1. A Three-Gene Assay for Monitoring Immune Quiescence in Kidney Transplantation
J Am Soc Nephrol 26: 2042–2053, 2015.
Roedder S., Li L., Alonso M.N., et al.

ABSTRACT
Organ transplant recipients face life-long immunosuppression and consequently are at high risk of comorbidities. Occasionally, kidney transplant recipients develop a state of targeted immune quiescence (operational tolerance) against an HLA-mismatched graft, allowing them to withdraw all immunosuppression and retain stable graft function while resuming immune responses to third-party antigens. Methods to better understand and monitor this state of alloimmune quiescence by transcriptional profiling may reveal a gene signature that identifies patients for whom immunosuppression could be titrated to reduce patient and graft morbidities. Therefore, we investigated 571 unique peripheral blood samples from348HLA-mismatched renal transplant recipients and 101 nontransplant controls in a four-stage study including microarray, quantitative PCR, and flow cytometry analyses. We report a refined and highly validated (area under the curve, 0.95; 95% confidence interval, 0.92 to 0.97) peripheral blood three-gene assay *(KLF6, BNC2, CYP1B1*) to detect the state of operational tolerance by quantitative PCR. The frequency of predicted alloimmune quiescence in stable renal transplant patients receiving long-term immunosuppression (n=150) was 7.3% by the three-gene assay. Targeted cell sorting of peripheral blood fromoperationally tolerant patients showed a significant shift in the ratio of circulating monocyte-derived dendritic cells with significantly different expression of the genes constituting the three-gene assay. Our results suggest that incorporation of patient screening by specific cellular and gene expression assays may support the safety of drug minimization trials and protocols.

2. Verification of Association of Elevated Serum IDO Enzyme Activity With Acute Rejection and Low CD4-ATP Levels With Infection

Transplantation 2013;96: 567-572

Dharnidharka V. R., Al Khasawneh E., Gupta S. et al.

ABSTRACT

Background. Both acute rejection (AR) and major infection events (MIE) can reduce long-term allograft survival. We assessed the simultaneous efficacy of serum and urine biomarker indoleamine 2,3-dioxygenase (IDO) enzyme activity and peripheral blood CD4-ATP levels for AR and MIE association, respectively.

Methods. We prospectively tested 217 blood and 167 urine serial samples, collected monthly for 12 months after transplantation from 29 consecutive children receiving a kidney transplant. The indoleamine 2,3-dioxygenase activity was assessed by mass spectrometry assays using the ratio of product L-kynurenine (kyn) to substrate tryptophan (trp). Kyn/trp ratios and blood CD4 T-cell ATP levels were correlated with AR, MIE, or stable group (no events) in the next 30 days.

Results. Using absolute cutoffs and allocating to samples to AR, MIE, or stable group, mean serum kyn/trp ratios were significantly elevated in the group that experienced AR (P=0.0007). Similarly, peripheral blood CD4-ATP levels were significantly lower in the group experiencing MIE (P=0.0351). Urine kyn/trp ratios and blood tacrolimus levels were not different between AR and stable groups. Within-subject analyses, accounting for repeated measures in subjects, also showed that, over time, serum kyn/trp ratios were higher before AR (P=0.031) and blood CD4-ATP levels were lower before MIE (P=0.008).

Conclusions. These results from our pilot discovery group suggest that a panel of biomarkers together can predict overimmunosuppression or underimmunosuppression. Further independent validation in a multicenter cohort is suggested.

3. Monitoring of intracellular adenosine triphosphate in CD4$^+$ T cells to predict the occurrence of cytomegalovirus disease in kidney transplant recipients

Transplant International 2016; 29: 1094–1105

Pérez-Jacoiste Asín M. A., Fernández-Ruiz M., López-Medrano F. et al.

ABSTRACT

The measurement of intracellular concentrations of adenosine triphosphate (iATP) in phytohemagglutinin-stimulated CD4$^+$ T cells constitutes a surrogate marker for post-transplant cell-mediated immunity (CMI). This assay has shown suboptimal accuracy for predicting infection after kidney transplantation (KT). We hypothesize that its predictive capacity depends on the specific contribution of the CMI to host–pathogen interactions. We assessed iATP levels in 100 KT recipients at baseline and months 1, 3, and 6 (363 measurements). No association was found between iATP at month 1 and the risk for overall or bacterial infection, although such association was evident for cytomegalovirus (CMV) disease (multivariate-adjusted hazard ratio [per 50-unit increment]: 0.83; P-value = 0.048). There were no significant differences in mean iATP between stable patients (319.4 ng/ml) and those developing overall (304.1 ng/ml) or bacterial infection (346.9 ng/ml) over the 45 days following monitoring. However, iATP was significantly lower in patients who developed CMV disease (223.5 ng/ml; P-values <0.002). The optimal cutoff (265 ng/ml) for predicting CMV disease in patients not receiving antiviral prophylaxis yielded sensitivity, specificity, positive, and negative predictive values of 85.7%, 68.3%, 15.2%, and 98.6%, respectively. In conclusion, a non-pathogen-specific monitoring of CMI by means of iATP informs the risk of CMV disease in KT recipients.

4. Risk Factors Associated With Early Invasive Pulmonary Aspergillosis in Kidney Transplant Recipients: Results From a Multinational Matched Case–Control Study

American Journal of Transplantation 2016; 16: 2148–2157

López-Medrano F., Silva J. T., Fernández-Ruiz M., et al.

