group B 0.4 ± 0.5, p = 0.79) or Aspergillus infections (group A 0.2 ± 0.4 vs. group B 0.13 ± 0.34, p = 0.49, respectively). Glomerular filtration rates after 1 year also were not different (group A 59 ± 30.7 vs. group B 54 ± 23.3, p = 0.5) between both groups. 3 patients developed BOS after 105, 302 and 517 days, all of group A. One patient of group B developed malignancy of the lung (adenocarcinoma) 884 days post TX (observation period 907 ± 278 days, range 231–1369 days).

Conclusions. Alemtuzumab induction in conjunction with reduced immunosuppression significantly reduces higher grade rejection rates with comparable survival results and infectious complications to high-dose standard immunosuppression. The incidence of early BOS was higher after alemtuzumab-induction.

055
Cardiac angiography and interventions via arteria radialis in patients after heart transplantation
S. Rödler1, T. Brunner2, T. Haberl1, G. Lauffer1, A. Zuckermann1
1Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria; 2Federal Hospital of Wiener Neustadt, Wiener Neustadt, Austria

Background. Cardiac allograft vasculopathy (CAV) is a major cause of allograft failure in long-term heart transplant patients. Even without typical angina symptoms and diffuse lesions, CAV resembles atherosclerosis, but shows more concentric rather than eccentric intimal proliferation. Both, proximal and distal portions of the coronary tree are involved. Cardiac angiographies are periodically performed in the routine long-term follow up after heart transplantation.

Methods. Cardiac angiographies and interventions have been performed on 19 patients (17 male and 2 female) without any complications and substantial advantage in this cohort of patients. 6 Patients already had previous interventions. Mean time after transplantation was 11.4 ± 5.8 years.

Results. Follow-up angiography showed no in-stent stenosis in the patients with previous interventions after a mean time of 36 ± 18 months. 3 patients were in need of interventions, 2 of them in LADp3 with endeavour stents and 1 patient in RCA1 with cypher stent. No complications have been observed.

Conclusions. Radial angiography is a safer method for routine follow-up for patients after heart transplantation, especially in long-term follow-up, as femoral approach often leads to complications.

056
Results of ABO-incompatible kidney transplantation in Upper Austria
T. Sailer1, W. Enkner1, R. Függer2, R. Oberbauer1
1Department of Nephrology, Krankenhaus der Elisabethinen Linz, Linz, Austria; 2Department of Surgery, Krankenhaus der Elisabethinen Linz, Linz, Austria

Background. Efforts to reducing waiting time for an allograft include ABO incompatible transplantation. We report on the outcome of seven ABO incompatible kidney transplantsations performed in our institution since November 2009.

Methods. The pre-conditioning regimen included rituximab (375 mg/m² body surface area) on day –14 of transplan-
Specific renal involvement of hereditary amyloidosis due to mutation of the fibrinogen Aα-chain at R554L: molecular and clinical characteristics

M. Haidinger1, J. Werzowa1, R. Kain2, T. Weichhart1, M. D. Säemann1

1Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria; 2Department of Clinical Pathology, Medical University of Vienna, Vienna, Austria

Background. Amyloidosis is a protein misfolding disorder where conformationally changed proteins are pathologically deposed as abnormal insoluble fibrils in distinct tissues potentially leading to morphological and functional disintegration. Hereditary amyloidosis is a rare autosomal-dominant disorder arising from mutations in several genes like in the fibrinogen Aα-chain that affect various organs. Mutations in the fibrinogen Aα-chain have been discussed to lead to a predominant renal deposition of amyloid generally leading to ESRD.

Results. A total of seven ABO incompatible kidney transplantations were performed. Patients’ characteristics are summarised in Table 1. All patients showed an immediate graft function and repeated antigen immunoadsorption (GlycosorbaBO) until the isoagglutinin titre was less than 1:8. In addition intravenous immunoglobulin (Intratect, Biotest Pharma) was administrated at a dose of 1.0 g/kg body weight after each immunoadsorption. A standard immunosuppressive regimen (tacrolimus with a target level of 10 to 12 ng/ml, mycophenolate mofetil at a dose of 1 g twice a day and prednisolone with IL-2 antibody induction was started approximately two weeks prior to kidney transplantation.

Conclusions. In conclusion, our small case series demonstrated that peripheratic isoagglutinin removal in combination with rituximab is an effective and safe protocol for ABO incompatible transplantation. Therefore we offer ABO incompatible kidney transplantation to patients as alternative to cadaveric kidney transplantation to shorten the waiting time on dialysis.

Outcome of pancreas transplantations for type 2 diabetes mellitus (DM)

C. Margreiter, R. Oberhuber, T. Resch, F. Aigner, C. Bösmüller, R. Öllinger, R. Margreiter, J. Pratschke, W. Mark

Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria

Background. New immunosuppressive protocols and advanced surgical technique resulted in a major improvement in the outcome of pancreatic transplantation.

Methods. 217 enteric drained whole pancreas transplants (PTx) in 208 patients performed at our center during a seven year period were retrospectively analysed. Prophylactic immunosup-
Durchwegs höhere Insulinsensitivität und differenziell veränderte Insulinsekretion in Nierentransplantierten mit und ohne Post-Transplant-Diabetes im Vergleich zur Normalbevölkerung mit und ohne Typ-2-Diabetes: präliminäre Ergebnisse der TAHG-Studie

M. Hecking1, A. Kainz1, J. Werzowa1, M. Haidinger1, D. Dößler1, A. Tura1, J. Zhang1, W. H. Hör1, M. Wolzt1, G. Pacini2, F. K. Port1, M. D. Säemann1

1Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria; 2National Research Council’s Institute of Biomedical Engineering, Padova, Italy; 3Arbor Research Collaborative for Health, Ann Arbor, MI, USA; 4Department of Clinical Pharmacology, Medical University of Vienna, Austria

Grundlagen. Post-Transplant-Diabetes (PTDM) ist mit erhöhter Mortalität assoziiert und ein gravierendes Problem nach Nierentransplantation. Wir haben die Prävalenz von PTDM erhoben und Insulinsensitivität sowie Insulinresistenz analysiert.

Methodik. Observationelle Kohortenstudie aller Patienten mit funktionsierendem Nierentransplantat >6 Monaten, die von III/2009-III/2010 am AKH Wien nachbetreut wurden (EK-Nr.566/2009). Prädioktoren: U.a. demographische Daten, Immunsuppressionsverfahren, Laborparameter, Grunderkrankung, Outcome: PTDM (definiert durch Analysedaten und Serumkreatinin erhöhter Patienten ohne Diabetes-Anamnese vor der Transplantation bzw. 2h-Blutzucker >200 mg/dL), im freiwiligen Routine-Oralen Glucose Toleranz Test (OGTT), der seit 1/2009 allen Patienten unserer Klinik angeboten wird), IGT (impaired glucose tolerance (2h-Blutzucker 140–199 mg/dL im OGTT), Insulinsensitivität, Insulinsekretion. Statistische Verfahren: Chi-Quadrat-Test und Fisher’s Exact Test; Student’s T-Test und Analysis of Variance (ANOVA); Loess-Regression.

Ergebnisse. Von allen 1064 Nierentransplantierten waren 132 Patienten (12 %) Typ-1- oder Typ-2-Diabetiker und hatten 113 Patienten (11 %) bereits PTDM. Aus n = 307 OGTTs ergab sich PTDM bei 29 Patienten (9 %) und IGT bei Patienten 62 (20 %). Signifikante Prädiktoren für PTDM und/oder IGT beinhalten höheres Lebensalter, Immunsuppression mit Tacrozim, höheres C-reactives Protein und niedrigeres Serum-Albumin. OGTTs mit Bestimmung von Insulin und C-Peptid (n = 105) zeigten im Vergleich mit 1357 OGTTs nicht-transplantierten Patienten (Datensatz G. Pacini) eine erhöhte Insulinsensitivität (OGIS: 414 ± 67 vs. 315 ± 53 mU·min⁻¹·m⁻²; ISIcomp: 6,6 ± 4,5 vs. 3,9 ± 2,4, beide p < 0,001). Diese Ergebnisse waren in Sensitivitäts-Analysen gematchter OGTTs (nach Alter, BMI, Geschlecht, 2h-Blutzucker im OGTT) konsistent, des weiteren hatten Nierentransplantierte mit Normoglykämie (2h-Blutzucker im OGTT < 140 mg/dL) ebenso wie mit Hyperglykämie (2h-Blutzucker im OGTT 140–199 mg/dL bzw. > 200 mg/dL) signifikant bessere Insulinsensitivität als die Normalbevölkerung ohne oder mit IGT bzw. Typ-2-Diabetes. Die Regressions-Kurven der Insulin-Ausschüttung und des insulinogenen Widerstands (Isosti-Verfahren: Chi-Quadrat-Test und Fisher’s Exact Test; Loess-Verfahren: Chi-Quadrat-Test und Fisher’s Exact Test; Loess-Verfahren: Chi-Quadrat-Test und Fisher’s Exact Test; Loess-Verfahren: Chi-Quadrat-Test und Fisher’s Exact Test; Loess-Verfahren: Chi-Quadrat-Test und Fisher’s Exact Test)

Hämaglobinvariabilität ist assoziiert mit Mortalität nach Nierentransplantation

A. Kainz1,2, J. Willingseder1,2, R. Fügner1, R. Kramar1, R. Oberbauer1,2,3

1Krankenhaus der Elisabethinen Linz, Linz, Österreich; 2Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Wien, Österreich; 3Österreichisches Dialyse- und Transplantationsregister, Österreich

Grundlagen. Etwa 35 % aller prävalenten Nierentransplantationen leiden an einer renalen Anämie, etwa 15 % werden mit ESA (erythropoietin stimulation agents) therapiert. Der Quotient aus Dosis und Response (Hb Anstieg) ist sehr variabel und multifaktoriell. Diese Studie untersuchte, ob die Variabilität des Hämaglobinwerts in 3-monatigen Intervallen über die ganze Transplantlebensdauer einen Einfluss auf die Mortalität hat.

Methodik. Patienten, die zwischen Jänner 1990 und Dezember 2008 eine erste Nierentransplantation erhielten, wurden in dieser offenen Kohortenanalyse untersucht. Kovariablen und Endpunkte wurden aus dem Österreichischen Dialyse- und Transplantationsregister eroben. Von den 1441 Patienten, erhielten 683 ESA über mindestens 10 % der Zeit
nach Transplantation. Daten wurden mittels Cox PH Regression mit kubischen Splines, sowie mit linearen Schätzern analysiert. Für die Auswahl der Kovariablen kam der Purposeful Selection Algorithmus zur Anwendung. Die Hämoglobinvariabilität wurde über die gleitende Standardabweichung über jeweils vier Quartale definiert.

**Ergebnisse.** Die Hazard Ratio (HR) für Mortalität und Transplantatversagen stieg signifikant mit der Hämoglobinvariabilität an. Im linearen Modell betrug der Anstieg für die Mortalität 2.35 (95% Konfidenzintervall 1.75–3.17; p < 0.001), für das funktionelle Transplantatversagen 2.45 (1.76–3.40; p < 0.001). In einem klinischen Expertenmodell, das für die Verwendung von ESA, Hämoglobin, Alter bei der Transplantation, Diabetes, Tage an der Dialyse, glomerulaäre Filtrationsrate, und Verwendung von ESA, Hämoglobin, Alter bei der Transplantation, Diabetes, Tage an der Dialyse, glomerulaäre Filtrationsrate und Verwendung von ESA, Hämoglobin, Alter bei der Transplantation, Diabetes, Tage an der Dialyse, glomerulaäre Filtrationsrate wurden variable deviating from normal distribution verwendet für statistischen Analysen. Continuous variables wurden analysiert. No pathologies. Continuous variables were analyzed by rank sum test and presented as median and range. Categorical variables are presented as percentages and were compared by chi-square test. The criterion for statistical significance was p < 0.05.

**Results.** Ninety-two liver transplant recipients participated in the study. CYP3A5 genotypes were successfully determined in all subjects and did not deviate from the Hardy-Weinberg equilibrium. 86% of the patients carried the CYP3A5 *3/*3 genotype and were thus classified as CYP3A5 non-expressors. 14% carried the CYP3A5 *1/*3 genotype and were classified as heterozygous expressors. No homozygous CYP3A5 expression (*1/*1) was found. Neither tacrolimus dose nor levels were significantly different between CYP3A5 expressors and non-expressors at any point of time (p = 0.669, p = 0.140, p = 0.117, p = 0.822).

**Conclusions.** The pharmacokinetics of tacrolimus in patients after liver transplantation is not influenced by the recipient CYP3A5 genotype. It is mostly the hepatic metabolism that contributes to the excretion of tacrolimus. The donor CYP3A5 genotype might be useful to predict the tacrolimus pharmacokinetics.

---

**061**

**Influence of recipient CYP3A5 genotypes on the pharmacokinetics of tacrolimus in liver transplant recipients**

D. Kniepeiss, D. Wagner, U. Posch, M. Truschnig-Wilders, F. Iberer, K. H. Tscheliessnigg, W. Renner

1Division of Transplantation, Department of Surgery, Medical University of Graz, Graz, Austria; 2Department of Blood Group Serology and Transfusion Medicine, Medical University of Graz, Graz, Austria; 3Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

**Background.** Tacrolimus, which is widely used in liver transplant recipients, shows high interindividual variability in pharmacokinetics. It is primarily metabolized by hepatic cytochrome P450 3A4 and 3A5 (CYP). CYP3A5 is also expressed in the kidney and in the intestine. In this study, we evaluated the influence of recipient CYP3A5 genotypes on the pharmacokinetics of tacrolimus in patients after liver transplantation.

**Methods.** Patients after liver transplantation with tacrolimus maintenance therapy were included into the study. CYP3A5 genotypes of the recipients were established. Clinical and laboratory data at various time points (1 month, 3 months, 1 year and 3 years after start of medication with tacrolimus) were evaluated retrospectively. Doses and trough levels of tacrolimus were noted and a screening of all concomitant medications with possible CYP3A5 interaction was performed. SPSS for windows (release 14.0; SPSS, Inc) was used for statistical analyses. Continuous variables were analyzed by ANOVA-test and presented as means ± standard deviation, variables deviating from normal distribution were analyzed by rank sum test and presented as median and range. Categorical variables are presented as percentages and were compared by chi-square test. The criterion for statistical significance was p < 0.05.

**Results.** Ninety-two liver transplant recipients participated in the study. CYP3A5 genotypes were successfully determined in all subjects and did not deviate from the Hardy-Weinberg equilibrium. 86% of the patients carried the CYP3A5 *3/*3 genotype and were thus classified as CYP3A5 non-expressors. 14% carried the CYP3A5 *1/*3 genotype and were classified as heterozygous expressors. No homozygous CYP3A5 expression (*1/*1) was found. Neither tacrolimus dose nor levels were significantly different between CYP3A5 expressors and non-expressors at any point of time (p = 0.669, p = 0.140, p = 0.117, p = 0.822).

**Conclusions.** The pharmacokinetics of tacrolimus in patients after liver transplantation is not influenced by the recipient CYP3A5 genotype. It is mostly the hepatic metabolism that contributes to the excretion of tacrolimus. The donor CYP3A5 genotype might be useful to predict the tacrolimus pharmacokinetics.
Reduktion von Anti-A/B Antikörpern mit semiselektiver versus ABO Blutgruppen-spezifischer Immunadsorption

M. Wahrmann 1, M. Schiemann 1, L. Marinova 1, G. F. Körmöczki 2, K. Derfler 1, T. Fehr 1, G. Stüssi 1, G. A. Böhmig 1

1Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Wien, Österreich; 2Universitätsklinik für Blutgruppen- und Transfusionsmedizin, Medizinische Universität Wien, Wien, Österreich; 3Universitätsklinik für Nephrologie, Departement Innere Medizin, UniversitätsSpital Zürich, Zürich, Schweiz; 4Labor für Transplantationsimmunologie, Departement Innere Medizin, UniversitätsSpital Zürich, Schweiz

Grundlagen. Empfänger-Desensibilisierung mittels Blutgruppen-spezifischer Immunadsorption (ABO-IA) ist derzeit das Mittel der Wahl, um eine erfolgreiche Transplantation über die ABO-Blutgruppen-Barriere zu ermöglichen. Zu diesem Zweck wäre der Einsatz von regenerierbaren, nicht-Antigen-spezifischen (semiselektiven) Adsorbern ebenfalls denkbar, aber die Effizienz dieser Immunadsorptionsmaterialien wurde in diesem Zusammenhang noch nicht getestet.

Methodik. Acht mit ABO-IA behandelte Transplantationskandidaten und 39 Patienten, die mit verschiedenen Indikationen außerhalb der ABO-inkompatiblen Transplantation mit semiselektiver Immunadsorption behandelt wurden, wurden in die Studie inkludiert. Die semiselective Behandlung basierte auf IA mit Protein A, Peptid-Ligand und Anti-human Immunglobulin (Sub-)Klassen

Ergebnisse. Die sensitive Durchflusszytometrie-Analyse der mit ABO-IA desensibilisierten Transplantationskandidaten ergab eine profunde, aber auch oft unvollständige Reduktion der ABO-Blutgruppen-spezifischen Antikörper (anti-A/B). Persistierende Komplement-fixierende Reaktivitäten (IgG, IgG1-4 Subklassen, IgM und Komplement-fixierende Reaktivitäten) wurden mit Durchflusszytometrie und konventionellen Agglutinationstests analysiert.