ABSTRACT

Risk factors for invasive pulmonary aspergillosis (IPA) after kidney transplantation have been poorly explored. We performed a multinational case–control study that included 51 kidney transplant (KT) recipients diagnosed with early (first 180 posttransplant days) IPA at 19 institutions between 2000 and 2013. Control recipients were matched (1:1 ratio) by center and date of transplantation. Overall mortality among cases was 60.8%, and 25.0% of living recipients experienced graft loss. Pretransplant diagnosis of chronic pulmonary obstructive disease (COPD; odds ratio [OR]: 9.96; 95% confidence interval [CI]: 1.09–90.58; p = 0.041) and delayed graft function (OR: 3.40; 95% CI: 1.08–10.73; p = 0.037) were identified as independent risk factors for IPA among those variables already available in the immediate peritransplant period. The development of bloodstream infection (OR: 18.76; 95% CI: 1.04–339.37; p = 0.047) and acute graft rejection (OR: 40.73, 95% CI: 3.63–456.98; p = 0.003) within the 3 mo prior to the diagnosis of IPA acted as risk factors during the subsequent period. In conclusion, pretransplant COPD, impaired graft function and the occurrence of serious posttransplant infections may be useful to identify KT recipients at the highest risk of early IPA. Future studies should explore the potential benefit of antimold prophylaxis in this group.

5. Prospective Analyses of Circulating B Cell Subsets in ABO-Compatible and ABO-Incompatible Kidney Transplant Recipients

American Journal of Transplantation 2017; 17: 542–550

Schloßer H. A., Thelen M., Dieplinger G. et al.

ABSTRACT

Immunosuppressive strategies applied in renal transplantation traditionally focus on T cell inhibition. B cells were mainly examined in the context of antibody-mediated rejection, whereas the impact of antibody-independent B cell functions has only recently entered the field of transplantation. Similar to T cells, distinct B cell subsets can enhance or inhibit immune responses. In this study, we prospectively analyzed the evolution of B cell subsets in the peripheral blood of ABO-compatible (n = 27) and ABO-incompatible (n = 10) renal transplant recipients. Activated B cells were transiently decreased and plasmablasts were permanently decreased in patients without signs of rejection throughout the first year. In patients with histologically confirmed renal allograft rejection, activated B cells and plasmablasts were significantly elevated on day 365. Rituximab treatment in ABO-incompatible patients resulted in long-lasting B cell depletion and in a naïve phenotype of repopulating B cells 1 year following transplantation. Acute allograft rejection was correlated with an increase of activated B cells and plasmablasts and with a significant reduction of regulatory B cell subsets. Our study demonstrates the remarkable effects of standard immunosuppression on circulating B cell subsets. Furthermore, the B cell compartment was significantly altered in rejecting patients. A specific targeting of deleterious B cell subsets could be of clinical benefit in renal transplantation.

6. Cryptococcosis in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 242–249

Baddley J. W., Forrest G. N. and the AST Infectious Diseases Community of Practice

Abstract not available

7. Subclinical Epstein–Barr Virus Viremia Among Adult Renal Transplant Recipients: Incidence and Consequences

American Journal of Transplantation 2013; 13: 656–562

Bamoulid J., Courivauda C., Coaquette A. et al.

ABSTRACT

The natural history and clinical significance of posttransplant Epstein-Barr virus (EBV) infection remain largely unknown. The aims of this study are to describe the incidence, risk factors and consequences of EBV infection after kidney transplantation. A total of 383 consecutive patients having received a kidney transplant between January 2002 and December 2010 were included. EBV polymerase chain reaction (PCR) was performed every 2 weeks for 3 months, and every 4 weeks for the next 9months. A total of 155 of the 383 patients (40%) had at least one positive viremia during the first year posttransplant. The median time to viremia was day 31 posttransplant (14–329). A total of 73 (47%) had EBV viremia > 10^3 log and 23 (15%) had positive viremia for more than 6 months. EBV D+/R− patients (12/18 (67%) versus 143/365 (39%), p = 0.02) and those having received antithymocyte globulins (ATG) (54% vs. 35%; p<0.001) were more likely to develop EBV infection. EBV infection (hazard ratio [HR], 3.03; 95% confidence interval [CI], 1.72–8.29; p = 0.01) was associated with the occurrence of opportunistic infections.

A positive EBV PCR during the first 6 months posttransplant was associated with graft loss (HR, 3.04; 95% CI, 1.36–6.79; p = 0.014). EBV reactivation is frequent after transplantation and reflects overimmunosuppression. Prospective studies should examine the association between EBV and graft loss.

8. Establishing Biomarkers in Transplant Medicine: A Critical Review of Current Approaches
Transplantation 2016;100: 2024–2038
Anglicheau D., Naesens M., Essig M. et al.

ABSTRACT
Although the management of kidney transplant recipients has greatly improved over recent decades, the assessment of individual risks remains highly imperfect. Individualized strategies are necessary to recognize and prevent immune complications early and to fine-tune immunosuppression, with the overall goal to improve patient and graft outcomes. This review discusses current biomarkers and their limitations, and recent advancements in the field of noninvasive biomarker discovery. A wealth of noninvasive monitoring tools has been suggested that use easily accessible biological fluids such as urine and blood, allowing frequent and sequential assessments of recipient's immune status. This includes functional cell-based assays and the evaluation of molecular expression on a wide spectrum of platforms. Nevertheless, the translation and validation of exploratory findings and their implementation into standard clinical practice remain challenging. This requires dedicated prospective interventional trials demonstrating that the use of these biomarkers avoids invasive procedures and improves patient or transplant outcomes.

9. Barcelona Consensus on Biomarker-Based Immunosuppressive Drugs Management in Solid Organ Transplantation

Ther Drug Monit 2016;38:S1–S20

Brunet M., Shipkova M., van Gelder T. et al.

ABSTRACT

Abstract: With current treatment regimens, a relatively high proportion of transplant recipients experience underimmunosuppression or overimmunosuppression. Recently, several promising biomarkers have been identified for determining patient alloreactivity, which help in assessing the risk of rejection and personal response to the drug; others correlate with graft dysfunction and clinical outcome, offering a realistic opportunity for personalized immunosuppression.
This consensus document aims to help tailor immunosuppression to the needs of the individual patient. It examines current knowledge on biomarkers associated with patient risk stratification and immunosuppression requirements that have been generally accepted as promising. It is based on a comprehensive review of the literature and the expert opinion of the Biomarker Working Group of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. The quality of evidence was systematically weighted, and the strength of recommendations was rated according to the GRADE system. Three types of biomarkers are discussed: (1) those associated with the risk of rejection (alloreactivity/tolerance), (2) those reflecting individual response to immunosuppressants, and (3) those associated with graft dysfunction. Analytical aspects of biomarker measurement and novel pharmacokinetic–pharmacodynamic models accessible to the transplant community are also addressed. Conventional pharmacokinetic biomarkers may be used in combination with those discussed in this article to achieve better outcomes and improve long-term graft survival. Our group of experts has made recommendations for the most appropriate analysis of a proposed panel of preliminary biomarkers, most of which are currently under clinical evaluation in ongoing multicentre clinical trials. A section of Next Steps was also included, in which the Expert Committee is committed to sharing this knowledge with the Transplant Community in the form of triennial updates.

10. Biomarkers of Over-Immunosuppression

Clinical pharmacology & Therapeutics | VOLUME 90 NUMBER 2 | august 2011

Budde K, Matz M, Dürr M and Glander P.

ABSTRACT

An important goal in transplantation is to tailor immunosuppression to the individual needs of the patient, avoiding both rejection and over-immunosuppression. Opportunistic infections and malignancies remain a significant cause of death after transplantation and are obvious consequences of over-immunosuppression. Currently, monitoring of immunosuppression is conducted mainly on the basis of pharmacokinetic characteristics, which do not necessarily predict clinical outcome in the individual. This review focuses on the potential of using biomarkers as a monitoring tool to prevent over-immunosuppression after transplantation.

11. Use of immune function test in monitoring immunosuppression in liver transplant recipients

Clin Transplant 2012: 26: 826–832

Te HS, Dasgupta KA, Cao D, Satoskar R, Mohanty et al.

ABSTRACT

Immune function test (Immuknow™) is a measure of cellmediated immunity based on peripheral $CD4^+$ T cell adenosine triphosphate activity (desired range, 225–525 ng/mL). We evaluated the role of immune function test (IFT) in monitoring and adjustment of immunosuppression in orthotopic liver transplant (OLT) recipients. A total of 289 IFTs were obtained from 171 patients from March 2007 to June 2008. Graft/patient status was classified as stable, serious infection, or malignancy. IFT levels were analyzed with duration of follow-up after OLT, graft/patient status, and the presence of hepatitis C (HCV) infection. The mean age was 54 ± 14 yr, with 62% men. The median follow-up was 65 (2–249) months. Mean IFT levels were significantly lower in patients who were <24 months than in those <24 months post- OLT (220 ± 19.5 vs. 257 ± 11.3 ng/mL, $p = 0.03$). Clinically stable patients had higher IFT levels than those with serious infection or malignancy (254 ± 11.1 vs. 162.5 ± 23.9, $p < 0.001$). HCV-infected patients had lower IFT levels than uninfected patients (206.7 ± 15.7 vs. 273 ± 12.0 ng/mL, $p < 0.001$). Immunosuppression was reduced in 58 patients with IFT levels <225 ng/mL, and 90% maintained stable graft function after a median follow-up of 22 (1–39) months. IFT may be a useful tool in monitoring and lowering of immunosuppression in longterm OLT recipients.

12. Assessment of Cytomegalovirus-Specific Cell-Mediated Immunity for the Prediction of Cytomegalovirus Disease in High-Risk Solid-Organ Transplant Recipients: A Multicenter Cohort Study

Clinical Infectious Diseases 2013;56(6):817–24

Manuel O., Husain S., Kumar D. et al.

ABSTRACT

Background. Cytomegalovirus (CMV) disease remains an important problem in solid-organ transplant recipients, with the greatest risk among donor CMV-seropositive, recipient-seronegative (D^+/R^-) patients. CMVspecific cell-mediated immunity may be able to predict which patients will develop CMV disease.

Methods. We prospectively included D^+/R^- patients who received antiviral prophylaxis. We used the Quantiferon-CMV assay to measure interferon-γ levels following in vitro stimulation with CMV antigens. The test was performed at the end of prophylaxis and 1 and 2 months later. The primary outcome was the incidence of CMV disease at 12 months after transplant. We calculated positive and negative predictive values of the assay for protection from CMV disease.

Results. Overall, 28 of 127 (22%) patients developed CMV disease. Of 124 evaluable patients, 31 (25%) had a positive result, 81 (65.3%) had a negative result, and 12 (9.7%) had an indeterminate result (negative mitogen and CMV antigen) with the Quantiferon-CMV assay. At 12 months, patients with a positive result had a subsequent lower incidence of CMV disease than patients with a negative and an indeterminate result (6.4% vs 22.2% vs 58.3%, respectively; $P < .001$). Positive and negative predictive values of the assay for protection from CMV disease were 0.90 (95% confidence interval [CI], .74–.98) and 0.27 (95% CI, .18–.37), respectively.

Conclusions. This assay may be useful to predict if patients are at low, intermediate, or high risk for the development of subsequent CMV disease after prophylaxis.

13. Cytomegalovirus infection in high-risk kidney transplant recipients receiving thymoglobulin induction—a single-center experience

Clin Transplant 2016; 30: 1159–1164

Puttarajappa C., Bhattarai M., Mour G. et al.