Schlussfolgerungen. Unsere Beobachtung einer limitierten Adsorptionskapazität bezüglich bestimmter Blutgruppen-spezifischer Immunglobulin-(Sub-)Klassen lässt zu erhöhter Vorsicht bei der Verwendung von semiselectiven Immunsorptionstechniken bei ABO-inkompatiblen Nierentransplantation raten.
tolerogene Strategien (14 Zentren; 21 Patienten) die temporäre IS beendet. Die Ergebnisse sind sehr heterogen (COT 10–90 %), der Follow-up sehr kurz.

LungenTx: Ein beschriebener Patient nach haploidem Stammzelltransplantation der Mutter toleriert die nachfolgende Transplantation eines Lungenlappens der Mutter ohne weitere IS.

Schlussfolgerungen. Weltweit wurden und werden zahlreiche Studien initiiert, mit dem Ziel der Vermeidung einer dauernden IS nach Organtransplantation. Zahlreiche unterschiedliche Tiermodelle weisen ebenso zahlreiche, mögliche Wege für die Zukunft. Natürliche Toleranz nach Organtransplantation ist wahrscheinlich deutlich häufiger als angenommen. Kriterien zur Spenderauswahl, toleranzinduzierende Strategien und prognostische Faktoren zur Organakzeptanz sind nicht einheitlich, daher sind die bisherigen Ergebnisse wenig konkursiv. Prospektive überregionale Studien sind gefordert, um den Fortschritt auf dem Gebiet der Toleranzinduktion zu beschleunigen.

Toleranzinduktion und Abstoßung: Was können wir von der Knochenmarktransplantation lernen?

R. Handgretinger
Abteilung für Hämatologie/Onkologie und Allgemeine Pädiatrie, Universitätskinderklinik Tübingen, Tübingen, Deutschland

Die allogene Knochenmarktransplantation ist für manche Patienten mit bösartigen und auch bestimmten gutartigen Erkrankungen der einzige kurative Therapieansatz. Dabei wird das Organ Knochenmark oder zugleich auch periphere Blutzellen nach Elimination des Empfängerknochenmarks durch Chemo- und/oder Strahlentherapie von einem gesunden Spender transplantiert. Damit das Knochenmark keine durch Spender T-Lymphozyten verursachte Graft-versus-Host-Reaktion (GVHD) auslöst, muß eine vorübergehende Immunsuppression durchgeführt werden. Eine lebenslange Abstoßungsprophylaxe ist nicht notwendig, da sich meistens eine Toleranz des neuen Immunsystems gegenüber dem Empfänger ausbildet. Falls das Empfängerimmunsystem nicht vollkommen eliminiert werden konnte, kann es zur Abstoßungsreaktion kommen, bei der respektive T-Lymphozyten des Empfängers die Spenderhämato poese abstoßen.

Das Ziel ist es daher, zum einen die Empfänger T-Lymphozyten zu eliminieren oder zu tolerisieren und zum anderen die Spender T-Lymphozyten zu tolerisieren. Eine Methode, die sich zur Eliminierung und Tolerisierung der Empfänger T-Lymphozyten in der Knochenmarktransplantation bewährt hat, ist, neben der medikamentösen Therapie, die total nodale Lymphknotenbestrahlung. Damit kommen Abstoßungsreaktionen selbst bei HLA-nichtidenten Knochenmarktransplantationen weitgehend verhindert werden. Zur Behandlung der GVHD hat sich in der allogen Knochenmarktransplantation die extracorporale Photopherese (ECP) bewährt, die durch das Medikament Photopherese bewirkt, welche die GVHD ohne intensive Immunsuppression zu mildern oder auch ganz zu eliminieren.

Anhand von Fallbeispielen wird diskutiert werden, dass die total nodale Lymphknotenbestrahlung und ECP auch in der Organtransplantation eine Rolle spielen könnten, da die Mechanismen der Toleranz oder Abstoßung sich prinzipiell nicht von einer Knochenmarktransplantation unterscheiden.

Over the past two decades, non-specific immunosuppression (I.S.) incorporating polyclonal and monoclonal antibodies, calcineurin inhibitors (CNI), mTOR inhibitors, anti-metabolites and steroids have greatly improved early allograft survival rates. However, the rate of chronic allograft loss has decreased only modestly over that observed earlier. Following kidney transplantation, for example, the rate of chronic attrition is discouragingly similar to that observed two decades ago, generally resulting from "chronic rejection" or, perhaps more accurately, "chronic allograft nephropathy". The relentless progression of similar histopathologic processes is manifested as vasculopathy in the coronary arteries of heart allografts (CAB) and in lung transplants as obliterative bronchiolitis (OB) despite the long-term administration of currently available I.S.

Thus, the ultimate goal of I.S. for transplant recipients is the development of long-term donor-specific nonresponsiveness which leaves responses to other foreign stimuli intact. Successful induction of "transplant tolerance" would avoid the complications of chronically administered I.S. and reduce the risks of chronic rejection. Numerous approaches employing both peripheral and central tolerance mechanistic strategies have been successfully developed in rodent models. Currently, several of these approaches appear to be clinically applicable, having now proved to be effective in large animal models and preliminary clinical trials. The most successful to date has been induction of hematopoietic mixed chimerism.

The mixed chimerism approach, an initially presumed central tolerance strategy, has been extensively studied in our laboratories, first in rodent, non-human primate, and porcine models, and now in human recipients of renal allografts. Using a non-myeloablative conditioning regimen followed by donor bone marrow (DBM) transplantation, we observed successful production of mixed chimerism in non-human primate renal allograft recipients, followed by normal kidney function with no evidence of chronic rejection for periods as long as thirteen years after discontinuing all I.S. In vitro studies of these recipients as well as of humans suggest that both central (clonal deletion) and peripheral (regulatory cells) mechanisms are involved.

Encouraged by the pre-clinical studies, we have to date extended this approach to 20 human renal allograft recipients. Ten individuals with ESRD secondary to multiple myeloma received a nonmyeloablative preparative regimen consisting of peritope-cyclophosphamide, equine ATG, CsA, and thymic irradiation. The recipients underwent HLA-matched kidney transplantation.
followed by iv infusion of DBM and subsequent donor lymphocyte infusions (DLI) to enhance the anti-myeloma effect. Transient lymphohematopoietic chimerism was achieved in all patients and only two reversible rejection episodes have occurred with a follow-up of 1 to 13 years after discontinuing IS. Long-term control of the underlying malignancy was better than with any other currently available treatment, but 4 of these individuals required additional therapy for recurrent myeloma.

Ten patients with ESRD and no myeloma received HLA-mismatched kidneys after a similar conditioning regimen except that MEDI-507, an anti-CD-2 mAb, was used in place of ATG and DLI was not used. Transient mixed chimerism and apparent allograft tolerance has been achieved in 7 of these recipients. These 7 patients have received no IS for periods of 2–9 years. Two allografts were lost: acute humoral rejection (1); thrombotic micro angiopathy (1) and the last recipient has been returned to chronic LS after developing acute rejection when IS was withdrawn.

These observations plus similarly encouraging observations in several clinical trials elsewhere suggest that tolerance induction may become a more widely applicable clinical reality.

**Experimental rationale for using hematopoietic stem cell transplantation for tolerance induction**

T. Wekerle

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

It was recognized a long time ago that an individual that shares hematopoietic cells with another, becomes tolerant to this individual. Thus, a recipient of a successful donor bone marrow (BM) transplant (BMT) becomes tolerant toward the donor. Triggered by this observation experimental studies have been systematically addressing why and how donor BM transplantation achieves tolerance. The concept of mixed chimerism – in which a substantial donor hematopoietic cell proportion co-exists with the recipient hematopoietic repertoire following donor BMT – has emerged as a promising BMT-based tolerance strategy.

Mixed chimerism leads to a particularly robust and durable type of tolerance. Central clonal deletion of immature donor-reactive T cells was identified as a key mechanism of tolerance in mixed chimeras and seems to be in large part responsible for the robust nature of tolerance achieved. Peripheral clonal deletion of mature donor-reactive T cells and non-deletional (i.e. regulatory) mechanisms also contribute to tolerance induction in some models. Overall, donor BMT emulates many of the physiologic mechanisms controlling self-tolerance, extending them to donor antigens.

While clinical translation of the mixed chimerism approach has been achieved in pilot trials, large-scale application in routine clinical practice awaits minimally toxic BMT regimens. Myelo-suppressive and cytotoxic pre-treatments commonly employed in conventional BMT recipients would be unacceptable in organ transplant recipients. Therefore, efforts to develop advanced, non-toxic murine BMT protocols are ongoing. The use of costi-

---

**Epidemiologie von Pilzinfektionen in Organ- und Stammzelltransplantationen**

C. Lass-Flörl

Sektion für Hygiene und Medizinische Mikrobiologie, Medizinische Universität Innsbruck, Innsbruck, Österreich

*Candida speciess oder Hefepilze. Candida repräsentieren 80 % aller schweren Pilzinfektionen. Ihre Prävalenz beträgt 2–20 pro 1000 Aufnahmen auf Intensivstationen in Europa und den USA. Infektionen werden vorwiegend durch C. albicans verursacht. Derzeit ist eine starke Zunahme von Infektionen mit C. glabrata, C. parapsilosis und C. krusei zu verzeichnen. In manchen Zentren machen die Non-albicans-Stämme bereits bis zu 44 % aller Candidosen aus; eine „shifting epidemiology“ ist somit zu dokumentieren. Dies ist von therapeutischer Bedeutung, da C. krusei gegen Fluconazol primär resistent ist und C. glabrata häufig eine Resistenz gegen Azole entwickelt. Als Ursache für den Wechsel im Erregerspektrum wird unter anderem der verstärkte Einsatz von Fluconazol betrachtet. In den aktuell veröffentlichten Daten der europäischen SOAP-Studie liegt Candida gemeinsam mit E. coli auf Rang 5 (13 %) aller Sepsisfälle. Candida spp. gehören zur normalen Darmflora beim Menschen, erst bei eingeschränkter Immunkompetenz wird eine invasive Infektion möglich. Die Letalität systemischer Candidosen liegt bei 20–50 %. Für die Sterblichkeit ist der Beginn der antymykotischen Therapie relevant. Wird innerhalb von 12 Stunden nach der ersten positiven Blutkultur antymykotisch behandelt, liegt die Letalität bei 11 %, nach über 48 Stunden bei 33 %.

*Aspergillus und seltene Schimmelpilzinfektionen. Die Inzidenz der Aspergillose bei der allogenen Stammzelltransplantation beträgt zwischen 8–25 %. Aspergillussporen kommen ubiquitär in der Umwelt vor; ungelüftete Luft aus Belüftungssystemen und Staub bilden die Hauptinfektionsquellen. Aspergillusporen werden exogen durch Inhalation erworben. Die Reduktion der Sporenlast in der Umgebung von Patienten „at risk“ ist die wichtigste prophylaktische Maßnahme. Der klinisch wichtigste Vertreter ist Aspergillus fumigatus. Die Letalität invasiver Aspergillose liegt bei 70–90 %. Zu den anderen Schimmelpilzinfektionen zählen die Zygomycosen (Absidia-, Mucor- und Rhizopus-Spezies), die insbesondere bei Patienten mit Diabetes mellitus oder zunehmend bei immunsupprimierten Patienten unter Voriconazol Therapie auftreten. Die Letalität beim Immungeschwächten ist annähernd 100 %. Bei Empfängern solider Organtransplantate konnte durch Neuerungen in der Chirurgie und Intensivierung der Immunsuppression das Transplantatüberleben verbessert werden. Mit bis zu 15 % ist die Inzidenz bei Herz- und Lungentransplantation am höchsten. Nach Lungentransplantation treten neben der typischen pulmonalen Aspergillose gehäuft ulzerierende Tracheobronchitis und Aspergillose der Bronchusansatome auf. Das geringste Risiko einer invasiven Aspergillose besteht bei Nierentransplantierten mit 1 % Inzidenz, die Mortalität ist generell hoch.*
Pilzinfektionen spielen bei Immunsupprimierten, vor allem bei Patientinnen und Patienten nach Organ- und Stammzelltransplantationen, eine steigende Rolle. Dabei reicht das Spektrum der verursachenden Pilze von Hefen der Gattung *Candida* zu Schimmelpilzen der Gattung *Aspergillus*, wobei auch eine Zunahme von Infektionen mit anderen Schimmelpilzen wie den Zygomyceten, Fusarien, *Scedosporium/Pseudallescheria* und anderen zu beobachten ist. Um eine zielgerichtete Therapie einleiten zu können, ist eine schnelle und genaue Diagnostik unumgänglich, da die einzelnen Pilzarten teils unterschiedliche Antimykotika-Empfindlichkeitsprofile aufweisen.

Neben den klassischen Kulturmethoden, die trotz ihrer relativen „Langsamkeit“ nach wie vor unverzichtbar sind, wurden in den letzten Jahren Techniken entwickelt, die teilweise innerhalb weniger Stunden Ergebnisse bringen können – vorausgesetzt, sie werden richtig angewandt und interpretiert. Dazu zählen insbesondere bildgebende Verfahren, molekularbiologische Methoden und Antigen-Nachweise.

Idealerweise beruht die Diagnose einer Pilzinfektion auf der Kombination mehrerer Techniken, man spricht auch von einer Puzzle-Diagnostik.

Die einzelnen Techniken zur Diagnose von Pilzinfektionen in der Organ- und Stammzelltransplantation sollen vorgestellt und deren Vor- und Nachteile diskutiert werden.

---

**Therapie von Pilzinfektionen in der Organ- und Stammzelltransplantation**

**R. Krause**

Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Graz, Österreich

Pilze verursachen bei Immunsupprimierten infektiöse Komplikationen, die von oberflächlichen Infektionen der Haut/Schleimhäute bis zu systemischen, lebensbedrohlichen Organinfektionen oder Fungämien reichen. Auslöser dieser Infektionen sind meist Candida-Arten, Aspergillus-Arten, andere Schimmelpilze wie *Zygomyceten*, Fusarien, *Scedosporium/Pseudallescheria* und anderen zu beobachten ist. Um eine zielgerichtete Therapie einleiten zu können, ist eine schnelle und genaue Diagnostik unumgänglich, da die einzelnen Pilzarten teils unterschiedliche Antimykotika-Empfindlichkeitsprofile aufweisen.

Neben den klassischen Kulturmethoden, die trotz ihrer relativen „Langsamkeit“ nach wie vor unverzichtbar sind, wurden in den letzten Jahren Techniken entwickelt, die teilweise innerhalb weniger Stunden Ergebnisse bringen können – vorausgesetzt, sie werden richtig angewandt und interpretiert. Dazu zählen insbesondere bildgebende Verfahren, molekularbiologische Methoden und Antigen-Nachweise.

Idealerweise beruht die Diagnose einer Pilzinfektion auf der Kombination mehrerer Techniken, man spricht auch von einer Puzzle-Diagnostik.

Die einzelnen Techniken zur Diagnose von Pilzinfektionen in der Organ- und Stammzelltransplantation sollen vorgestellt und deren Vor- und Nachteile diskutiert werden.

---

**25th Annual Meeting of the Austrian Society of Transplantation**

**070**

Diagnostik von Pilzinfektionen in der Organ- und Stammzelltransplantation

**W. Buzina**

Institut für Hygiene, Mikrobiologie und Umweltmedizin, Medizinische Universität Graz, Graz, Österreich

---

**071**

Therapie von Pilzinfektionen in der Organ- und Stammzelltransplantation

**R. Krause**

Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Graz, Österreich

---

**072**

Erleben – überleben – und dann? Lebensqualität nach Herztransplantation

**B. Bunzel**

Klinische Abteilung für Herzchirurgie, Universitätssklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich

Aus wissenschaftlicher Perspektive ist der Begriff „Lebensqualität“ ein nicht direkt beobachtbares Konstrukt, das die Bewertung des physischen, psychischen und sozialen Zustandes einer Person in seiner Zusammenschnitt bezeichnet. Eine gute Annäherung kann auch durch den Begriff „Lebensorzufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schucksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genommen werden: wie ändert sich das Leben der PatientInnen nach einer oft schicksalhaften schweren Erkrankung und lebenserhaltenden Transplantation? In einer prospektiven Studie unserer Abteilung über Lebensqualität ein, fünf und 10 Jahre nach Herztransplantation zeigte sich z. B. eine Schere zwischen konstant durchaus guter Lebensqualität in physischer Hinsicht, aber zunehmend erheblicher Abnahme in psychischer und sozialer Hinsicht. Eine gute Annäherung kann auch durch den Begriff „Lebenszufriedenheit“ erfolgen. Im Vortrag soll vor allem auf Langzeit-Lebensqualitätsstudien und die psychische Verarbeitung der Herztransplantation Bezug genomen
Lebensqualität nach Organs transplantation bei Kindern

K.-H. Schulz
Klinik und Poliklinik für Hepatobiläre Chirurgie und Transplantationschirurgie und Institut für Medizinische Psychologie Universitätssklinikum Hamburg Eppendorf, Hamburg, Deutschland

Während sich die gesundheitsbezogene Lebensqualität (LQ) in der Erwachsenenmedizin als wichtiger Outcome-Parameter zur Bewertung der Wirksamkeit verschiedener Therapien etabliert hat, steht die Lebensqualitätsforschung in der pädiatrischen Medizin noch am Anfang. Gesundheitsbezogene LQ bei Kindern und Jugendlichen als multidimensionales Konstrukt akzentuiert über die der Erwachsenenmedizin berücksichtigten Dimensionen hinaus Bereiche wie Schule, Familie und Gleichaltrige sowie die körperliche und geistige Entwicklung. Insbesondere die Adoleszenz mit ihren Entwicklungsaufgaben ist hier hervorzuheben.