ABSTRACT

Background: The burden of cytomegalovirus infection in CMV high-risk (donor positive to recipient negative) kidney transplant recipients getting thymoglobulin induction and six months of valganciclovir is not well characterized. Additionally, the role of post-prophylaxis surveillance remains unclear.

Methods: One-year observational study of forty-eight high-risk CMV kidney transplant recipients transplanted under thymoglobulin between January 2013 and July 2014. All received valganciclovir for six months, followed by monthly CMV PCR for three months.

Results: CMV infection defined as viremia with or without symptoms occurred in 40% (19/48). Of these, 47% (9/19) occurred during prophylaxis, 32% (6/19) during surveillance and 21% (4/19) during post-surveillance period (9–12 months). Among breakthrough infections, suboptimal valganciclovir dosing was present in 55% (5/9). With routine surveillance, there was a trend toward lower CMV-related hospitalization (17% vs 56% and 75% during prophylaxis and post-surveillance, respectively [*P*=.23]) and lower mean peak viral loads (19 432 copies/mL vs 97 925 copies/mL and 536 021 copies/mL during prophylaxis and post-surveillance, respectively [*P*=.07]).

Conclusion: CMV infection remains a significant problem with thymoglobulin induction despite six months of valganciclovir. Suboptimal valganciclovir dosing was common among breakthrough infections. Monthly surveillance post-prophylaxis appears to detect early CMV infection with lower degree of viremias requiring fewer hospitalizations.

14. Correlation between pharmacokinetics of tacrolimus and pharmacodynamics on NFATregulated gene expression in stable kidney transplant recipients

Clinical Nephrology, Vol. 87 – No. 2/2017 (93-99)

Keller F., Sommerer C., Giese T. et al.

ABSTRACT

Gene expression regulated by the transcription factor NFAT (nuclear factor of activated T-cells) has been proposed for monitoring the pharmacodynamic effect of calcineurin inhibitors. We aimed to correlate the pharmacokinetics of tacrolimus with the suppression of NFAT-regulated gene expression. Tacrolimus trough (C_{trough}) and peak concentrations (C_{peak}) were measured by LC-MS. The effect on NFAT-regulated gene expression at trough (E_{trough}) and at peak levels (E_{peak}) were determined by qRT-PCR. The pharmacodynamic concentration producing the half-maximum effect (CE_{50}) and the Hill coefficient (H) were estimated from E_{trough} and from E_{peak}. Ten stable kidney transplant recipients on triple immunosuppression with prednisolone, mycophenolate, and tacrolimus were analyzed. Median age was 58 years, median time since transplant was 84 months, and median serum creatinine was 249 µmol/L. The immunosuppressive effect on NFAT-regulated genes at trough concentrations was 38% (E_{trough}), and the effect at peak concentrations was 59% (E_{peak}) of maximum immunosuppression (E_{max}). The pharmacodynamic parameters of the action of tacrolimus were estimated with the Hill coefficient H at 1.5 and the CE_{50} at 6.7 ng/mL. Accordingly, the pharmacodynamics threshold concentration was estimated at 0.9 ng/mL and the ceiling concentration at 48 ng/mL, indicating a wide span between target trough and peak levels. The low Hill coefficient indicates concentration-dependent pharmacodynamics of tacrolimus on NFAT transcripts. Therefore, the extension of the administration interval to 24 hours is not likely to jeopardize the immunosuppressive effect of the prolonged-release tacrolimus preparations.

15. 5year follow-up of a randomized clinical study comparing everolimus plus reduced-dose cyclosporine with mycophenolate mofetil plus standard-dose cyclosporine in de novo kidney transplantation: Retrospective single center assessment

International Immunopharmacology 39 (2016) 192–198

Hiramitsu T., Okada M., Futamura K. et al.

ABSTRACT

The aim of this study is to evaluate the efficacy and safety of everolimus plus reduceddose cyclosporine compared with mycophenolate mofetil plus standarddose cyclosporine 5 years after living donor kidney transplantation. Between March 2008 and August 2009, 24 living donor kidney transplantations were enrolled in a 2-year, multicenter, randomized phase 3 study (RAD001A1202 study). 24 recipients were randomly classified into two groups and closely observed for 5 years. 13 recipients were administered steroid, reduced dose cyclosporine, everolimus and basiliximab (EVR group). 11 recipients were administered steroid, standard-dose cyclosporine, mycophenolate mofetil and basiliximab (STD group). Two groups were compared not only in graft function including estimated glomerular filtration rate (eGFR), and proteinuria, but also in adverse events such as de novo donor-specific antibody (DSA) production, rejection, new-onset diabetes, hyperlipidemia, and cytomegalovirus (CMV) infection.

No graft loss was identified in 5 years. The incidences of acute T cell rejection, de novo DSA production, hyperlipidemia, and new-onset diabetes were similar. eGFR levels throughout the observation periods were similar. Three cases of proteinuria were identified in STD group. One case of proteinuria observed in EVR group was well controlled with angiotensin receptor blocker. Incidence of CMV infection in CMV antibody-positive recipients was significantly lower in EVR group. The safety and efficacy of reduced-dose cyclosporine and everolimus protocol were similar to those of standard-dose cyclosporine and mycophenolate mofetil other than for superior prevention of CMV infection.

16. Immune monitoring in renal transplantation: The search for biomarkers

Eur. J. Immunol. 2016. 46: 2695–2704

Danger R., Sawitzki B. and Brouard S. et al.

ABSTRACT

It is now widely accepted that in order to improve long-term graft function and survival, a more personalized immunosuppressive treatment of transplant patients according to the individual anti-donor immune response status is needed. This applies to the identification of potentially "high-risk" patients likely to develop acute rejection episodes or display an accelerated decline of graft function, patients who might need immunosuppression intensification, and operationally tolerant patients suitable for immunosuppression minimization or weaning off. Such a patient stratification would benefit from biomarkers, which enable categorization into low and high risk or, ideally, identification of operational tolerant patients. Here, we report on recent developments regarding identification and performance analysis of noninvasive biomarkers such as mRNA and miRNA expression profiles, chemokines, or changes in immune cell subsets in either blood or urine of renal transplant patients. We will also discuss which future steps are needed to accelerate their clinical implementation.

17. Impact of Desensitization on Antiviral Immunity in HLA-Sensitized Kidney Transplant Recipients

Journal of Immunology Research, Volume 2017, Article ID 5672523, 24 pages

Toyoda M., Shin B., Ge S. et al.

ABSTRACT

Viral infections represent significant morbidity and mortality factors in kidney transplant recipients, with CMV, EBV, and BKV infections being most common. Desensitization (DES) with IVIg and rituximab with/without plasma exchange followed by kidney transplantation with alemtuzumab induction increased successful transplant rates in HLA-sensitized patients but may represent an increased risk for viral infections due to severe lymphocyte depletion. Here, we report on the posttransplant viral infection status in 372 DES versus 538 non-DES patients. CMV and EBV viremia were significantly lower in DES patients, while BKV viremia was similar. This trend was observed primarily in CMV sero(−), EBV sero(+), and sero(−) patients. No patient developed PTLD. The incidence of BKAN, allograft, and patient survival was similar in both groups. These viral infections were not associated with subsequent allograft rejection which occurred within 6 months after the infection.

Conclusions. The IVIg + rituximab desensitization combined with alemtuzumab induction with triple immunosuppression maintenance does not increase the risk for CMV, EBV, and BKV infections. Possible factors include, in addition to posttransplant antiviral prophylaxis and PCR monitoring, presence of memory T cells and antibodies specific toCMVand likely EBV,NKcell-mediated ADCC despite lymphocyte depletion, elimination of EBV and CMV reservoirs by rituximab and alemtuzumab, and use of IVIg with antiviral properties.

18. CMV: Prevention, Diagnosis and Therapy
American Journal of Transplantation 2013; 13: 24–40
Nelson Kotton C.

ABSTRACT
Cytomegalovirus (CMV) is the most common infection after organ transplantation and has a major impact on morbidity, mortality and graft survival. Optimal prevention, diagnosis and treatment of active CMV infection enhance transplant outcomes, and are the focus of this section. Methods to prevent CMV include universal prophylaxis and preemptive therapy; each has its merits, and will be compared and contrasted. Diagnostics have improved substantially in recent years, both in type and quality, allowing for more accurate and savvy treatment; advances in diagnostics include the development of an international standard, which should allow comparison of results across different methodologies, and assays for cellular immune function against CMV. Therapy primarily involves ganciclovir, now rendered more versatile by data suggesting oral therapy with valganciclovir is not inferior to intravenous therapy with ganciclovir. Treatment of resistant virus remains problematic, but is enhanced by the availability ofmultiple novel therapeutic agents.

19. Persistent Epstein-Barr viral load in Epstein-Barr viral naïve pediatric heart transplant recipients: Risk of late-onset posttransplant lymphoproliferative disease

World J Transplant 2016 December 24; 6(4): 729-735

Das B., Morrow R., Huang R. and Fixler D.

ABSTRACT

AIM: To examine the risk of late-onset post-transplant lymphoproliferative disorder (PTLD) in the presence of persisting high Epstein-Barr virus (EBV) in EBV naïve pediatric heart transplant (HT) recipients.

METHODS: A retrospective review of the medical records of the 145 pediatric HT recipients who had serial EBV viral load monitoring at our center was performed. We defined EBV naive patients whose EBV serology either IgM or IgG in the blood were negative at the time of HT and excluded passive transmission from mother to child in subjects less than 6 mo of age.

RESULTS: PTLD was diagnosed in 8 out of 145 patients (5.5%); 6/91 (6.5%) in those who were EBV seropositive and 2/54 (3.7%) in the EBV naïve group at the time of HT (P = 0.71). We found 32/145 (22%) patients with persistently high EBV load during continuing follow-up; 20/91 (22%) in EBV seropositive group vs 12/54 (22%) in EBV naïve group (P = 0.97). There was no significant association between pre-HT serostatus and EBV load after transplant (P > 0.05). In the EBV seropositive group, PTLD was diagnosed in 15% (3/20) of patients with high EBV *vs* 4.2% (3/71) of patients with low or undetectable EBV load (P = 0.14) whereas in EBV naïve patients 8.3% (1/12) of those with high EBV load and 2.3% (1/42) with low or undetectable EBV load (P = 0.41). There was a highly significant association between occurrence of PTLD in those with high EBV load and duration of follow up (4.3 ± 3.9 years) after HT by Cochran-Armitage test for the entire cohort (P = 0.005). At least one episode of acute rejection occurred in 72% (23/32) of patients with high EBV *vs* 36% (41/113) patients with low or undetectable EBV after HT (P < 0.05).

CONCLUSION: There is an association between persistently high EBV load during post-HT follow up and the occurrence of late-onset PTLD in pediatric HT recipients irrespective of serostatus at the time of transplant. The occurrence of allograft rejection increased in patients with high EBV load presumably due to reduction in immunosuppression.

20. Posttransplant peripheral blood donor–specific interferon-g enzyme-linked immune spot assay differentiates risk of subclinical rejection and de novo donor-specific alloantibodies in kidney transplant recipients

Kidney International (2017)

Crespo E., Cravedi P., Martorell J. et al.