Zwar sind Organs transplantationen lebensrettend, doch eine terminale Erkrankung wird gegen ein chronisches Syndrom trotz guter Organfunktion eingetauscht. Die Wiederherstellung der Organfunktion bedeutet nicht die Rückkehr in ein normales Leben, es ist vielmehr gekennzeichnet durch z. B. Angst vor Organverlust und Komplikationen, Nebenwirkungen der Immunsuppressiva, etwaige Komorbiditäten oder Entwicklungsrückstände bis hin zu psychiatrischen Störungsbildern. Über die medizinischen Outcome-Parameter hinaus sollte deshalb die LQ der transplantierten Kinder und ihrer Familien ebenso routinemäßig gemessen werden und bei Bedarf gezielte Interventionen erfolgen.

Für die drei am häufigsten durchgeführten pädiatrischen Organtransplantationen (Niere, Leber, Herz) wird der jeweils aktuelle Forschungsstand referiert. Darüber hinaus werden zwei spezifische Problembereiche in der pädiatrischen Organs transplantation dargestellt, das Problem der Compliance/Adherence und der Transition von der Kinder- und Jugendmedizin in die Erwachsenenmedizin. Die Studien unterscheiden sich hinsichtlich der Operationalisierung der LQ, des Studiendesigns, der Dauer des Follow-ups und des Altersbereichs der Kinder. Prospektive Längsschnittstudien mit größeren Stichproben in multiplen Dimensionen hinaus Bereiche wie Schule, Familie und Gleichaltrige sowie die körperliche und geistige Entwicklung. Insbesondere die Adoleszenz mit ihren Entwicklungsaufgaben ist hier hervorzuheben.

Abstract nicht verfügbar.

075

Is autologous bone marrow harvest still an option for patients with stem cell mobilization failure in the era of plerixafor?

N. Worel1, G. Leitner2, M. Horvath1, P. Kalhs2, W. R. Sper2, H. T. Greinix, H. Agis3

1Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria; 2Bone Marrow Transplantation Unit, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; 3Division of Hematology and Hemostasology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

Background. Autologous stem cell transplantation (ASCT) is a curative procedure for a variety of haematologic malignancies and depends on the transplantation of sufficient CD34+ cells (threshold of $2 \times 10^6$/kg to ensure sustained engraftment. In the last decade, peripheral blood stem cells (PBSC) have completely replaced bone marrow (BM) as preferred stem cell graft in ASCT. However, a number of patients fail to mobilize the threshold of $2 \times 10^6$/kg of CD34+ cells. In these poor mobilizers, BM harvest was the only possibility to collect sufficient numbers of stem cells so far. Recently, the chemokine-receptor antagonist plerixafor has shown to enhance stem cell mobilization in patients who demonstrated with previous mobilization failure with an overall success rate of about 70%. We here report 4 patients with mobilization failure in whom G-CSF primed BM as well as plerixafor primed PBSC were collected.

Methods. Four heavily pretreated patients (median of 10 chemotherapy cycles, range 8–17) with non-Hodgkin lymphoma (NHL, n=3) and germ cell cancer (n=1) presented with mobilization failure after 1–7 mobilization attempts. In the 3 NHL patients BM was harvested after unsuccessful PBSC collection with plerixafor. In the patient with germ cell tumor before plerixafor primed PBSC collection was done after insufficient BM harvest.

Results. In the 3 NHL patients plerixafor enhanced PBSC revealed an insufficient number of CD34+ cells (i.e. $0.64–1.15 \times 10^6$/kg CD34+ cells in 2–3 leukaphereses procedures). Therefore BM was harvested after G-CSF stimulation. However, again we failed to obtain enough CD34+ cells in all of them (0.16 to 0.62 \times 10^6$/kg CD34+ cells). In the patient with germ cell cancer a collection of CD34+ cells from the BM was carried out as first salvage procedure after the failure of conventional mobilization ($0.9 \times 10^6$/kg CD34+ cells). Thus, in a next attempt PBSCs were mobilized with G-CSF and plerixafor resulting in a successful harvest ($3.36 \times 10^6$/kg CD34+ cells in one leukapheresis).

Conclusions. Reviewing our cases one might speculate that a BM harvest after failure of stem cell mobilization with G-CSF and plerixafor does not yield in sufficient CD34+ cell numbers.

074

Chimerismusinduktion: von der Tumor eradikation bis zur Toleranz

D. Niederwieser
Abteilung Hämatologie, Internistische Onkologie, Hämostaseologie, Universitätssklinik Leipzig, Leipzig, Deutschland

Abstract nicht verfügbar.
**076**

Transient Elastography ( FibroScan) for the prediction of liver toxicity following autologous or allogeneic HSCT

J. Auburger¹,², I. Graziaedi¹, W. Vogel¹, J. Clausen¹,², D. Nachbaur¹

¹Universitätsklinik für Innere Medizin V, Hämatologie und Onkologie, Medizinische Universität Innsbruck, Innsbruck, Österreich; ²Universitätsklinik für Innere Medizin III mit Hämatologie, internistischer Onkologie, Infektionologie, Hämostaseologie und Rheumatologie, Paracelsus Medizinische Privatuniversität Salzburg, Salzburg, Österreich; ³Universitätsklinik für Innere Medizin II, Gastroenterologie und Hepatologie, Medizinische Universität Innsbruck, Innsbruck, Österreich

**Grundlagen.** Lebertoxizität oder das Sinusoidale Obstruktionssyndrom (SOS) gehören zu den häufigsten Organotoxizitäten nach zytoreduktiver Hochdosis-Chemotherapie/Radiotherapie bei autologer oder allogener HSCT. Die transiente Elastographie ( Fibroscan, FS) ist eine neue, schnell zugängliche und nicht-invasive Methode eine Leberfibrose über die Lebersteifigkeit (LS) zu bestimmen und wird bereits erfolgreich bei Patienten mit Hepatitis C und alkoholischer Lebererkrankung eingesetzt.

**Methodik.** Zwischen April 2009 und Oktober 2010 wurden 67 Patienten FS-Messungen während der Routine-Abdomensonographie im Rahmen der Transplantuntersuchungen vor autologer (n = 37) oder allogener (n = 30) Transplantation zugewiesen. Die Konditionierung bestand aus HD MEL (140–200 mg/m²), BEAM oder anderen krankheits spezifischen Hochdosischemotherapien im Rahmen autologer Transplantationen. Allogene Transplantationen wurden mit myeloablative Konditionierung (MAC, n = 18) oder in reduzierter Intensität, hauptsächlich BUFLU basiert (RIC, n = 12) durchgeführt. Die Lebertoxizität wurde anhand des maximalen Serum-Bilirubins, der Anzahl der Tage mit einem Bilirubin > 2mg/dL und der prozentualen maximalen Gewichtszunahme bis zum Tag + 20 definiert.

**Ergebnisse.** Das maximale Serum-Bilirubin vor Tag + 20 betrug 1,18 (range, 0,44–11,72) mg/dl, der mediane Zeitpunkt mit einem Serum-Bilirubin > 2mg/dL war 10,5 (range, 1–20) Tage und die mediane prozentualen Gewichtszunahme war 5,2% (range, 0,1–17,2). Lebertoxizität wurde häufiger nach MAC als RIC Konditionierung beobachtet, wenngleich nicht statistisch signifikant (50% vs. 33%, p = 0,25). Patienten, die eine Immunsuppression (iS) mit CsA/MMF erhielten, zeigten häufiger Anzeichen einer Lebertoxizität verglichen mit Pat., die CsA/MMF oder keine IS erhielen (83% vs. 18%). Die mediane LS vor Transplantation war 5,4kP (range, 2,3–62,7). Die LS korrelierte signifikant mit der GOT und GPT vor Transplantation in der gesamten Kohorte und mit GPT, GGT und AP bei Patienten mit mehr als 10d Bilirubin > 2mg/dL bis zum Tag + 20. Zwischen der LS vor HSCT und Zeichen der Lebertoxizität (definiert als max. Serumbilirubin, Anzahl der Tage mit Bilirubin > 2mg/dL und prozentualer Gewichtszunahme) nach HSCT konnte keine signifikante Korrelation hergestellt werden.

**Schlussfolgerungen.** Die nicht-invasive transiente Elastographie ( Fibroscan) ist nicht wegzudenken, um Patienten zu identifizieren, die ein hohes Risiko für die Entwicklung einer Lebertoxizität nach autologer oder allogener Transplantation aufweisen.

---

**077**

Norovirus associated hemophagocytic lymphohistiocytosis (HLH) after unrelated bone marrow transplantation (BMT) in a boy with refractory AML

G. Kropshofer, C. Salvador, R. Crazzolara, B. Meister

Department of Pediatrics II, Center of Pediatrics, Medical University of Innsbruck, Innsbruck, Austria

**Background.** HLH is a potentially life threatening macrophage activating syndrome which leads to massive hyperinflammation through an exaggerated but ineffective immune response. Diagnosis after BMT is complicated by other inflammatory syndromes like engraftment syndrome, capillary leak syndrome, veno-occlusive disease and systemic infections. **Methods and Results.** We report on a meanwhile 24-month-old boy with AML (M4) relapse. Already in phase of maintenance chemotherapy he acquired a gastrointestinal infection with norovirus. Reinduction chemotherapy was performed with FLAG/Daunoxome and FLAMSA – he never reached a complete remission. So we decided to perform an allogeneic BMT (MUD) in aplasia. Conditioning regimen consisted of iv busulfan, cyclophosphamide and melphalan. There were no early complications despite his ongoing norovirus infection. Leukocyte engraftment was obtained on day +20. Bone marrow at day +28 showed a newly normocellular bone marrow and full donor chimeraism. At day +40 the patient impressed with persistent fever despite antimicrobial therapy, his general status deteriorated. He developed CNS symptoms with vertical nystagmus, increasing hepatosplenomegaly and respiratory insufficiency. Laboratory findings showed hyperferritinemia (45000µg/l), a subsequent pancytopenia, hypofibrinogenemia, elevated D-Dimer (34000µg/l) and hypertriglyceridemia (723 mg/dl). Intensive care was necessary including high doses of catecholamines. Subsequent bone marrow aspiration revealed an aplastic bone marrow and hemophagocytosis. The patient underwent ventilation support for 17 days. Treatment included DXM 10mg/m²/d for 14 days, then DXM was tapered to 5mg/kg/d. Etoposide (150mg/kg) was given three times until now. Considering the long aplastic phase and the ongoing hemophagocytosis we decided to give him stem cell support (remaining frozen bone marrow from the same donor) without reconditioning. Four days later we went on with a monoclonal anti-CD25 antibody (Simulect®). The boy improved but therapy is still ongoing. The outcome at the moment is unclear. **Conclusions.** HLH still is a rarely seen complication after BMT, therefore early diagnosis is necessary to start therapy promptly. The role of monoclonal anti-CD25 antibody and anti TNF-α antibody as part of therapy is unclear yet. Up to now there is no report of norovirus triggering HLH.
Therapeutic effect of allogeneic bone marrow mesenchymal stem cell transplantation on liver chronic damage in rats

A. Lyundup¹, N. Onishchenko¹, M. Shagidulin¹, M. Krasheninnikov¹, I. Trubitsyna²

¹Federal V. Shumakov Research Center of Transplantology and Artificial Organs Ministry of Health and Social Development RF, Moscow, Russia; ²CRI of Gastroenterology BH, Moscow, Russia

Background. Research was to assess possibilities of using cultivated allogeneic bone marrow mesenchymal stem cells (MSC) for treatment of liver fibrosis.

Methods. 75 male rats divided in 3 groups in which chronic hepatitis was modeled by means of CCL₄. 1st (n = 25) received single transplantation of 2.5 × 10⁶ MSC on 3rd day after modelling. In 2nd (n = 25) MSC were injected twice in a dose of 2.5 × 10⁶ cells on days 3 and 10 after modelling, 3rd group was control group (CG, n = 25). Biochemical indices: ALT, AST, ALP; cytokines (IFN-γ, TNF-α, IL-4, IL-10) were studied during 5 weeks. Liver histology were studied after 7, 14, 21, 28, 60, 90 days. Immunohistochemical methods: α-SMA, caspase-3, AFP and PCNA were used.

Results. At the 1–3 weeks the AST, ALT and ALP were increased in all groups, but in the CG level of indices above was higher. Analysis of morphologic changes in liver resulted in following findings: on 7th and 14th day liver fatty degeneration was in all groups, but its appearance was stronger in the 1st and especially in especially in 2nd. It is important to note that connective tissue forming in liver after MSC application had two-phase dynamics: at first an area of connective tissue sharply increased and then gradually decreased. It was found out that the α-SMA and caspase 3 expression after MSC application had also two-phase dynamics: at 1–2 weeks these indices were increased and then (3–4 weeks) began to decrease, becoming lower than in CG. At first weeks cytokines disbalance was identified in all groups, but in MSC groups cytokines disbalance was less expressed on 5th week. AFP and PCNA expression rates were higher in MSC groups, than in CG up to end of examination.

Conclusions. MSCs transplantation for therapy of liver damage can reduce liver fibrosis, but this process has two-phase dynamics (firstly increasing and then decreasing of fibrosis) which can explain the contradictory information on the cell therapy of chronic hepatitis.

Organotypic remodeling of biounits containing liver cells and bone marrow stem cells in 1 year after transplantation into rats with toxic damaged liver

M. Shagidulin, N. Onishchenko, M. Krasheninnikov, I. Iljinsky, N. Mogeiko, A. Lyundup, P. Avramov, N. Petrova, V. Sevastjanov, S. Gautier

Department of Transplantology and Artificial Organs, Federal V. Shumakov Research Center of Transplantology and Artificial Organs, I. M. Sheckenov Moscow State Medical University, Moscow, Russia

Background. Treatment of chronic liver failure in pretransplant period is an actual problem of medicine. This investigation was undertaken for working out for biounit containing viable liver cell (LC) and multipotent mesenchymal stromal cells (MMSC), which could support the functioning and recovered regeneration of damaged liver for a long time.

Methods. Chronic liver damage was modeled on Wistar rats by means of 0.3 ml CCL₄ on 100 g rat weights within 6 weeks. Adult Wistar rats were also used as donor cells. Isolated cells were cultivated in 10 days: at first MMSC during 7 days then the same MMSC together with LC in 3 days on Cytodex. Suspension of LC 2.5–4.0 × 10⁶ cells/cm² and MMSC 0.5–0.8 × 10⁶ cells/cm² was applied on biodegradable matrices “Sphero® Gel”. Formed biounits were transplanted into rat liver. Survival of transplanted cells and liver morphology were investigated in 365 days after transplantation by using hematoxylin and eosin staining, Masson’s trichrome staining. Cell viability and cellular phenotype were investigated by trypan blue staining and immunohistochemically (cytokeratine 18 and mitochondrial antigen).

Results. Before biounit transplantation liver damage was characterized by: fatty, lymphoid-cellular infiltration and proliferation of histioblasts and macrophages; porto-portal sclerosis; hydropic dystrophia and focal necrosis of hepatocytes. In 365 days after biounit transplantation it was detected: viable hepatocytes, neogenic plethoric vessels, neogenic plethoric bile duct in biounit. Liver damage (dystrophia, safe structure of a liver, beam structure, fatty vacuoles inside hepatocytes and other indices) were significant less after biounit transplantation than in control group without biounit transplantation. Restoration of hepatic lobe structure was better in studied group.

Conclusions. Our preliminary studies demonstrate that in biounit after transplantation into damage liver there is formation of morphologic structures of liver (viable cell, vessels, bile ducts); other words the used method allows to carry out organotypic liver remodeling into biounit and to support the function of the damaged liver. Thereby the suggested method is a perspective one and can be used as technology of building intracorporeal biounit for the long-term auxiliary supporting of the damaged organs.

Liposomales Amphotererin B als Prophylaxe invasiver Pilzinfektionen nach hämatopoietischer Stammzelltransplantation bei pädiatrischen und adoleszenten Patienten

P. Sovinz, W. Schwinger, H. Lackner, M. Benesch, V. Strenger, S. Schmidt, C. Urban

Klinische Abteilung für Pädiatrische Hämato-/Onkologie, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Graz, Graz, Österreich

Grundlagen. Für die antifungale Prophylaxe nach hämatopoietischer Stammzelltransplantation (HSZT) existieren für pädiatrische – im Gegensatz zu erwachsenen – Patienten keine evidenzbasierten Empfehlungen. Vorteile von liposomalem Am-
photerin B (LAMB) sind ein breites antifungales Spektrum, eine lange Eliminations-Halbwertszeit, und im Vergleich zu den neuen Azolen wenige Medikamenten-Interaktionen.

**Methodik.** Im Zeitraum 2009–2010 wurden bei 20 konsekutiven Patienten (medianes Alter: 11,4 Jahre; m:w = 8:12) insgesamt 23 HSZT durchgeführt; 12 autologe (davon 3 Tandem-Transplantationen) und 11 allogene SZT, wegen soliden Tumoren (n = 7), rezidivierter schwerer aplastischer Anämie (n = 5), malignen hämatologischen Erkrankungen (n = 5), Mb. Hurler (n = 2) bzw. Mb. Crohn (n = 1). Autolog transplantierte Patienten erhielten im Median 7,46 × 10⁴/kg CD34⁺-Zellen/kg und erreichten am Median Tag + 9,5 das leukozytaire Engraftment. Allogene Stammzellquellen waren periphere Stammzellen (CD34⁺ selektioniert und/oder CD3/19 depletiert) in 9 und Knochenmark in 2 Fällen; Spender waren HLA-idente Fremd (n = 9) bzw. Geschwisterspender (n = 1) und ein haploidenter Elternteil. Die mediane Stammzellzahl lag bei 15,37 × 10⁶/kg CD34⁺-Zellen/kg; das leukozytaire Engraftment erfolgte im Median am Tag + 11. Bei 5 Patienten trat eine Graft-versus-host-Erkrankung (GVH) auf, davon einmal eine GVH IV. Die LAMB-Prophylaxe wurde in einer Dosis von 5 mg/kg in 3-tägigen (n = 15) oder 2-tägigen (n = 8) Intervallen gestartet, bei 2 Patienten mit refraktärer AML am Tag – 46 bzw. – 42, bei allen anderen Patienten im Median am Tag – 3. Die Patienten erhielten im Median 11,5 (5–45) prophylaktische Dosen bis zu Median Tag + 20,5 (+11 bis +43).

**Ergebnisse.** Bei 8 Patienten wurden wegen Fieber oder CIP-Anstieg die Infusionsintervalle verkürzt. Eine intermittierende Candida-Kolonisation wurde durch wöchentliche Überwachungskulturen bei 9 Patienten detektiert. Wöchentliche Galaktomannan-Test blieben bei 17 Patienten durchgehend negativ, 2 Patienten hatten je ein einzelnes positives Testergebnis; keiner dieser 19 Patienten entwickelte während einer medianen Nachbeobachtungszeit von 10 Monaten eine invasive Pilzinfektion. Eine Patientin mit GVH IV unter multimedialer Immunsuppression und wiederholt positiven Galaktomannan-Tests entwickelte trotz kontinuierlicher präemptiver Therapie mit LAMB alternierend mit Caspofungin präformal eine Aspergillose-Pneumonie und verstarb am Tag + 140. Bei keinem Patienten mußte LAMB wegen infusionsassoziierter Nebenwirkungen abgesetzt werden; die Hauptnebenwirkung war eine Hypokaliämie, die in 20/23 Anwendungen substitutionsbedürftig war.

**Schlussfolgerungen.** Die intermittierende antifungale Prophylaxe mit LAMB nach autologer bzw. allogener SZT war bei 19/20 Patienten erfolgreich. Die Nebenwirkungen beschränkten sich auf eine substitutionsbedürftige Hypokaliämie.

---

**Basic Research**

**081**

Different implantation sites of sodium cellulose sulfate microencapsulated porcine islet cells in five beagle dogs

G. Haimel¹, S. Köstenbauer², M. Asslaber³, F. Zeugwetter¹, G. Duprén, K. H. Tschelissnigg³, P. Stiegler²

¹Department for Small Animals and Horses, University of Veterinary Medicine Vienna, Vienna, Austria; ²Division of Transplantation Surgery, Department of Surgery, Medical University of Graz, Graz, Austria; ³Institute of Pathology, Medical University of Graz, Graz, Austria

**Background.** Late complications including diabetic vasculopathy, retinopathy and neuropathy are still serious problems in the treatment of diabetes mellitus. Whole pancreas transplantation or human islet cell transplantation are alternatives but limited due to the organ shortage and lifelong immunosuppression. The use of immune isolated porcine islet cells (PIC) could offer a feasible alternative. In this study, the safety and applicability of three possible implantation sites for Sodium Cellulose Sulfate (SCS) microencapsulated PIC were evaluated in five healthy beagle dogs.

**Methods.** Five healthy, male castrated Beagle dogs were used for this study. SCS microencapsulated PIC were implanted in the subcutaneous tissue, the omentum and the gastric submucosa. Surgery time and intraoperative complications were monitored. Implantation in the omentum and gastric submucosa was performed laparoscopically assisted. All animals were continuously monitored including 15:30 clinical examinations and complete blood counts for possible occurring side effects. On day – 3, 30 and 90 a glucagon stimulation test was performed to assess β-cell function and glucose metabolism. On day – 3, 1, 3, 12, 30, 60 and 90 fasting glucose and insulin were measured. Blood samples were taken to check a possible porcine endogenous retrovirus (PERV) transmission. Biopsies of all implantation sites were obtained for histopathology on day 90.

**Results.** No technical complications occurred at the subcutis and omentum site. At the gastric submucosa only a limited amount of cells could be implanted. Delayed wound healing at the subcutaneous implantation site was observed in three out of five dogs. No further side effects occurred during the study period. Transmission of PERV was not detected. Glucagon stimulation tests showed a trend towards a faster response to a glucagon stimulus and an increased insulin peak. Histopathology results have not been completely evaluated yet.

**Conclusions.** First results show that SCS microencapsulated PIC do not cause any harmful side effects to the recipients concerning application. No transmission of PERV was detected. The outcome of histopathology in combination with the clinical results will display the efficacy of this treatment and the expected differences in transplantation sites.

---

**082**

Secretome of apoptotic peripheral blood cells (APOSEC) confers cytoprotection to cardiomyocytes and inhibits tissue remodelling after acute myocardial infarction

M. Lichtenauer¹,², M. Mildner³, M. Zimmermann¹,², B. K. Podesser¹, W. Sipos⁴, E. Tschachler⁴, M. Gyöngyösi⁵, H. J. Ankersmit¹,²

¹Department of Surgery, Medical University of Vienna, Vienna, Austria; ²Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis and Regeneration, Vienna, Austria; ³Department of Dermatology, Medical University of Vienna, Vienna, Austria; ⁴Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria; ⁵Clinical Department for Farm Animals and Herd Management, University of Veterinary Medicine Vienna, Vienna, Austria; ⁶Department of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria
Background. Heart failure following acute myocardial infarction (AMI) is a major cause of morbidity and mortality. Our previous observation that injection of apoptotic peripheral blood mononuclear cells (PBMC) was able to restore cardiac function in a rat acute ischaemia model prompted us to study the effect of soluble factors derived from apoptotic PBMC on ventricular remodelling after AMI.

Methods. Cell culture supernatants derived from irradiated apoptotic peripheral blood mononuclear cells (APOSEC) were collected and injected as a single dose intravenously after myocardial infarction in an experimental AMI rat model and in a porcine reperfused AMI model. MRI and echocardiography were used to quantitate cardiac function. Immunohistology and flow-cytometry were used to analyse the cellular components. Analysis of soluble factors present in APOSEC was performed with proteome membrane arrays and activation of signalling cascades in human cardiomyocytes by APOSEC in vitro was studied by immunoblot-analysis.

Results. Intravenous administration of APOSEC resulted in a reduction of scar extension in both models. Hearts explanted from animals infused with APOSEC evidenced less myocardial necrosis after 24 hrs. Troponin-I release was less than in animals treated with medium as control. In the porcine AMI model APOSEC led to an improvement of ejection fraction (57.0% vs. 40.5%, *p < 0.01), cardiac output (4.0 vs. 2.4 l/min., *p < 0.001) and a reduced infarction size (12.6% vs. 6.9%, *p < 0.02) as determined by MRI. Administration of APOSEC in the rat AMI model caused increased presence of CD68+ macrophages and c-kit+ endothelial progenitor cells (EPC) in the infarcted myocardium within 72 hrs. Exposure of human cardiomyocytes with APOSEC in vitro triggered activation of pro-survival signalling-cascades (AKT, p38 MAPK, Erk1/2, CREB, c-Jun) and anti-apoptotic gene products (Bcl-2, BAG1).

Conclusions. Intravenous infusion of APOSEC attenuated myocardial remodelling in both models of experimental AMI. This effect seems to be due to the activation of pro-survival signalling cascades in the affected cardiomyocytes and to a higher presence of regenerative cells (EPCs, macrophages) within the ischaemic tissue. APOSEC represents a “biological” which prevents myocardial infarction by causing peri-infarct conditioning and stimulation of regenerative effects in the hypoxic myocardium.

Anti-thymocyte globulin (ATG) reduces damage caused by ischaemia and preserves cardiac function after experimental myocardial infarction

G. Werba1,2, M. Mildner3, A. Baumgartner4, L. Beer1,2, M. Gyöngyösi1, B. K. Podesser1, H. J. Ankersmit1,2, M. Lichtenauer1,2

1Department of Surgery, Medical University of Vienna, Vienna, Austria; 2Christian Doppler Laboratory for the Diagnosis and Regeneration of Cardiac and Thoracic Diseases, Vienna, Austria; 3Department of Dermatology, Medical University of Vienna, Vienna, Austria; 4Ludwig Boltzmann Cluster for Cardiovascular Research, Vienna, Austria; 5Department of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria

Background. Myocardial infarction (MI) is one of the leading causes of death in the western world. Consequent inflammatory reactions initiate and sustain remodeling of the damaged myocardium, which can worsen the outcome additionally. Our previous findings suggest that apoptotic peripheral blood mononuclear cells (PBMCs), injected intravenously after MI in rats, can attenuate inflammation and subsequently improve cardiac function after MI. In this study we sought to investigate, if anti-thymocyte globulin (ATG) as a therapeutic agent inducing apoptosis in white blood cells, evidences similar effects after experimental MI in rats.

Methods. To study effects of ATG in vitro, we incubated whole blood and PBMC cell cultures with this polyclonal antibody for 24 hours. ELISA was utilized to assess changes in the secretion profile of various cytokines. Furthermore, we conducted an in vivo study in an experimental rat model of myocardial infarction. Rodents were injected with ATG (10 mg/rat) after ligation of the left anterior descending (LAD) artery. Untreated and sham operated animals served as controls. Short term effects were evaluated by immunohistology after three days. Echocardiography and assessment of infarction size by planimetry depicted the outcome after six weeks.

Results. Cytokines and chemokines held responsible for cardioprotective and neo-angiogenic effects (e.g. IL-1RA, IL-8, MCP-1) were significantly elevated in ATG groups over controls in vitro. Histology of in vivo experiments confirmed these data, as ATG treated animals had a reduced area of necrosis three days after AMI (10.7% vs. 20.6%), smaller infarct scars after six weeks and an increased infiltration of macrophages. Echocardiography revealed a treatment advantage of ATG, as rodents enrolled in this study group evidenced an ejection fraction of 52.35% ± 1.96% compared to 42.91% ± 2.22% in controls (n = 13, p < 0.001).

Conclusions. Via the mechanism of apoptosis, ATG induces a plethora of pro-angiogenic and immune-modulatory factors. Secretion of this ensemble of cytokines and chemokines attracts macrophages/monocytes into the infarcted area, and attenuates inflammation after myocardial infarction. In conclusion, interaction of these factors can significantly reduce infarction size and improve left ventricular function after experimental myocardial infarction in rats.
these mediators systemic in immune activation/sepsis, wound healing, autoimmune-diseases, atherosclerosis and myocardial infarction. However, cytokines and chemokines are usually not considered to be very stable after blood collection, which might therefore alter test.

Results. Thus, the aim of the pilot study was to obtain better knowledge about stability of these mediators in blood samples for interpretation of test results.

Methods. Venous blood was taken from healthy probands \((n=7)\) using different blood tubes (serum, heparin plasma and EDTA plasma). Blood tubes were either centrifuged initially within 20 minutes after venipuncture and kept frozen at \(-80^\circ\text{C}\) until further testing or were stored at 4 °C, at room temperature (RT), or at 37° for up to 24 hours. Samples were evaluated for IL-18, IL-6, TNF-α and for selected chemokines such as interleukin-8, epithelial neutrophil-activating protein 78 (ENA-78) and granulocyte chemotactic peptide-2 (GCP-2) using commercially available enzyme-linked immunosorbent assay (ELISA) kits.

Results. Interestingly all examined mediators rise when samples were stored above room temperature for more than 4 hours in serum tubes. The rise of serum chemokine and cytokine levels culminated in a 79-fold increase for IL-6 \((p<0.0081)\), a 22-fold increase for ENA-78 \((p<0.0006)\) and a 17-fold increase for GCP-2 \((p<0.0026)\) compared to basic values. Serum levels of IL-1/β and TNF-α were not detectable at basic samples but rise up to 1157 pg/ml (mean IL-1/β, \(p<0.03\)) and 488 pg/ml (mean TNF-α, \(p<0.03\)).

Conclusions. These data indicate that the most chemokine and cytokine levels remain stable when analysed within a short interval after venipuncture. When tubes were exposed to temperatures higher than 24° (RT), levels of measured chemokines increased dramatically.

Induction of circulating endothelial cells (CECs) and circulating progenitor cells (CPCs) after polyclonal antithymocyte globulin (ATG) therapy in liver transplantation

C. Fabritius\(^1,\) D. Stauch\(^2,\) A. Yayahzadeh\(^3,\) A. Pascher\(^4,\) P. Neuhaus\(^5,\) J. Pratschke\(^6,\) K. Kotsch\(^1\)

\(^1\)Department of Visceral, Transplantation and Thoracic Surgery, Medical University of Innsbruck, Innsbruck, Austria; \(^2\)Institute of Medical Immunology, Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany; \(^3\)Department of General, Visceral and Transplantation Surgery, Charité-Universitätsmedizin Berlin, Berlin, Germany

Background. Rabbit antithymocyte globulin (rATG) is widely used as induction agent in solid organ transplantation. Beside depletion of circulating lymphocytes there is a growing body of evidence suggesting that rATG may also play a pivotal role in modulating the immune system. As blood circulating endothelial cells (CECs) and circulating hematopoietic progenitor cells (CPCs) represent two minute fractions (CECs: 0.1% to 6.0% and CPCs: 0.01–0.2%) of blood mononuclear cells that are thought to play important roles in tissue vascularisation, the study of both cell types is currently suggested as surrogate markers for numerous pathologies. Especially the noninvasive endothelial evaluation as an early index of vascular injury following kidney transplantation has been already demonstrated.

Methods. We used four surface markers to identify viable CECs as CD31bright, CD34dim, CD45-, CD133- and viable CPCs (175 mg/kg Körpergewicht) induziert. Der erste Gruppe wurden 250 Langerhans Inseln unter die Nierenkapsel transplantiert. Die Inseln für die zweite Gruppe wurden vor deren Transplantation einem „simulierten Transport“ in einer Rotationskammer ausgesetzt (15 h). In beiden Gruppen wurde die Zellvitalität nach der Isolierung als auch vor der Transplantation mittels Real Time Live Confocal Imaging überprüft. Die in vivo Vitalität der transplantierten Inselzellen wurde mittels wöchentlicher Gewichts- und Blutzuckermessungen dokumentiert. Nach 120 Tagen wurde die Vaskularisierung der transplantierten Inseln unter der Nierenkapsel mittels invasivem Real Time Live Confocal Imaging überprüft.

Ergebnisse. Die Messungen der Zellvitalität, als auch funktionalen Parameter nach der Transplantation der Inselzellen unter die Nierenkapsel zeigen, dass ein simulierter Transport unter Rotationsbedingungen sich nicht negativ auf die Viabilität und Vitalität der Inselzellen auswirkt. Die mittels Real Time Live Confocal Imaging erhobenen Viabilitätsmessungen stimmen mit den funktionalen Messungen überein.

Schlussfolgerungen. Ein Transport unter Rotationsbedingungen ermöglicht die Aufrechterhaltung der Viabilität und Funktionalität von frisch isolierten murinen Inselzellen. Darüber hinaus konnten wir zeigen, dass Real Time Live Confocal Imaging als eine vielseitig einsetzbare Methode zur Qualitätssicherung eingesetzt werden kann.
as CD34bright, CD133+, CD45dim, CD31+ cells in the peripheral blood of liver transplanted recipients \((n=28)\) until day 20 post transplantation via FACS-analysis.

**Results.** An induction of CECs was exclusively observed for rATG-treated patients \((n=17)\) increasing from \(0.56\% \pm 0.98\%\) pre transplantation to \(1.83\% \pm 1.85\%\) at day \(1–2\) post transplantation compared with control patients receiving standard immunosuppression \((n=11)\) \((p<0.04)\). In addition, the induction of CPCs was even more pronounced illustrating an increase in rATG treated patients from \(0.20\% \pm 0.26\%\) pre transplantation to \(1.55\% \pm 1.75\%\) at day \(1–2\) post transplantation \((p<0.001)\). A significant elevation of blood CPCs is still detectable at day \(5\) \((p=0.0379\) compared with controls) and starts to decline at day \(10\) post transplantation.

**Conclusions.** In summary we illustrated that both CECs and CPCs were detectable in numbers that allows kinetic monitoring of these cell types post transplantation and that rATG treatment results in a transient induction. As clinical correlations between the concentration of these two populations and the effect of immunosuppressive regimens has been already proven, validation of these cell populations as biomarkers in the setting of solid organ transplantation remains to be determined.

### Lipocalin-2 as possible predictive marker of acute allograft rejection in patients undergoing liver transplantation

**N. Vallant, H. Maier, M. Kofler, P. Schumpp, S. Schneeberger, J. Pratschke, F. Aigner**

Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria

**Background.** Lipocalin-2 (Lcn-2) has been described as a marker and potential positive modulator of inflammation during ischemia/reperfusion injury (IRI) following solid organ transplantation. Data on Lcn-2 expression during allograft rejection have been missing so far.