ABSTRACT

Noninvasive diagnosis of kidney allograft inflammation in transplant recipients with stable graft function (subclinical rejection) could permit more effective therapy and prevent later development of *de novo* anti-donor HLA antibodies and/or graft dysfunction. Here we tested whether quantifying posttransplant donor-specific alloreactive T-cells by IFN-γ ELISPOT assay noninvasively detects subclinical T–cell mediated rejection and/or predicts development of anti-donor HLA antibodies. Using an initial cross-sectional cohort of 60 kidney transplant patients with six-month surveillance biopsies, we found that negative donor-specific IFN-g ELISPOT assays accurately ruled out the presence of subclinical T–cell mediated rejection. These results were validated using a distinct prospective cohort of 101 patients where donor-specific IFN-g ELISPOT results at both three- and six-months posttransplant significantly differentiated patients with subclinical T–cell mediated rejection at six months, independent of other clinical variables (odds ratio 0.072, 95% confidence interval 0.008-0.653). The posttransplant donor-specific IFN-γ ELISPOT results independently associated with subsequent development of significant anti-donor HLA antibodies (0.085, 0.008-0.862) and with significantly worse two-year function (estimated glomerular filtration rate) compared to patients with a negative test. Thus, posttransplant immune monitoring by donor-specific IFN-γ ELISPOT can assess risk for developing subclinical T–cell mediated rejection and anti-donor HLA antibodies, potentially limiting the need for surveillance biopsies. Our study provides a guide for individualizing immunosuppression to improve posttransplant outcomes.

21. Current preventive strategies and management of Epstein–Barr virusrelated post-transplant lymphoproliferative disease in solid organ transplantation in Europe. Results of the ESGICH Questionnaire-based Cross-sectional Survey

Clin Microbiol Infect 2015; 21: 604.e1–604.e9

San-Juan R., Manuel O., Hirsch H. H., Fernández-Ruiz M., López-Medrano F., Comoli P., Caillard S., Grossi P. and Aguado J. M., ESGICH PTLD Survey Study Group, on behalf of the European Study Group of Infections in Compromised Hosts (ESGICH) from the European Society of Microbiology and Infectious Diseases (ESCMID)

ABSTRACT

There is limited clinical evidence on the utility of the monitoring of Epstein–Barr virus (EBV) DNAemia in the pre-emptive management of post-transplant lymphoproliferative disease (PTLD) in solid organ transplant (SOT) recipients. We investigated current preventive measures against EBV-related PTLD through a web-based questionnaire sent to 669 SOT programmes in 35 European countries. This study was performed on behalf of the ESGICH study group from the European Society of Clinical Microbiology and Infectious Diseases. A total of 71 SOT programmes from 15 European countries participated in the study. EBV serostatus of the recipient is routinely obtained in 69/71 centres (97%) and 64 (90%) have access to EBV DNAemia assays. EBV monitoring is routinely used in 85.9% of the programmes and 77.4% reported performing pre-emptive treatment for patients with significant EBV DNAemia levels. Pre-emptive treatment for EBV DNAemia included reduction of immunosuppression in 50.9%, switch to mammalian target of rapamycin inhibitors in 30.9%, and use of rituximab in 14.5% of programmes. Imaging by whole-body 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) is used in 60.9% of centres to rule out PTLD and complemented computer tomography is used in 50%. In 10.9% of centres, FDG-PET is included in the first-line diagnostic workup in patients with high-risk EBV DNAemia. Despite the lack of definitive evidence, EBV load measurements are frequently used in Europe to guide diagnostic workup and pre-emptive reduction of immunosuppression. We need prospective and controlled studies to define the impact of EBV monitoring in reducing the risk of PTLD in SOT recipients.

22. Use of Everolimus-based Immunosuppression to Decrease Cytomegalovirus Infection After Kidney Transplant

Experimental and Clinical Transplantation (2016) 4: 361-366

P. Malvezzi, T. Jouve and L. Rostaing

ABSTRACT

Objectives: *Cytomegalovirus* infection and disease remain an issue in solid-organ transplant. Universal prophylaxis is more cost-effective than a preemptive strategy and is associated with significantly less cytomegalovirus resistance after kidney transplant, especially in cytomegalovirus-seropositive donors and *cytomegalovirus*-seronegative recipients.

Materials and Methods: Registry data and metaanalyses have shown that mammalian target of rapamycin inhibitors (sirolimus- and everolimus-based immunosuppression) are associated with significantly less *cytomegalovirus* events in de novo kidney transplant patients than in patients who are treated with calcineurin inhibitors plus mycophenolate-based immunosuppression.

Results: Recent pooled analyses of 3 randomized controlled trials in de novo kidney transplant patients, where immunosuppression was based on cyclosporine with either mycophenolate or everolimus, showed that patients who received everolimus had significantly less *cytomegalovirus* events (*cytomegalovirus* viremia, cytomegalovirus infection/disease) than those who received mycophenolate, with or without *cytomegalovirus* as prophylaxis. An even more recent prospective randomized controlled study on de novo kidney transplant patients with no anti*cyto* - *megalovirus* prophylaxis demonstrated that everolimus-based immunosuppression plus low-dose tacrolimus was associated with significantly less *cytomegalovirus* infection than standard-dose tacrolimus plus mycophenolate.

Conclusions: The potential benefits are not fully known of such a therapeutic strategy to limit the longterm indirect effects mediated by *cytomegalovirus* infections.

23. Cytomegalovirus post kidney transplantation: prophylaxis versus pre-emptive therapy?
Steunstichting ESOT 28 (2015) 1351–1356
Fehr T., Cippà P. E. and Mueller N. J.