**Methods.** Sera of 68 patients undergoing orthotopic liver transplantation were collected preoperatively and postoperative from day 1 to 15. Lcn-2 was analyzed by ELISA and expression levels were correlated with parameters of allograft rejection. Lcn-2 expression was further correlated with preexistent malignancy, postoperative renal failure and various immunosuppressive regimens.

**Results.** Lcn-2 serum levels were elevated 3 to 7 fold immediately after liver transplantation due to IRI and also increased prior to clinically diagnosed acute rejection, however not statistically significant \((p>0.05)\) but closely related to an elevation of routinely used laboratory parameters.

**Conclusions.** Our data suggest Lcn-2 to be a chemoattractant stimulus for infiltrating immune competent cells into the allograft following solid organ transplantation. It is an inflammatory marker which is upregulated during acute graft rejection and its elevation prior to routinely used parameters of acute rejection might be an important tool for therapeutic intervention.

### Effect of oxidative stress and endotoxin on albumin in brain death

**B. Leber**\(^1\), **V. Stadlbauer**\(^*\), **P. Stiegler**\(^1\), **S. Stanzer**\(^3\), **U. Mayrhauser**\(^1\), **S. Kistenbauer**\(^1\), **B. Leopold**\(^1\), **M. Sereinig**\(^1\), **A. Puntschart**\(^1\), **T. Stojakovic**\(^1\), **K. H. Tscheliessnigg**\(^1\), **K. Ott**\(^1\)

\(^1\)Division of Transplantation Surgery, Department of Surgery, Medical University of Graz, Graz, Austria; \(^2\)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; \(^3\)Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; \(^4\)Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria; \(^5\)Institute of Physiological Chemistry, Medical University of Graz, Graz, Austria; *Both authors contributed equally to this work.

**Background.** Albumin binds and detoxifies endotoxin in healthy people. Oxidative stress leads to protein oxidation and thus to impaired binding properties of albumin. This, in combination with increased gut permeability leads to appearance of endotoxin in the systemic circulation and further to impaired organ function. We hypothesise that these processes occur in serum of brain-dead organ donors.

**Methods.** Endotoxin was determined with an adapted limulus amoeocyte lysate assay. Albumin fractions and binding capacity were determined by HPLC. FlowCytomixTM was used for determination of cytokine levels.

**Results.** Eighty-four brain-dead organ donors were enrolled and categorized by the length of intensive care unit (ICU) stay. Albumin binding capacity for dansylsarcosine was reduced in brain-dead patients compared to controls. Endotoxin positivity in 16.7% of donors was associated with decreased binding capacity in donors and worse survival of recipients. Lengths of ICU stay increased albumin oxidation. In addition, IL-6, IL-8, IL-10 and IL-13 levels were elevated in patients, whereas IFN-γ levels were within the normal range.

**Conclusions.** We conclude that oxidative stress and systemic endotoxemia is present in brain-dead organ donors what might affect recipient survival. High endotoxin levels might be due to increased gut permeability and decreased binding capacity of albumin influenced not only by higher albumin oxidation.

### Evidence of lymphoid neogenesis in skin biopsies of human hand allografts during rejection

**T. Hautz**\(^1\), **B. Zeiler**\(^2\), **N. Isam**\(^3\), **F. Brandacher**\(^1,4\), **A. Weissnacker**\(^1\), **P. Cavadas**\(^3\), **R. Margreiter**\(^1\), **W. F. A. Lee**\(^1\), **J. Pratschke**\(^1\), **F. G. Lakkis**\(^3\), **S. Schneeberger**\(^1,4\)

\(^1\)Division of Transplantation Surgery, University of Innsbruck, Innsbruck, Austria; \(^2\)Department of Surgery, Medical University of Graz, Graz, Austria; \(^3\)Division of Transplantation Surgery, Medical University of Graz, Graz, Austria; \(^4\)Division of Transplantation Surgery, Medical University of Graz, Graz, Austria; *Both authors contributed equally to this work.
Background. Expression of peripheral-node-addressin (PNAd) on endothelial cells indicates presence of tertiary lymphoid organs (TLO) in chronic autoimmunity and allotransplantation. We herein investigated the expression of PNAd in skin biopsies of human hand allografts for evidence of TLO after composite tissue allotransplantation.

Methods. 167 skin biopsies of 11 hand allografts were collected over 10 years and assessed by HE-histology and immunohistochemistry using antibodies for PNAd, CD3, CD4, CD8, CD20, CD45, LFA-1, ICAM-1, E-selectin, P-selectin, VE-cadherin, HLA-DR, Psoriasin, IDO and Foxp3. Levels of PNAd expression was assessed semiquantitatively (% of PNAd+ vessels: 0, 1, 2, 3 and PNAd staining intensity: 0, 1, 2, 3) and correlated with rejection grade, characterization of the infiltrate, expression of adhesion molecules and time after transplantation.

Results. Rejection ranged from grade 0 to IV (mean score: 0.79 ± 1.05). Upon rejection, expression of PNAd was increased in endothelial cells (grade 0: 0.24 ± 0.48 vs. all grades of rejection: 0.44 ± 0.62). Most often PNAd expression was only found in few vessels (1–10%). PNAd staining intensity was increased the higher the grade of rejection (grade 0: 0.38 ± 0.76; grade I: 0.41 ± 0.74; grade II: 0.67 ± 0.80; grade III: 0.73 ± 0.91; grade IV: 0.50 ± 0.58). Intense PNAd-staining was associated with rejection grade, characterization of the infiltrate, expression of adhesion molecules and time after transplantation.

Conclusions. PNAd expression in endothelial cells is increased in skin biopsies of human hand allografts indicating presence of TLO. Further investigations are needed to enlighten the role of PNAd and TLOs in composite tissue allotransplantation.

Background. Excessive production of reactive oxygen species (ROS) is a major contributor to the development of ischemia-reperfusion injury (IRI) in the course of solid organ transplantation. In particular mitochondria-derived ROS are critical for the initiation and progression of IRI, which restricts the pool of donor organs and results in elaborate follow up treatments. In various in vivo (IR) and in vitro (hypoxia/reoxygenation, HR) models we observed a consistent pattern in the activation of key intracellular signaling pathways. Most strikingly the use of p38 specific inhibitors prevented mitochondrial ROS production and cell death. Here we further dissected the contribution of p38 to IR- and HR-induced damage and provide first evidence for a therapeutic benefit of p38 inhibition by BIBR-796 in vitro.

Methods. Kidney transplantation and kidney clamping in the rat were used for the induction of IRI. H/R was analyzed in HL-1 cardiomyocytes and primary MEFs. Intracellular signaling was monitored by using phosphorylation specific antibodies. Mitochondrial ROS levels were determined by imaging of Mitotracker Red CM-H2XROS. ROS/NOS-induced tissue damage was visualized by 3-nitrotyrosine specific antibodies. To assess acute kidney injury (AKI) HSP70 expression was monitored by immunoblotting, serum creatinine and urea were determined, and serum cystatin c and NGAL concentrations were measured by ELISA.

Results. The expression patterns for all p38 isoforms were established in HL-1 cells and siRNA-mediated knockdown of the predominant isoform (p38α) reduced ROS production, confirming the critical role of p38. Preliminary data suggested the requirement of MAPKAP kinase 2 (MK2) rather than the transcription factor ATF-2 downstream of p38. As observed in other settings reperfusion following kidney clamping or transplantation was marked by a profound increase in the activity of p38, its upstream kinases MKK3/6 and the putative effector MK2. Application of BIBR-796 prevented deterioration of kidney function following IR based on reduced serum creatinine, urea, cystatin c and NGAL levels in animals treated with the inhibitor. P38 inhibition also protected from oxidative damage. Thus the inhibition of p38 prevents key processes, which are essential for the development of IRI.

Conclusions. Inhibiting p38 signaling during IR and HR may provide a potent strategy for limiting IRI.

Targeting intracellular signaling pathways for the prevention of ischemia/reperfusion-induced damage during solid organ transplantation

M. I. Ashraf1, M. Ebner1, C. Wallner1, S. Sickinger1, M. Haller1, M. Hermann2, A. Soleiman1, S. Vallant1, R. Öllinger1, G. Brandacher1, J. Tropmpair1

The role of constitutively expressed nitric oxide synthases in ischemia-reperfusion-injury

B. Cardini1, K. Watschinger1, M. Hermann2, R. Oberhuber2, P. Obrist1, G. Brandacher1, J. Pratschke3, E. R. Werner1, M. Maglione3
Background. Single shot donor therapy with the essential nitric oxide synthase cofactor (NOS) tetrahydrobiopterin (H4B) was shown to attenuate ischemia-reperfusion-injury-related pancreatitis in a murine pancreas transplantation (PTX) model. Since underlying mechanisms of tetrahydrobiopterin-mediated protection are still controversially discussed, we aimed to investigate, whether the two constitutively expressed NOS-isoforms represent its major targets using endothelial (eNOS-/-) and neuronal NOS (nNOS-/-) knockout mice.

Methods. In a heterotopic PTX-model syngeneic C57BL6 mice (wild-type, eNOS-/- and nNOS-/-) were used as donor-recipient pairs. Non-transplanted animals served as controls. Following a reperfusion time of 4 h, graft microcirculation was analyzed by intravital fluorescence microscopy. Parenchymal damage as well as peroxynitrite-formation were assessed by H&E-staining and immunohistochemistry. H4B levels were determined by high-performance liquid chromatography (HPLC). Finally, all groups where tested for recipient survival.

Results. Compared to non-transplanted controls, prolonged CIT significantly worsened microcirculation in untreated wild-type and eNOS-/- grafts (p < 0.05), whereas no deterioration was measured in untreated nNOS-/-. While H4B-pre-treatment significantly restored capillary blood flow in wild-types and eNOS-/- (p < 0.01), no further beneficial effect was observed in nNOS-/- (p > 0.05). In contrast to untreated wild-type and eNOS-/- graft, nNOS-/- grafts developed minor parenchymal damage following prolonged CIT, which could be slightly ameliorated by tetrahydrobiopterin pre-treatment. There weren't any significant differences between the analyzed groups regarding intragraft nitrotyrosine formation. While H4B pre-treatment extended survival of all recipients, significantly prolonged recipient survival was also achieved if donors were untreated nNOS-/- (p < 0.01).

Conclusions. These observations in pancreatic grafts lacking nNOS suggest, that instead of the endothelial isoform, it is the neuronal isoform to be crucially involved in the promotion of tetrahydrobiopterin-mediated protection.

Nutrazeutika optimieren die Organfunktion in einem Rattenieren-Ischämie-Reperfusionsmodell

P. Gehwolf1, F. M. Struller1, A. Kostron1, M. Wolzt2, F. Bach1, L. Otterbein1, B. Wegiel1, J. Pratschke1, R. Öllinger1

1Division of Biological Chemistry, Biocenter, Medical University of Innsbruck, Innsbruck, Austria; 2Department of Anesthesiology and Critical Care Medicine, Medical University of Innsbruck, Innsbruck, Austria; 3Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria; 4Institute of Pathology, St. Vinzenz Hospital Zams, Zams, Austria

Grundlagen. Die zum Hämabbau notwendige induzierbare Hämoxigenase-1 (HO-1) wirkt stark antinflammatorisch und schützt vor Ischämie- und Reperfusionsschäden (IRS). Eine klinische Anwendung im Sinne einer HO-1-Induktion ist aufgrund der Hepatotoxizität der experimentell verwendeten HO-1-Indukto- ren nicht möglich. Ziel der Studie war es, natürlich vorkom- mende Nutrazeutika auf ihr Potential zur HO-1 Induktion zu untersuchen.

Methodik. Verschiedene Nutrazeutika wurden in Hinblick auf die HO-1-Induktion mittels PCR getestet. In einem etablierten Ratten-Nierenarterien-Klemmmodell wurde ein IRS gesetzt, Nierenfunktionsparameter und HO-1 Expression wur- den zu festgelegten Zeitpunkten bestimmt, histologische Untersuchungen wurde durchgeführt. Die Nutrazeutika wur- den 24 h vor Ischämie und unmittelbar nach Reperfusion oral appliziert.

Ergebnisse. Zwei der getesteten Nutrazeutika führten zu einer starken Hochregulation (Resveratrol: 11-fach, Ginseng: 17- fach) der HO-1 Expression. Im Nierenarterien-Klemmmodell kam es nach 48 Stunden zu einem Anstieg des Serum-Kreatinin von 0,38 mg/dl ± 0,07 auf 3,06 mg/dl ± 0,86 in den Kontrollieren. Die Applikation von beiden Nutrazeutika in einer Dosierung von 10 mg/kg (Resveratrol, 48h-Kreatinin 0,54 mg/dl ± 0,23) bzw. 30 mg/kg (Ginseng, 48h-Kreatinin 0,53 mg/dl ± 0,06) verhinderte dramatisch die Einschränkung der Nierenfunktion (p < 0,001 für beide vs. Kontrolle). Die kompetitive Antagonisierung durch SnPP (5 mg/kg/KG) konnte diesen positiven Effekt vermindern. Histologische und immunhistochemische Auswertungen unter- stützen die Ergebnisse.

Schlussfolgerungen. Die Anwendung von für Menschen ungefährlichen Nutrazeutika stellt eine ausgezeichnete Möglichkeit dar, die HO-1 zu induzieren und den IRS zu minimieren.

The novel compound 5'-methoxy leolign increases the ejection fraction of infarcted rat hearts by promoting CYP26B1-dependent angiogenesis

D. Wiedemann1,2, J. Kern2, S. Schweiger2, A. Trockenbacher2, B. Messner2,3, C. Steger2, N. Bonaros2, W. Schgör2, A. Kocher2, G. Laufer2, H. Stuppnner2, G. Untergasser2, D. Bernhard1,2

1Medical University of Vienna, Vienna, Austria; 2Medical University of Innsbruck, Innsbruck, Austria

Background. In times of organ shortage strategies to re-covery damaged organs seem to be valuable options to face this problem. Cellular based strategies to recover ischemic myocardium have shown promising experimental results but the clinical evidence is scarce. Especially the lack of angiogen-esis in cardiac peri-infarction and Infarction areas is one of the most important problems in functional cardiac recovery after myocardial infarction (MI). While searching for possible phar-macological strategies to stimulate angiogenesis after MI we conducted a screen for plant compounds with pro-neoangiog-enic properties.

Methods and Results. 5’-methoxy leolign, a compound isolated from the roots of Leontopodium alpinum (Edelweiss) potently stimulated endothelial cell migration, tube forma-
tion, and angiogenic sprouting in vitro, and angiogenesis in a chicken embryochorioallantoic membrane assay. 5'-methoxy leoligin was consequently analyzed in an in vitro rat MI model. The novel compound potently stimulated angiogenesis in the peri-infarction zone and led to a significant increase in the cardiac ejection fraction (plus 20% 28 days after MI) in animals treated with 5'-methoxy leoligin. Based on micro-array analyses followed by knockdown and over-expression experiments in vitro Cyp26B1 was identified as the central players in 5'-methoxy leoligin-induced angiogenesis induction.

Conclusion. The data presented herein indicate that 5'-methoxy leoligin induces angiogenesis in the peri-infarction area after MI via upregulation of Cyp26B1. 5'-methoxy leoligin-induced capillarisation is capable of partially restoring cardiac function after MI. Therefore this novel compound could be able to positively influence post MI myocardial remodeling and even induce myocardial recovery. This or other pharmacological strategies to induce neoangiogenes could preserve organ function and avoid several patients ending on the waiting list for cardiac transplantation.

Immunosuppression

095
Pediatric kidney transplantation in Vienna: 70 months of TABIC – tacrolimus based immunosuppression in children

V. Zaller, T. Müller-Sacherer, C. Aufricht
Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

Background. Based on international recommendations combined immunosuppression is used after kidney transplantation in children. A common regimen is based on steroids, mycophenolat-mofetil and cyclosporin A with IL-2 antagonist induction. One third of the patients had to be switched from cyclosporin A to tacrolimus, due to dermatologic cosmetic side effects. Thus, TABIC was established as a novel immunosuppressive regimen. Aim of the present registry is to perform quality assurance and to evaluate a risk/benefit analysis of the TABIC-regimen compared to previous immunosuppressive regimens in children undergoing kidney transplantation at our center.

Methods. In this observational single-center study, 32 consecutive patients undergoing kidney transplantation between December 2005 and October 2011 at our center, were enrolled. Patients who were not treated according to the TABIC-scheme served as a historic control. The end-point was a combination of death and graft loss.

Results. 5 patients (16%) had to be switched from tacrolimus to rapamycin due to side effects. Furthermore, 5 patients (16%) suffered from acute rejection, but no graft loss was observed. Within follow-up, no patient reached the combined end-point (100% kidney transplant as well as 100% patients survival). A Kaplan-Meier-analysis revealed a significantly better outcome for patients treated with the TABIC-scheme compared to controls (5 years event free survival, TABIC vs. non-TABIC: 100% vs. 79%, p = 0.048).

Conclusions. Our data show that the TABIC-regimen is efficient and safe compared to cyclosporin A based immunosuppression. Tacrolimus is associated with a significantly better graft and patient survival. Therefore, it should be considered as standard therapy after kidney transplantation in children.
096
Falsely elevated tacrolimus concentrations in two kidney allograft recipients using the affinity column-mediated immunoassay (ACMIA) method: identification of IgG isotype rheumatoid factor as causative endogenous antibodies

M. Antlanger¹, M. Hecking¹, J. Werzowa¹, M. Haidinger¹, M. Säemann¹, R. Schmid¹, G. Ziebinger¹
¹Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria; ²Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria; ³Institute of Immunology, Medical University of Vienna, Vienna, Austria

Background. Therapeutic monitoring of tacrolimus is currently performed employing ACMIA in several transplant centers. Here we report on two renal transplant patients displaying excessive tacrolimus levels either not corresponding to oral drug dosage or without taking the drug at all. Various antibodies, such as anti ds-DNA antibodies or heterophile antibodies, have been identified in previous cases of falsely elevated tacrolimus measurements and have been suggested as a possible cause for interaction with the tacrolimus assay.

Methods and Results. In our observations, both patients were on a stable, long-term tacrolimus-based immunosuppressive regimen. In the first patient the elevated tacrolimus trough levels were only observed after loss of graft function (6 years post-transplant) while the patient was not longer on tacrolimus, as the levels were only observed after loss of graft function (6 years post-transplant). The second patient currently still has a functioning graft, although he is taking minute amounts of tacrolimus. All rheumatoid and immunologic tests with immunoglobulin blocking reagents specific for the IgG isotype rheumatoid factor, which proved to be highly positive in both patients.

Conclusions. Our results show that certain patients with positive IgG isotype rheumatoid factor can exhibit false-positive tacrolimus trough levels when using the ACMIA assay. It can therefore be concluded that abnormally high drug levels should be verified by mass spectrometry methods. Further studies are underway to determine whether non-transplanted patients with positive rheumatoid factors also display falsely elevated tacrolimus values and also if this can be suppressed after preincubation with immunoglobulin blocking reagents specific for the IgG isotype rheumatoid factor.

097
Impact of vesico-ureteral reflux (VUR) after renal transplantation

G. Györi¹, M. Margreiter², G. Böhmig³, S. Trubel², F. Mühlbacher¹, R. Steininger¹
¹Department of Surgery, Medical University of Vienna, Vienna, Austria; ²Department of Urology, Medical University of Vienna, Vienna, Austria; ³Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

Background. The impact of vesico-ureteral reflux after renal transplantation has been a matter of debate in the past with small studies reporting controversial results. The aim of the present study was to evaluate the effect of early post-transplantation VUR on long-term renal allograft performance, incidences of urinary tract infections (UTI), rejection rates, graft and patient survival in a large cohort series.

Methods. Retrospective study of 646 consecutive renal transplant patients with routine post-transplantation vesico-cystourethrogram (VCUG). Uretero-neocystostomy was performed in an antirefluxive fashion using extravesical submucosal tunneling. VCUG was performed prior to discharge according to the international grading system and reviewed by an independent radiologist and urologist.

Results. Overall, 263 of the 646 (40.7%) kidney transplant recipients were diagnosed with VUR by VCUG at discharge. Patients had VUR grade I, II, III and IV in 7.9%, 19.8%, 10.2%, and 2.8%, respectively. No grade V reflux was seen. VUR showed no significant impact on death-censored graft survival, patient survival, proteinuria or UTI. Patients with VUR had a significantly lower GFR at one year after transplantation than patients without VUR (60 vs. 52 ml/min/1.73 m², p = 0.021), this difference was no longer seen at 3 and 5 years.

Conclusions. Although VUR is a common finding in patients after renal transplantation, it has no impact on death-censored graft survival, patient survival, proteinuria or UTI and only a short term effect on renal graft function that was no longer seen in long term follow up.

098
Pathologische de novo Detektion von heptozellulären Karzinomen nach Lebertransplantation

G. Györi, V. Hoffmann, G. Silberhummer, F. Mühlbacher, G. Berlakovich
Klinische Abteilung für Transplantation, Universitätsklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich
Grundlagen. Der Einfluss von primär unentdeckten hepatzellulären Karzinomen (HCC) auf das Überleben nach Lebertransplantation wird in der Literatur kontrovers diskutiert. Ziel dieser Studie war es, die Rate von okkulten Karzinomen in unserem Kollektiv an alkoholtoxischer Zirrhose zu erheben und den Einfluss auf das rezidivfreie und Gesamtüberleben nach Lebertransplantation zu untersuchen.

Methodik. Retrospektive Analyse von 285 wegen alkoholtoxischer Zirrhose gelisteten und transplantierten Patienten im Zeitraum von 1998 bis 2008. Neben den Baseline Parametern wurden alle Explantihistologien ausgewertet.

Ergebnisse. Dreizehn Patienten (4,5 %) zeigten ein HCC in der Explantihistologie. Drei Patienten waren außerhalb der Mailand Kriterien und 2 von 19 Herden waren größer als 1 cm. Die Warteszeit der Patienten betrug im Median 2,7 Monate. Nach 2004 gab es keine okkulten HCCs in unserem Kollektiv. Ein Überlebensnachteil für Patienten mit okkultem HCC gegenüber der Normalgruppe konnte in diesem Kollektiv nicht gezeigt werden.

Schlussfolgerungen. Die kurze Wartezzeit der Patienten mit okkultem HCC sowie die Tumorgröße legt nahe, dass bei diesen Patienten bereits vor der Listung das HCC unentdeckt blieb, während es später mit Verbesserung der radiologischen Technik sowie längerer Wartezzeit im Rahmen des Screenings entdeckt wurde. Rein deskriptiv zeigte sich in unserem Kollektiv kein Überlebensnachteil für Patienten mit okkultem HCC.

Ist die ungeplante Reoperation nach Nierentransplantation ein Indikator für Organverlust?

K. Huber1, A. Krause1, O. Gangl1, W. Enkner1, R. Oberbauer2, R. Függer2
1Chirurgische Abteilung, Krankenhaus der Elisabethinen Linz, Linz, Österreich; 23. Interne Abteilung für Nieren- und Hochdruckerkrankungen, Transplantationsmedizin, Rheumatologie, Krankenhaus der Elisabethinen Linz, Linz, Österreich

Grundlagen. Ungeplante Reoperationen dienen als Indikator der Qualitätskontrolle in der Chirurgie. Daten für die Nierentransplantation liegen noch nicht vor.

Methodik. Retrospektive Analyse von 320 Nierentransplantationen zwischen 2002 und 2010. Die Anzahl der ungeplanten Reoperationen und Ursachen, Mortalität, Kreatininpiegel 1 Monat und 1 Jahr post TX und die Art der Immunsuppression in Bezug zum Organverlust wurden als mögliche Risikofaktoren evaluiert.

Ergebnisse. In der Analyse unseres Patientenkollektivs (320 Nierentransplantationen über 160 Monate) zeigt sich eine 14 %ige Reoperationsrate, dies entspricht 46 Reoperationen, wobei bei 16 % der Reoperierten mehr als eine Reoperation notwendig war. Ursächlich dafür waren vordergründig Gefäßkomplikationen (30 %) gefolgt von Hämatomausrimungen und Wundinfektionen, welche einer operativen Sanierung bedurften (28 %). Sel tener kam es zu Reoperationen aufgrund urologischer Ursachen (20 %), Lymphozeelen und abdomineller Komplikationen (je 6,5 %). Von insgesamt 40 Organverlusten waren 17 bei reoperierten Patienten (das entspricht 43 % der reoperierten Patienten) und 23 (9 %) bei nicht reoperierten Patienten zu verzeichnen (p < 0,001). In der Subanalyse der Komplikationen, welche zu Reoperationen führten, sind Gefäßkomplikationen die häufigste Ursache für vorzeitigen Organverlust (64 %, das entspricht 9 von 14 Reoperationen vs. 33 % bei Lymphozelen, 33 % bei abdominellen Komplikationen, 31 % bei Weichteilproblemen und 11 % bei urologischen Komplikationen). In Bezug zur Immunsuppression konnten keine statistisch signifikanten Unterschiede erhoben werden. Ein erhöhtes Serum-Kreatinin nach 1 Monat (Kreatinin >2) fand sich bei 42 % der reoperierten vs. 16,5 % der nicht reoperierten Patienten (p < 0,001). Nach einem Jahr war das Kreatinin bei 37 % der reoperierten Patienten >2, hingegen nur bei 16,5 % der nicht reoperierten Patienten (p = 0,005). Patienten mit Organverlust innerhalb des ersten Monats bzw. verstorbenen Patienten wurden aus den Berechnungen ausgeschlossen.

Schlussfolgerungen. Komplikationen mit chirurgischem Interventionsbedarf nach Nierentransplantation sind statistisch signifikant häufiger mit einem vorzeitigen Organverlust assoziiert als Transplantationen mit komplikationslosem Verlauf. Ebenso ist die Transplantatfunktion gemessen am Serum-Kreatinin bei reoperierten Patienten signifikant schlechter. Insbesondere vas kuläre Komplikationen prädisponieren zu einem frühzeitigen Organversagen.

Transösophageale Echokardiographie bei Patienten mit Ösophagusvarizen im Zuge der orthotopen Lebertransplantation

M. Thum1, R. Schwarzer1, R. Karatosic2, U. Burger-Klepp2, V. Fuhrmann2, G. Berlakovitch1, A. Bacher2, P. Faybik2
1Klinische Abteilung für Transplantation, Universitätsklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich; 2Klinische Abteilung für Allgemeine Anästhesie und Intensivmedizin, Universitätsklinik für Allgemeine Anästhesie, Intensivmedizin und Schmerztherapie, Medizinische Universität Wien, Wien, Österreich; Klinische Abteilung für Hepatologie und Gastroenterologie, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Wien, Österreich

Grundlagen. Das intraoperative Monitoring mittels transösophagealer Echokardiographie (TEE) während orthotoper Lebertransplantation (oLT) wird bei Patienten mit Anzeichen für portale Hypertension divers diskutiert. Das Ziel dieser retrospektiven Analyse ist es, die Risiken von möglichen Ösophagus- bzw. Magenblutungen zu evaluieren.

Methodik. Retrospektive Analyse von 396 Patienten an der Medizinischen Universität Wien, die zwischen 2002 und 2010 während oLT mittels TEE überwacht worden sind. Wir analysier ten Ösophago-Gastroskopie-Berichte (portale hypertensive Gastro pathie, Qualität und Lage der Varizen), Labor-Parameter und die Verwendung von Blutprodukten während der oLT bei jedem Empfänger.

Ergebnisse. Varizen wurden mittels Ösophago-Gastroskopie in 287 (72,5 %) von 396 untersuchten Patienten dokumentiert, wobei nur in einem Fall schwere Blutungen aus
Entwicklung des Anteils an Leberverspender mit erweiterten Spenderkriterien innerhalb der letzten Dekade an der Universitätsklinik für Transplantationschirurgie Wien

R. Schwarzer 1, M. Thum 1, M. Pones 2, J. Machalek 3, I. Kristo 1, G. Berlakovich 1, T. Soliman 1, S. Roka 1, F. Mühlbacher 1, R. Steininger 1

1 Klinische Abteilung für Transplantation, Universitätsklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich; 2 Universitätsklinik für Kinderchirurgie, Medizinische Universität Wien, Wien, Österreich; 3 Universitätsklinik für Frauenheilkunde, Medizinische Universität Wien, Wien, Österreich

Grundlagen. Die Anzahl der jährlich durchgeführten Lebertransplantationen ist von der Anzahl der gemeldeten Organ spendern abhängig. Allerdings eignet sich nicht jeder Organspender als Leberverspender. Ziel dieser Studie ist es, die Evolution der Leberverspender innerhalb der letzten 10 Jahre zu verfolgen.

Methodik. Hierfür wurden die Daten aller Spender von 2000 bis 2001 sowie die von Juni 2009 bis Juni 2011 erhoben, die der Universitätsklinik für Transplantationschirurgie gemeldet wurden. Es wurde untersucht, wie viele Leberverspender erweiterte Spenderkriterien [extended donor criteria (EDC)] erfüllten. Zu den EDC zählen: Serum Natrium > 165, GOT > 90, GPT > 105, Spen deralter > 65 Jahren, BMI > 30 und ein Bilirubin > 3 U/L.

Ergebnisse. Zwischen 2000 und 2001 eigneten sich 67% (103/153) der Spender als Leberverspender. Zehn Jahre später eigneten sich 51% (78/153) als Leberverspender. Zwischen 2000 und 2001 erfüllten 28,2% der Spender (29/103) EDC (23 Spender mit 1 EDC und 6 Spender 2 EDC). Zwischen Juni 2009 und Juni 2011 erfüllten 48,7% der Spender (38/78) EDC (25 mit 1, 12 Spender 2 und 1 Spender 3 EDC). Bei der Gegenüberstellung der Parameter Geschlecht, Spendergewicht, Spendergröße, Todesursache und Liegezeit in den beiden Perioden konnte kein ersichtlicher Trend erkannt werden.

Schlussfolgerungen. Innerhalb der letzten 10 Jahre kann man zum einen einen Rückgang der Leberverspender und zum anderen einen Anstieg an Leberverspender mit EDC feststellen.
Orthotopic liver transplantation (OLT) under the use of a protective filter against phototoxicity in a patient suffering from erythropoietic protoporphyria (EPP) with liver cirrhosis

A. Bradatsch, S. Schaffellner, D. Kniepeiss, D. Wagner, S. Pirker, K. H. Tschelissnigg
Division of Transplantation Surgery, Department of Surgery, Medical University of Graz, Graz, Austria

Background. Erythropoietic protoporphyria (EPP) is a rare condition arising from a deficiency in the enzyme ferrochelatase, leading to abnormally high levels of protoporphyrin in the tissue. Apart from increased photosensitivity leading to acute and chronic skin changes, in a small number of cases protoporphyrin deposits and pigment loading of the hepatocytes cause liver cirrhosis. In these patients liver transplantation is the therapy of choice. Nevertheless intestinal ulceration, bleeding and ultimately multiorgan failure can occur if no protective measures are taken against phototoxic injury during surgery.

Methods and Results. We would like to present the case of a 36-year-old patient who was admitted to our department for liver transplantation. EPP had been diagnosed 32 years ago. The patient suffered from typical skin changes and cholestatic liver cirrhosis had been histologically confirmed. OLT was performed successfully using protective measures to prevent phototoxic injury to the abdominal organs. A flexible yellow filter omitting wavelengths below 470 nm was applied to operating room luminaires to avoid phototoxic injury while maintaining visual colour perception of the surgeons. The immediate postoperative period was without any complications related to the EPP. Seven months after transplantation the patient is in good general health and liver function tests show good results.

Conclusions. OLT is a suitable treatment for patients suffering from EPP with hepatic involvement and cholestatic cirrhosis if protective measures against phototoxic injuries are used during surgery.

Bullous pemphigoid 11 years after bilateral hand transplantation

T. Hautz1, A. Weissenbacher1, B. Zelger2, H. Müller2, B. G. Zelger3, J. Pratschke1, S. Schneeberger2

1Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria; 2Department of Dermatology and Venerology, Medical University of Innsbruck, Innsbruck, Austria; 3Institute of Pathology, Medical University of Innsbruck, Innsbruck, Austria

Case Report. 11 years after bilateral hand transplantation a patient developed a bullous pemphigoid (BP), which is an autoimmune blistering skin disease, characterized by autoantibodies targeting the type XVII collagen component of hemidesmosomes in the skin basement membrane zone. This is the first report on an autoimmune complication in a patient after vascularized composite allotransplantation (VCA). The patient showed a quite
uneventful course after transplantation with only three mild acute rejection episodes within 11 years. Due to a fracture of the right allograft radius requiring surgery at 10.5 years posttransplant immunosuppression (IS) was switched from sirolimus-monotherapy to prednisone. One month thereafter the patient experienced metabolic deterioration (hypothyroidism, hyperlipidemia and hyperglycemia) and developed an exanthema and pruritus on the trunk and the upper extremities, including both the recipient’s own skin and the allograft skin. BP was diagnosed upon direct immunofluorescence of skin biopsies (linear C3 and IgG deposits along the basement membrane zone) and detection of serum autoantibodies against the BP antigen 2 (BP180nc16a: 142 U/l). Histology showed a partial separation along the dermal-epidermal junction and a mild perivascular infiltration consisting of lymphocytes, eosinophils and granulocytes. Cell counts were within normal range. No donor specific antibodies were detected. Skin lesions disappeared under intensified therapy with prednisone. While conversion of IS and metabolic deterioration might have contributed to development of BP after hand transplantation, the pathomechanism remains unclear.

Belatacept treatment for 2 years after liver transplantation is not associated with overt immunomodulation

C. Schwarz, S. Rasoul-Rockenschaub, T. Soliman, G. Berlakovitch, R. Steininger, F. Mühlbacher, T. Wekerle

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

Background. Belatacept is a costimulation blocker with immunomodulatory properties in the experimental setting. Moreover, the liver graft itself has been claimed to have ‘tolerogenic’ properties. The belatacept multi-center phase II liver transplantation trial was terminated during the long-term extension period on the recommendation of the Data Monitoring Committee. This situation gave us the unique opportunity to evaluate the minimum immunosuppression required in liver transplant recipients after > 2 years of treatment with belatacept.

Methods. In our center all belatacept patients (n = 4) were switched to MMF monotherapy (2 g/C2 1 g/day) after discontinuation of belatacept. We prospectively assessed the occurrence of acute rejection and evaluated kidney function (calculated GFR; MDRD) over time in comparison to tacrolimus-treated patients enrolled in the control groups of the multi-center trial (n = 4).