ABSTRACT
Cytomegalovirus is the most important pathogen causing opportunistic infections in kidney allograft recipients. The occurrence of CMV disease is associated with higher morbidity, higher incidence of other opportunistic infections, allograft loss and death. Therefore, an efficient strategy to prevent CMV disease after kidney transplantation is required. Two options are currently available: pre-emptive therapy based on regular CMV PCR monitoring and generalized antiviral prophylaxis during a defined period. In this review, we describe those two approaches, highlight the distinct advantages and risks of each strategy and summarize the four randomized controlled trials performed in this field so far. Taken this evidence together, pre-emptive therapy and anti-CMV prophylaxis are both equally potent in preventing CMV-associated complications; however, the pre-emptive approach may have distinct advantages in allowing for development of long-term anti- CMV immunity. We propose a risk-adapted use of these approaches based on serostatus, immunosuppressive therapy and availability of resources at a particular transplant centre.

24. Monitoring of Immunoglobulin Levels Identifies Kidney Transplant Recipients at High Risk of Infection

American Journal of Transplantation 2012; 12: 2763–2773

Fernández-Ruiz M., López-Medrano F., Varela-Peña P. et al.

ABSTRACT

We aimed to analyze the incidence, risk factors and impact of hypogammaglobulinemia (HGG) in 226 kidney transplant (KT) recipients in which serum immunoglobulin (Ig) levels were prospectively assessed at baseline, month 1 (T_1), andmonth 6 (T_6). The prevalence of IgG HGG increased from 6.6% (baseline) to 52.0% (T_1) and subsequently decreased to 31.4% (T_6) ($p < 0.001$). The presence of IgG HGG at baseline (odds ratio [OR] 26.9; $p = 0.012$) and a positive anti-HCV status (OR 0.17; $p = 0.023$) emerged as risk factors for the occurrence of posttransplant IgG HGG. Patients with HGG of any class at T_1 had higher incidences of overall ($p = 0.018$) and bacterial infection ($p = 0.004$), bacteremia ($p=0.054$) and acute pyelonephritis ($p=0.003$) in the intermediate period (months 1–6). Patients with HGG at T_6 had higher incidences of overall ($p = 0.004$) and bacterial infection ($p < 0.001$) in the late period (>6 month). A complementary log–log model identified posttransplant HGG as an independent risk factor for overall (hazard ratio [HR] 2.03; $p < 0.001$) and bacterial infection (HR 2.68; $p < 0.0001$). Monitoring of humoral immunity identifies KT recipients at high risk of infection, offering the opportunity for preemptive immunoglobulin replacement therapy.

25. Hypocomplementemia in Kidney Transplant Recipients: Impact on the Risk of Infectious Complications

American Journal of Transplantation 2013; 13: 685–694

Fernández-Ruiz M., López-Medrano F., Varela-Peña P. et al.

ABSTRACT

The usefulness of monitoring of complement levels in predicting the occurrence of infection in kidney transplant (KT) recipients remains largely unknown. We prospectively assessed serum complement levels (C3 and C4) at baseline and at months 1 and 6 in 270 patients undergoing KT. Adjusted hazard ratios (aHRs) for infection in each posttransplant period were estimated by Cox regression. The prevalence of C3 hypocomplementemia progressively decreased from 21.5% at baseline to 11.6% at month 6 ($p = 0.017$), whereas the prevalence of C4 hypocomplementemia rose from 3.7% at baseline to 9.2% at month 1 ($p = 0.004$). Patients with C3 hypocomplementemia at month 1 had higher incidences of overall ($p = 0.002$), bacterial ($p = 0.004$) and fungal infection ($p = 0.019$) in the intermediate period (months 1–6). On multivariate analysis C3 hypocomplementemia at month 1 emerged as a risk factor for overall (aHR 1.911; $p = 0.009$) and bacterial infection (aHR 2.130; $p = 0.014$) during the intermediate period, whereas C3 hypocomplementemia at month 6 predicted the occurrence of bacterial infection (aHR 3.347; $p = 0.039$) in the late period (>6 month). A simple monitoring strategy of serumC3 levels predicts the risk of posttransplant infectious complications in KT recipients.

26. Kinetics of peripheral blood lymphocyte subpopulations predicts the occurrence of opportunistic infection after kidney transplantation

Transplant International 27 (2014) 674–685

Fernández-Ruiz M., López-Medrano F., Allende L. M. et al.

ABSTRACT

Serial monitoring of peripheral blood lymphocyte subpopulations (PBLSs) counts might be useful in predicting post-transplant opportunistic infection (OI) after kidney transplantation (KT). PBLSs were prospectively measured in 304 KT recipients at baseline and post-transplant months 1 and 6. Areas under receiver operating characteristic curves were used to evaluate the accuracy of different subpopulations in predicting the occurrence of overall OI and, specifically, cytomegalovirus (CMV) disease. We separately analyzed patients not receiving (n = 164) or receiving (n = 140) antithymocyte globulin (ATG) as induction therapy. In the non-ATG group, a $CD8^+$ T-cell count at month 1 <0.100 x 10^3 cells/μl had negative predictive values of 0.84 and 0.86 for the subsequent occurrence of overall OI and CMV disease, respectively. In the multivariate Cox model, a $CD8^+$ T-cell count <0.100 x 10^3 cells/μl was an independent risk factor for OI (adjusted hazard ratio: 3.55; P-value = 0.002). In the ATG group, a $CD4^+$ T-cell count at month 1 <0.050 x 10^3 cells/μl showed negative predictive values of 0.92 for the subsequent occurrence of overall OI and CMV disease. PBLSs monitoring effectively identify KT recipients at low risk of OI, providing an opportunity for individualizing post-transplant prophylaxis practices.

27. Post-transplant monitoring of NK cell counts as a simple approach to predict the occurrence of opportunistic infection in liver transplant recipients

Transpl Infect Dis 2016: 18: 552–565

Fernández-Ruiz M., Silva J. T., López-Medrano F. et al.