Results. The mean period from transplantation to withdrawal of belatacept was 30 months (range 25–35). GFR at the time of withdrawal was more than 60 ml/min/1.73 m² in the belatacept group (4/4; mean: 101 ml [range 89–114]), whereas 3 out of 4 patients in the control group had a GFR below 60 ml/min/1.73 m² with a mean of 57.92 ml/min/1.73 m² (range 36–98) (p = 0.026). Five months after belatacept discontinuation kidney function declined on average by 19.22 ml (range –45 to +3.5) (follow-up ongoing). After belatacept withdrawal all 4 patients developed 3-fold elevated liver enzymes (ASAT, ALAT) within 10.3 weeks after EOT (7–14). Patients were therefore switched to triple therapy with corticosteroids, CNIs and MMF. Graft dysfunction resolved within one to three weeks after switch.

Conclusions. Consistent with results from the multi-center trial, patients treated with belatacept showed better kidney function compared to those treated with CNIs. MMF monotherapy following withdrawal of belatacept is associated with a high risk of rejection. Thus belatacept has no obvious immunomodulatory effect in liver transplant recipients that would be sufficient to allow a high success rate of minimization strategies.

Ausgezeichnete Blutdruckkontrolle nach Nierentransplantation durch antihypertensive Mehrfachtherapie – Entwicklungen der letzten 20 Jahre

K. Hohenstein¹, A. Habicht¹, T. Prikoszovich¹, D. Dunkler², B. Watschinger¹

¹Klinische Abteilung für Nephrologie und Dialyse, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Wien, Österreich; ²Institut für Medizinische Statistik, Informatik und intelligente Systeme, Medizinische Universität Wien, Wien, Österreich

Grundlagen. Studien der letzten Jahre weisen auf die Bedeutung der arteriellen Hypertonie für das Organ- und Patientenüberleben nach Nierentransplantation hin. Ziel der vorliegenden Studie ist es zu untersuchen, ob sich seit 1990 die Blutdruckkontrolle und die Art der antihypertensiven Therapie bei nierentransplantierten Patienten verändert/verbessert hat.

![Systolischer RR (mmHg)](image1.png)

![Diastolischer RR (mmHg)](image2.png)
Methodik. Bei 836 Patienten mit funktionierendem Transplantat ein Jahr nach der Transplantation, die in unterschiedlichen Perioden 1990/1991 (n = 129), 1995/1996 (n = 103), 2000/2001 (n = 188), 2002/2003 (n = 128), 2004/2005 (n = 138) und 2008/2009 (n = 150) transplantiert und in unserem Zentrum nachbetreut wurden, wurden die Anzahl der antihypertensiven Medikamente, sowie die im Rahmen von Patientenselbstmessungen erhobenen Blutdruckwerte analysiert.

Ergebnisse. Seit 1990, vor allem aber zwischen 1996 und 2000 kam es zu einem deutlichen Anstieg antihypertensiver Mehrfachkombinationstherapien (Anstieg der mittleren Zahl von Substanzklassen von 1,9 ± 1,2 (1990/1991) auf 2,6 ± 1,5 (2008/2009), p < 0,001). Parallel dazu ist sowohl im systolischen, als auch im diastolischen Blutdruck ein signifikanter Abfall in normotone Blutdruckbereiche nachweisbar (p < 0,001) (Abb. 1). Im Beobachtungszeitraum kam es gleichzeitig zu einem signifikanten Anstieg des Empfängeralters von 46,8 (2001) auf 52,6 ± 14,3 Jahre.

Schlussfolgerungen. In den letzten 15 Jahren ist es gelungen die Blutdruckeinstellung nierentransplantierter Patienten wesentlich zu verbessern. Dies gelang durch den verstärkten therapeutischen Einsatz antihypertensiver Mehrfachkombinationen. Ähnlich wie in anderen Studien sind im Mittel zwei bis drei Substanzen notwendig, um normotone Blutdruckwerte unter 130/80 mmHg zu erzielen.

Bei Patienten, die auf der Leberwarteliste stehen, korrelieren ösophagoastrale Varizen mit dem Grad der Lebererkrankung

R. Schwarzer1, M. Thum1, R. Karatosic2, U. Burger-Klepp2, V. Fuhrmann3, G. Berlakovich1, A. Bacher2, P. Faybik2

1 Klinische Abteilung für Transplantation, Universitätsklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich; 2 Universitätsklinik für Anästhesie, Allgemeine Intensivmedizin und Schmerztherapie, Medizinische Universität Wien, Wien, Österreich; 3 Klinische Abteilung für Gastroenterologie und Hepatologie, Universitätsklinik für Innere Medizin III, Medizinische Universität Wien, Wien, Österreich

Grundlagen. Patienten mit terminalen Lebererkrankungen entwickeln gehäuft Ösophagusvarizen auf Basis einer portalen Hypertension. Ziel dieser Studie ist es, die Inzidenz von Ösophagusvarizen und deren Korrelation mit dem Grad der Lebererkrankung bei Patienten, die auf der Leberwarteliste stehen, zu erheben.

Methodik. Hierfür wurden die Daten von 512 Patienten, die zwischen 2002 und 2010 an der Universitätsklinik für Chirurgie lebertransplantiert wurden, analysiert. Patienten, die die Lebertransplantation aufgrund eines akuten Leberausfalls benötigten und solche, bei denen die Daten unvollständig waren, wurden aus der Studie ausgeschlossen. Somit umfasste die Studie 396 Patienten (77 %). Die Ergebnisse werden median in der 25. und 75. Perzentile angegeben.

Ergebnisse. Die Lebertransplantierten waren im Median 54 (48–60) Jahre alt. Im Median lagen 227 Tage (125–368) zwischen der letzten Ösophagogastroduodenoskopie und der Lebertransplantation. 287 Patienten (72,5 %) zeigten Varizen: 130 (32,8 %) Varizen Grad I (< 5 mm bei Insufflation) und 157 (39,6 %) Varizen Grad II (> 5 mm bei Insufflation). Red Spot Signs fand man bei 40 Patienten (10,1 %). 82,2 % der Varizen lokализierten sich im Ösophagus, 42,2 % im Magen und 13,6 % im Ösophagus und Magen. Patienten mit ösophagealen Varizen zeigten signifikant niedrigere Serum-Natrium Werte und Thrombozytenzahlen und signifikant höhere Ammoniak-Spiegel, Prothrombinzeiten und MELD-Scores als solche ohne Varizen.

Schlussfolgerungen. Ösophagusvarizen treten gehäuft bei Patienten mit terminalen Lebererkrankungen auf und werden von einer Verschlechterung der Labor- und MELD-Werte begleitet.

Transplant Procurement Management training courses in transplant coordination, a way to increase donation rates? – a single center analysis

M. Thum, R. Schwarzer, I. Kristo, M. Zyskowski, S. Róka, T. Soliman, G. Berlakovich, R. Steininger, F. Mühlbacher

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

Background. A project called Transplant Procurement Management (TPM) was created in Barcelona, Spain. The aim of this project is to provide profound knowledge and skills for health care professionals, working in the transplantation field with the final purpose of promoting and increasing donation rates. We evaluated the effects of this program on donor outcome and the organ procurement in a single center analysis.

Methods. Number of donor procurements over a 1-year period, from June 1st, 2010 to May 31st, 2011, evaluated at the transplant center of the Medical University Vienna, the six-month period before and after participation in the TPM-course (Nov 22nd to Nov 26th, 2010).

Results. In the 1st evaluation period from June 1st to Nov 30th, 2010 74 potential donors were reported in our center out of which 31 became actual donors. Within the 43 missed donors 23 did not fulfill brain dead criteria. Moreover twelve donors could not be realized because of their co-morbidities and eight due to opposition against organ donation. In the comparable 2nd period from Dec 1st to May 31st, 2011 we registered an increase of 42 actual donors out of 69 potentials. Thirteen donors were missed because of an unaccomplished brain dead criteria. Moreover eight donors were lost due to their co-morbidities and six because of opposition against organ donation. However during this evaluation period the donor rates increased for about 35 %. The procurement of transplantable kidneys increased from 60 to 66, transplantable lungs increased from 12 to 13 and in liver procurement, we could even register an increase from 13 to 22 transplantable organs. These results show a remarkable effect of this training program as well as the fluctuation of potential donors and the diverse potential of organ recovery during this year.

Conclusions. After all training programs in organ donation are an interesting field and seem to increase organ donation rates. Efforts have to be made to provide and spread profound knowledge and skills for health care professionals, working in the transplantation field.
Die Enteroskopie als neue Methode des immunologischen Monitorings nach Pankreastransplantation

C. Margreiter¹, F. Aigner¹, T. Resch¹, A.-K. Berenji¹, R. Oberhuber¹, R. Sucher¹, L. Veits¹, R. Öllinger¹, R. Margreiter¹, J. Pratschke¹, W. Mark¹

¹Universitätsklinik für Viszeral-, Transplantations- und Thoraxchirurgie, Medizinische Universität Innsbruck, Innsbruck, Österreich; ²Institut für Pathologie, Medizinische Universität Innsbruck, Innsbruck, Österreich

Grundlagen. Obwohl die perkutane Biopsie als Goldstandard für die Diagnosesicherung einer Pankreastransplantatabstoßung gilt, wird diese in den meisten Zentren aufgrund der damit verbundenen möglichen Komplikationen nicht durchgeführt. Dennoch ist eine sichere Abstoßungsdagnostik unabdingbar und kann besonders in Fällen einer solitären Pankreas- oder Pankreas-nach-Nierentransplantation schwierig sein, wenn kein Nierentransplantat als Indikatororgan vorhanden ist.

Methodik. Alle pankreastransplantierten Patienten, die zwischen Mai 2005 und September 2009 enteroskopiert wurden, fanden Eingang in diese retrospektive Studie. Die Untersuchung wurde mittels Doppelballonenteroskop oder pädiatrischem Colonoskop durchgeführt. Die Biopsien wurden entsprechend dem Abstoßungsschema bei Diätadaptationstherapie von Grad 1 bis 4 klassifiziert.

Ergebnisse. Insgesamt wurden 102 Enteroskopien an 79 Pankreastransplantatempfängern (65 kombinierte Nieren-Pankreas-Transplantationen, 13 Pankreas-nach-Nieren und vier solitäre Pankreastransplantationen) durchgeführt. Dreizehnsechzig Patienten unterzogen sich einer Enteroskopie, von den Patienten hatten zwei und sechs Patienten hatten drei oder mehr. Die Indikation dafür waren Protokollenteroskopen (n = 73), Verschlechterung der Transplantatfunktion (n = 17), gastrointestinalen Blutungen (n = 3) und andere (n = 3). Das Duodenalsegment konnte in 76 Fällen (73 %) erreicht werden, in 23 Fällen zeigte sich dabei ein auffälliger Befund. Schleimhautbiopsien konnten in 69 Fällen gewonnen werden. Diese ergaben in 49 Fällen (71 %) eine unauffällige Histologie und in elf Fällen eine akute Abstoßung. Alle Untersuchungen verliehen komplikationsfrei.

Schlussfolgerungen. Diese Serie an Enteroskopien zeigt die endoskopische Zugänglichkeit des Pankreastransplantatates bei proximaler Anastomose des Duodenalsegmentes bei exokrin-enterischer Drainage. Dabei bietet sich die Möglichkeit zur Intervention und Biopsie für eine verlässliche Abstoßungsdagnostik.

Transplantportal

S. Blum, B. Vetr

3. Interner Abteilung für Nieren- und Hochdruckerkrankungen, Transplantationsmedizin, Rheumatologie, Krankenhaus der Elisabethinen Linz, Linz, Österreich

Recipient and donor body mass index (BMI) as important risk factors for delayed kidney graft function

A. Weißenbacher¹, M. Jara¹, M. Biebl¹, H. Ulmer², T. Resch¹, P. Gehwolf¹, C. Bösmüller¹, J. Pratschke¹, R. Öllinger¹

¹Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria; ²Department of Medical Statistics, Informatics and Health Economics, Medical University of Innsbruck, Innsbruck, Austria

Background. Recipient obesity is associated with worse outcome after kidney transplantation, whilst the number of overweight patients on the waiting list is increasing. We investigated
whether donor and/or recipient BMI correlate with the occurrence of delayed graft function (DGF) after kidney transplantation.

Methods. Retrospective analysis of 1132 consecutive cadaveric kidney transplants between 01/2000 and 12/2009. Recipients/donors were divided into four groups according to their BMI (<20, 20–25, >25–30, >30). DGF was defined as the requirement for more than one dialysis within the first post-transplant week. Impact of recipient-, donor- and transplant-characteristics were analyzed using uni- and multivariate analyses.

Results. Overall DGF rate was 32.4%, mean BMI was 23.75 (SD ± 3.8) for all recipients and 24.68 (SD ± 3.6) for all donors (median age 44.0; 40.3% female). In univariate analyses DGF rate was 25.2%, 29.8%, 40.9% and 52.6% in recipients with a BMI < 20, 20–25, >25–30 and >30, respectively (p < 0.0001). Donor BMI < 20, 20–25, >25–30 and >30 resulted in a DGF rate of 22.5%, 31.0%, 37.3% and 51.2% (p < 0.0001) in univariate analyses. Acute rejection (AR) rate in the DGF-group was 24.9% vs. 9.7% (p < 0.0001). BMI in AR-group was 24.72 vs. 22.4 (p 0.0001). Multivariate analyses revealed overweight in the recipient as an independent risk factor for DGF.

Conclusions. Not only recipient but donor BMI as well closely correlates with the incidence of DGF after cadaveric kidney transplantation. Awareness thereof should have an impact on peri- and post transplant measures in order to avoid DGF and complications thereof in cadaveric renal transplant recipients.

Thorakale Transplantation

Upregulation of MMPs and no evidence of chromosomal changes in Mounier-Kuhn Syndrome: report of a case

K. Hoetzenecker1, A. Mitterbauer1, P. Birner2, M. Mildner3, H. Prosch1, B. Streubel2, W. Klepetko1, H. J. Ankensmit1

1Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria; 2Department of Dermatology, Medical University of Vienna, Vienna, Austria; 3Department of Radiology, Medical University of Vienna, Vienna, Austria; *Both authors contributed equally to this work.

Background. The Mounier-Kuhn syndrome (MKS) is a rare disease characterized by a pathological dilation of the trachea and the bronchial system. The etiology of the disorder remains elusive but genetic alterations and degradation of elastic fibers are thought to be involved in the pathogenesis. No causative treatment is available although transplantation is an option for endstage disease. Here, we describe a patient suffering from MKS who received a lung transplant at our department.

Methods. A 39-year-old male never-smoker presented at our department for evaluation for a lung transplant. The patient suffered from Mounier-Kuhn syndrome (MKS) with greatly dilated trachea and bronchi. Since a familial clustering of Mounier-Kuhn syndrome is discussed in the literature, we performed a chromosomal analysis and an array-CGH to search for genetic abnormalities. At the time of transplantation we collected samples from the bronchi and performed hematoxylin and eosin (HE), Elastic van-Gieson’s (EVG) and immunohistochemical stains. Specimens of main bronchi from the donor lung harvested for transplant served as control.

Results. The chromosomal analysis and array-CGH revealed that the patient’s genome was completely unremarkable, the karyogram as well as the genome hybridization showed no significant gain or loss in known encoding regions. Through the histological evaluation we found considerably lower amounts of elastic and collagen fibers in the submucosal layer in the patient compared to healthy controls. Furthermore inflammatory infiltrates were present in the connective tissue throughout the whole histological specimen. Since chronic inflammation is known to result in tissue remodeling we performed immunohistological staining of different matrix metalloproteinases. MMP1, MMP2, MMP3 and MMP9 were detected in MKS tissue, but were totally absent in control bronchi.

Conclusions. Based on these findings we hypothesize that the pathophysiology of MKS is of a chronic inflammatory type leading to tissue destruction and a loss of elastic fibers, possibly due to upregulation of MMP. The triggering mechanism(s) for this inflammatory reaction remain elusive, but since MKS has been reported to be associated with autoimmune diseases, an autoimmune reaction against components of the major airways could be one possible explanation.

Influenza infection in lung transplant recipients 2010/2011

M.-B. Ernst1, P. Jakusch1, T. P. Kraupp2, R. Strassl6, C. Hongis1, A. Scheed1, C. Aigner1, G. Lang1, S. Taghavi1, W. Klepetko1

1Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria; 2Department of Virology, Medical University of Vienna, Vienna, Austria

Background. Lung transplant recipients (LTRs) are uniquely predisposed in developing severe complications associated with community acquired respiratory viral infections (CARV). We report the outcomes of influenza infections in a cohort of 82 screened lung transplant recipients at our center.

Methods. Data were collected from December 2010 to March 2011 on using real-time polymerase chain reaction (PCR) from nasal secretion. During this period 245 patients frequented our out patient department for thoracic surgery. All LTRs (n = 82) with respiratory symptoms were screened. There were 9 (10, 9%) confirmed cases. H1N1 infection was diagnosed in 5, influenza B in 4 lung transplant recipients, median age 36 (26–65) years, with a median of 6 (1,1–12) years post lung transplantation.

Results. All patients with BOS grade 0 (bronchiolitis obliterans syndrome, n = 5) were treated symptomatically alone, with no further impact on their lung function. Two patients of this group were vaccinated for seasonal influenza. Among the group of patients with pre-existing BOS (n = 4), two lung transplant recipients, one with BOS I, the other with BOS II developed...
Ischämiezeit der rechten Lunge betrug 340 Minuten und links versehene Antibiotika werden am häufigsten als Ursache für interstitielle toxischen Nebenwirkungen auf den Respirationstrakt genannt. Bronchoskopie eine offene Lungenbiopsie durchgeführt, welche eine Lungenfibrose mit funktionell reduzierten Werten: VC 3,49 l, FEV1 3,28 l, MEF50 6,52 l und TLC 5,88 l. Logisch bereits der Verdacht auf eine Amiodaron-induzierte Lungenfibrose nach Herztransplantation erhielt. Zu diesem Zeitpunkt bestand radiologisch bereits die Verdacht auf eine Amiodaron-induzierte Lungenfibrose mit funktionell reduzierten Werten: VC 3,49 l, FEV1 3,28 l (86%), MEF50 6,52 l (135%) und TLC 5,88 l (84%). Der postoperative Verlauf gestaltete sich aufgrund einer respiratorischen Einschränkung zunehmend. Der Weaningprozess gestaltete sich aufgrund einer veno-arteriellen ECMO Unterstützung durchgeführt. Die ECMO konnte am Ende der Operation bei hämodynamisch und respiratorisch stabilen Verhältnissen wieder explantiert werden. Die Inschämiedauer der rechten Lunge betrug 340 Minuten und links 460 Minuten. Am 19. postoperativen Tag konnte der Patient auf die Normalstation verlegt und nach weiteren 23 Tagen aus dem Krankenhaus entlassen werden.

Schlussfolgerungen. Entgegen der allgemeinen Erwartung, dass eine Fibrose unter immunsuppressiver Therapie ein geringes Risiko für Progression hat, zeigte sich in diesem Fall eine dramatische Entwicklung nach der Herztransplantation. Deshalb sollte eine Lungenfibrose vor einer HTX genau abgeklärt und engmaschige postoperative Kontrollen durchgeführt werden.

**115**

Lungentransplantation bei medikamentös induzierter Lungenfibrose nach Herztransplantation

A. Scheed1, A. Aliabadi2, P. Jaksch1, S. Taghavi1, W. Klepetko1, A. Zuckermann2

1Klinische Abteilung für Thoraxchirurgie, Universitätsklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich; 2Klinische Abteilung für Herzchirurgie, Universitätsklinik für Chirurgie, Medizinische Universität Wien, Wien, Österreich

**Grundlagen.** Eine Vielzahl von Medikamenten mit potentiell toxischen Nebenwirkungen auf den Respirationstrakt sind bekannt. Zytoxische Substanzen wie Methotrexat oder Bleomycin und andere Pharmaka wie Amiodaron oder diverse Antibiotika werden am häufigsten als Ursache für eine medikamentös induzierte interstitielle Lungenfibrose genannt.

**Methodik und Ergebnisse.** Wir berichten den Fall eines 64-jährigen Patienten, der im Oktober 2010 wegen dilatativer Kardiomyopathie mit terminaler Herzinsuffizienz eine orthotope Herztransplantation erhielt. Zu diesem Zeitpunkt bestand radiologisch bereits die Verdacht auf eine Amiodaron-induzierte Lungenfibrose mit funktionell reduzierten Werten: VC 3,49 l (73%), FEV1 3,28 l (86%), MEF50 6,52 l (135%) und TLC 5,88 l (84%). Der postoperative Verlauf gestaltete sich aufgrund einer Lobärpneumonie prothraub. Auch auf der Normalstation fand bei geringsten Belastungen die Sauerstoffsättigung auf bis zu 87%. Die Lungenfunktion 2 Monate nach HTX ergab eine restriktive Ventilationssstörung mit VC 1,33 l (37,9%), FEV1 1,29 l (34,3%), MEF50 3,3 l (71,2%), TLC 2,76 (39,4%), PaO2 52,8 % und PaCO2 38,7 %. Zur Histologiegewinnung wurde nach inkonklusiver Bronchoskopie eine offene Lungenbiopsie durchgeführt, welche das Vorliegen einer Lungenfibrose vom UIP-Typ ergab. Die Kontroll-Echokardiographien zeigten durchwegs eine gute rechts- und linksventrikuläre Funktion, allerdings verschlechterte sich der respiratorische Zustand des Patienten zunehmend, sodass er „high urgent“ zur Lungentransplantation gelistet werden musste. Ein größen- und blutgruppenkompatibles Spenderorgan wurde verfügbar und eine bilaterale Lungentransplantation mit veno-arterieller ECMO Unterstützung durchgeführt. Die ECMO konnte am Ende der Operation bei hämodynamisch und respiratorisch stabilen Verhältnissen wieder explantiert werden. Die Inschämiedauer der rechten Lunge betrug 340 Minuten und links 460 Minuten. Am 19. postoperativen Tag konnte der Patient auf die Normalstation verlegt und nach weiteren 23 Tagen aus dem Krankenhaus entlassen werden.

**Conclusions.** Invasive mycosal infection acquired by immune suppressed patients after heart transplantation is associated with prolonged time of stay on the ICU as well as rates of co-infections and a significant increase of mortality post transplant.

**116**

Invasive mycoses after heart transplantation: outcome and long-term prognosis

T. Haberl1, D. Hutschala2, C. Pelaneck2, A. Aliabadi1, G. Lauffer1, A. Zuckermann1

1Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria; 2Department of Anesthesiology, Medical University of Vienna, Vienna, Austria

**Background.** Although orthotopic heart transplantation has become a routine procedure in treatment of end-stage cardiac failure, postoperative mycosal infections are still a serious risk for the patients. Objective of the current study is to show the influence of various parameters on the severity of infection and the outcome for patients.

**Methods.** This is a single-center retrospective study including 338 patients who underwent heart transplantation from 2000–2008 at our center in Vienna. The analyzed data were collected during the post transplant course in the intensive care unit (ICU). Mycoses were diagnosed by cultures of blood, bronchoalveolar lavages (BAL) and smear tests of central arterial and venous catheters, wounds and drainages.

**Results.** Mean age at time of transplantation was 49 years, 260 patients (76.9%) were male (age 5–71 years) and 78 patients (23.1%) were female (age 3 weeks–76 years). 90 patients (34%) acquired an invasive mycosal infection with candida species (94.3%), aspergillus (3.8%) and pneumocystis carinii (1.9%). Diagnosis was performed in 24.1% by cultures of blood, in 23.5% by BAL, 18.8% by smear tests of vena-cava catheters and in 11.1% from pulmonary artery catheters. In 77.6% treatment with a single antimycosal therapy was sufficient. 20.9% of patients were in need of a double-drug-theraphy and 1.5% needed a triple-drug-therapy. Patients with mycosal infection had an median stay in the ICU of 16 days (1st Quartile: 7,25, 3rd Quartile: 24,75) with a median of 4.5 (Q1: 0, Q3: 7) respirator-days compared with patient without infection who had median 9 (Q1: 4, Q3: 16) days in ICU with 1 (Q1: 0, Q3: 2) respirator-days. 100% of the patients with mycosis compared to 49% of the patients without mycosis developed or already had bacterial co-infection (p < 0.001). The 1-year survival of patients with mycosis was 63.3% compared to 248 patients without infection where 1-year survival was 83.3% (p < 0.001). Average time to first fungal infection was 7.6 ± 5.3 days.

**Conclusions.** Invasive mycosal infection acquired by immune suppressed patients after heart transplantation is associated with prolonged time of stay on the ICU as well as higher rates of co-infections and a significant increase of mortality post transplant.
Lebensqualität

Blutdruck und Stress bei Kindern nach Nierentransplantation

K. Sacherer, T. Müller-Sacherer, C. Aufricht

Klinische Abteilung für pädiatrische Nephrologie und Gastroenterologie, Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Wien, Wien, Österreich

**Grundlagen.** Nach Nierentransplantation (NTX) liegen die Blutdruckwerte vieler Kinder im hypertensiven Bereich. Stressverarbeitungsmechanismen (SVM) können bei der Regulation des Blutdruckes (RR) eine Rolle spielen. Unterschiede zwischen RR in der Klinik versus 24h-RR zuhause könnten einen Marker für abnorme Stressreaktivität darstellen.

**Methodik.** Bei Kindern nach NTX an der Kinderklinik Wien wurden Klinik-RR und 24h-RR, sowie ein Stressverarbeitungsfraßgebogen erhoben. Ein RR-Index aus mittlerem 24h-RR und längen- und geschlechtsspezifischen Sollwerten wurde gebildet. Weiters wurde die RR-Differenz aus Klinik-RR und 24h-RR errechnet. Diese RR-Parameter wurden mit den SVM-Ergebnissen in Beziehung gesetzt.

**Ergebnisse.** Alle untersuchten Kinder waren hypertensiv (RR-Index >1). Kinder mit hoch ungünstigem SVM hatten höhere 24h-RR Werte. Die RR-Differenz aus Klinik-RR und 24h-RR war jedoch höher bei Kindern mit günstigem SVM. Es konnte kein Zusammenhang zwischen SVM und Klinik-RR gefunden werden.

**Schlussfolgerungen.** Unsere Ergebnisse zeigen, dass Stressverarbeitungsmechanismen bei der Blutdruck-Regulation nach NTX eine Rolle spielen. Die besseren Werte im 24h-RR bei Kindern mit günstigem SVM werden jedoch im Klinik-RR durch größere Blutdruck-Differenzen maskiert. Weitere Studien sollen diese Phänomene in der Normalbevölkerung (White Coat Hypertension und SVM) untersuchen.

Attitude towards xenotransplantation of patients prior and after human organ transplantation

V. Stadlbauer¹, P. Stiegler², S. Müller³, M. Schweiger³, M. Sereingg², K. H. Tscheliessnigg³, W. Freidl³

¹Department of Internal Medicine, Medical University of Graz, Graz, Austria; ²Division of Transplantation Surgery, Department of Surgery, Medical University of Graz, Graz, Austria; ³Institute of Social Medicine and Epidemiology, Medical University of Graz, Graz, Austria

**Background.** Xenotransplantation is a potential strategy to overcome the shortage of human donor organs. Since this technique has a major medical and psychological impact on patients and their family and friends, the attitude of patients currently waiting for organ transplantation is important.

**Methods.** Therefore we conducted a survey on the attitude towards xenotransplantation of patients on the waiting list and already transplanted patients. Patients received detailed information before being asked to fill in the questionnaire.

**Results.** We found that 65% would accept xenotransplantation, irrespective of gender, education level or if the patients were on the waiting list or already transplanted. The most common concern was transmission of diseases or genetic material, followed by psychological concerns and ethical issues. More patients had a positive attitude towards accepting cell or tissue transplantation as compared to whole organs. Pig pancreas islet cell transplantation is generally well accepted, patients with diabetes mellitus show even higher acceptance rates than patients without diabetes.

**Conclusions.** Xenotransplantation seems to be well accepted in patients who are potential future candidates for organ transplantation. Informing patients about the current status of research tended to decrease acceptance rates slightly.
Author index

A
Agarwal, M. 10
Agis, H. 35
Aigner, C. 27, 52
Aigner, F. 11, 28, 41, 48, 51
Aliabadi, A. 13, 14, 26, 53
Andreff, M. 23
Ankersmit, H. J. 38, 39, 52
Antlanger, M. 10, 45
Arausoglu, L. 24
Asraf, M. I. 42
Assalber, M. 38
Auberger, J. 36
Aufrecht, C. 44, 54
Augustin, V. 27
Avramov, P. 37

B
Bach, F. 43
Bacher, A. 46, 50
Baranyi, U. 17, 18
Baumann, M. 8
Bauerngartner, A. 39
Beer, L. 39
Beham-Schmid, C. 7, 22, 23
Benesch, M. 4, 21, 31, 37
Berenji, A.-K. 51
Berger, F. 16
Berkovits, G.W. 12, 45, 46, 47, 49, 50
Bernhard, D. 14, 43, 44
Biebl, M. 48, 51
Binder, M. 6
Binner, P. 52
Blatt, D. 1
Blum, S. 51
Böhm, A. 5, 6
Böhmg, G. 16, 45
Böhmg, G. A. 31
Boira, J. M. G. 31
Bonaros, N. 43, 44
Bösmüller, C. 9, 14, 28, 48, 51
Bradatsch, A. 8, 48
Brandacher, G. 13, 22, 41, 42
Brunner, T. 27
Bunzel, B. 34
Burger-Klepp, U. 46, 50
Buzina, W. 34
Burger-Klepp, U. 46, 50

C
Cardini, B. 42
Cavadas, P. 41
Clausen, J. 36
Cosmi, A. B. 32
Crazzolara, R. 24, 36
Curcie, P. 8

D
Dandel, M. 16
Dekan, G. 26
Derfler, K. 31
Deutchesmann, A. 4
Döbler, D. 29
Draxl, A. 40
Dunkler, D. 14, 49
Dupre, G. 38

E
Ehner, M. 42
Eder, S. 5
Ehrlich, M. 44
Eller, K. 11
Enckner, W. 27, 46
Ensinger, C. 48
Ernst, M.-B. 26, 27, 52
Eskandary, F. 14, 26
Etchart, N. 23

F
Fabian, W. 15
Fabius, C. 40
Farkas, A. 17, 18
Faybik, P. 46, 50
Fehr, T. 31
Feng, S. 10
Ferk, M. 12
Feuchtinger, T. 20, 21
Florhinger, B. 10
Fühlwirth, M. 7, 23
Freud, W. 54
Freund, M. 24
Fuchs, G. 7
Függer, R. 27, 29, 46
Fuhrmann, V. 46, 50

G
Gabl, M. 13
Gagli, M. 12
Gangl, O. 46
Garcia-Valdecasas, C. 10
Gatteringer, M. 17
Gautier, S. 37
Gehwolf, P. 43, 51
Geleff, S. 26
Gorkiewicz, G.
Grömmner, M. 13, 14, 26
Grauhaus, O. 16
Graziani, I. 36
Greinix, H. T. 5, 21, 35
Greinix, H. 5
Grumm, M. 24
Größkotthöfer, M. 4
Grub, B. 20
Güeli, E. D. 4
Gyongyossi, M. 38, 39
Györ, G. 45

H
Haberl, T. 14, 26, 27, 53
Habicht, A. 49
Haidinger, M. 15, 28, 29, 45
Hamel, G. 38
Haller, M. 42
Hallström, S. 8
Handgretinger, R. 20, 21, 32
Hängler, H. 24
Hauer, A. 4
Hauser, H. 6
Hautz, T. 9, 13, 41, 48
Hecking, M. 10, 15, 29, 45
Heemann, U. 8
Hengster, P. 40
Hermann, M. 40, 42
Hermann, R. 8
Hetzler, R. 16, 25
Hiemann, N. 16
Hock, K. 17, 18
Hoerlzecker, K. 52
Hofmann, V. 45
Hofmann, N. A. 7, 23
Högenauer, C. 7
Hohenstein, K. 49
Honsig, C. 52
Horkl, V. 8
Hör, W. H. 29
Horvath, M. 35
Huber, K. 46
Hübler, M. 16
Hutschenreiter, D. 53

I
Iberer, F. 30
Iljinisky, I. 37
Isam, N. 41

J
Jacamos, R. O. 23
Jakoby, E. 30
Jakobs, P. 26, 27, 52, 53
Jara, M. 51
Jomrich, G. 47
Jonie, S. 10
Just, U. 21
Jürgens, G. 8

K
Kainz, A. 27
Kalsch, P. 5, 21, 35
Kanatos, R. 46, 50
Katholung, K. 10
Kern, J. 43
Kienz-Wagner, K. 14
Kilo, J. 24
Kimelman, M. 9
Kircher, B. 6
Kirsch, A. H. 11
Kizner, L. 25
Klaus, C. 17
Klepetko, W. 26, 27, 52, 53
Klintmalm, G. B. 10
Kneer, A. 24
Kniepeiss, D. 30, 48
Knobler, R. 21
Knoela, C. 16
Kocher, A. 43, 44
Kofler, M. 11, 41
Körmöcczi, G. F. 31
Köstchen, H. 38, 41
Kostron, A. 43
Kotsch, K. 15, 40
Kumar, R. 29
Krasheninnikov, M. 37
Kraup, T. P. 52
Krause, A. 46
Krause, R. 7, 34
Kreutmayr, S. 14
Kristo, I. 47, 50
Kropphofer, G. 24, 36
Kunzig, M. 13
Kumer, K. 15
Kuzmina, Z. 5, 21

L
Lackner, H. 4, 21, 31, 37
Ladenstein, R. 21
Lake, J. R. 10
Lakiss, F. G. 41
Lakiss, F. 22
Lang, G. 27, 52
Lang, P. 20, 21
Langer, R. M. 9
Langner, C. 7
Lass-Förl, C. 24, 33
Lauffer, G. 14, 26, 27, 43, 44, 53
Lawitschka, A. 4
Leber, B. 8, 41
Leberling, O. 14
Lechner, F. 15
Lee, W. P. A. 22, 41
Lee, Y.-L. 17
Lehmkuhl, H. 16
Leitner, G. 21, 35
Leopold, B. 8, 41
Lichtenauer, M. 38, 39
Liechtenstein, N. 7
Lin, C.-H. 22
Lindner, B. 6
Linksches, W. 22
Lode, H. 21
Lüöser, W. 13
Lutz, J. 8, 12
Lyuandup, A. 37

M
Machalek, J. 47
Maglione, M. 9, 42
Mahr, S. 14, 16, 26
Maier, H. 11, 41
Mann, G. 4
Margreiter, C. 28, 51
Margreiter, J. 44
Margreiter, M. 45
Margreiter, R. 9, 13, 28, 40, 41, 51
Marinova, L. 31
Mark, W. 28, 51
Marschalek, J. 47
Matthes-Martin, S. 4
Mauz-Kortholz, C. 20
Mayer, B. 9
Mayerhofer, S. 12