ABSTRACT

Background. Monitoring of peripheral blood lymphocyte subpopulation (PBLS) counts might be useful for estimating the risk of infection after liver transplantation (LT).

Methods. We prospectively measured total lymphocyte and PBLS counts at baseline and post-transplant months 1 and 6 in 92 LT recipients. PBLS were enumerated by single-platform 6-color flow cytometry technology. Areas under receiver operating characteristic (ROC) curves were used to evaluate the accuracy of different PBLS for predicting cytomegalovirus (CMV) disease and overall opportunistic infection (OI). Adjusted hazard ratios (aHRs) for both outcomes were estimated by Cox regression.

Results. After a median follow-up of 730.0 days, 29 patients (31.5%) developed 38 episodes of OI (including 22 episodes of CMV disease). The counts of $CD3^+$, $CD4^+$, and $CD8^+$ T cells, and $CD56^+$ $CD16^+$ natural killer (NK) cells at month 1 were significantly lower in patients subsequently developing OI. The NK cell count was the best predictive parameter (area under ROC curve for predicting CMV disease: 0.78; P-value = 0.001). Patients with an NK cell count <0.050 x 10^3 cells/lL had higher cumulative incidences of CMV disease (P-value = 0.001) and overall OI (P-value <0.001). In the multivariate models, an NK cell count <0.050 x 103 cells/ μL at month 1 post transplantation remained as an independent risk factor for CMV disease (aHR: 5.54; P-value = 0.003) and overall OI (aHR: 7.56; P-value <0.001).

Conclusion. Post-transplant kinetics of NK cell counts may be used as a simple and affordable proxy to the cell-mediated immunity status in LT recipients and to their associated risk of OI.

28. Infection in Organ Transplantation

American Journal of Transplantation 2017; 17: 856–879

Fishman J. A.

ABSTRACT

The prevention, diagnosis, and management of infectious disease in transplantation are major contributors to improved outcomes in organ transplantation. The risk of serious infections in organ recipients is determined by interactions between the patient's epidemiological exposures and net state of immune suppression. In organ recipients, there is a significant incidence of drug toxicity and a propensity for drug interactions with immunosuppressive agents used to maintain graft function. Thus, every effort must be made to establish specific microbiologic diagnoses to optimize therapy. A timeline can be created to develop a differential diagnosis of infection in transplantation based on common patterns of infectious exposures, immunosuppressive management, and antimicrobial prophylaxis. Application of quantitative molecular microbial assays and advanced antimicrobial therapies have advanced care. Pathogen-specific immunity, genetic polymorphisms in immune responses, and dynamic interactions between the microbiome and the risk of infection are beginning to be explored. The role of infection in the stimulation of alloimmune responses awaits further definition. Major hurdles include the shifting worldwide epidemiology of infections, increasing antimicrobial resistance, suboptimal assays for the microbiologic screening of organ donors, and virus-associated malignancies. Transplant infectious disease remains a key to the clinical and scientific investigation of organ transplantation.

29. What Is the Impact of Hypogammaglobulinemia on the Rate of Infections and Survival in Solid Organ Transplantation? A Meta-Analysis

American Journal of Transplantation 2013; 13: 2601–2610

Florescu D. F., Kalil A. C., Qiu F. et al.

ABSTRACT

Hypogammaglobulinemia has been described after solid organ transplantation and has been associated with increased risk of infections. The aim of the study was to evaluate the rate of severe hypogammaglobulinemia and its relationship with the risk of infections during the first year posttransplantation. Eighteen studies (1756 patients) that evaluated hypogammaglobulinemia and posttransplant infections were included. The data were pooled using the DerSimonian and Laird random-effects model. Q statistic method was used to assess statistical heterogeneity. Within the first year posttransplantation, the rate of hypogammaglobulinemia (IgG < 700 mg/dL) was 45% (95% CI: 0.34–0.55; Q = 330.1, p < 0.0001), the rate of mild hypogammaglobulinemia (IgG = 400–700 mg/dL) was 39% (95% CI: 0.22–0.56; Q = 210.09, p < 0.0001) and the rate of severe hypogammaglobulinemia (IgG < 400 mg/dL) was 15% (95% CI: 0.08–0.22; Q = 50.15, p < 0.0001). The rate of hypogammaglobulinemia by allograft type: heart 49% (21%–78%; Q = 131.16, p < 0.0001); kidney 40% (30%–49%; Q = 24.55, p = 0.0002); liver 16% (0.001%–35%; Q = 14.31, p = 0.0002) and lung 63% (53%–74%; Q ¼ 6.85, p = 0.08). The odds of respiratory infection (OR = 4.83; 95% CI: 1.66–14.05; p = 0.004; I^2 = 0%), CMV(OR = 2.40; 95% CI: 1.16–4.96; p = 0.02; I^2 = 26.66%), *Aspergillus* (OR = 8.19; 95% CI: 2.38–28.21; p = 0.0009; I^2 = 17.02%) and other fungal infections (OR = 3.69; 95% CI: 1.11–12.33; p = 0.03; I^2 = 0%) for patients with IgG <400 mg/dL were higher than the odds for patients with IgG >400 mg/dL. The odds for 1-year all-cause mortality for severe hypogammaglobulinemia group was 21.91 times higher than those for IgG >400 mg/dL group (95% CI: 2.49– 192.55; p = 0.005; I^2 = 0%). Severe hypogammaglobulinemia during the first year posttransplantation significantly increased the risk of CMV, fungal and respiratory infections, and was associated with higher 1-year all-cause mortality.

30. Impact of Everolimus and Low-Dose Cyclosporin on Cytomegalovirus Replication and Disease in Pediatric Renal Transplantation

American Journal of Transplantation 2016; 16: 921–929

Höcker B., Zencke S., Pape L. et al.

ABSTRACT

In order to investigate the hypothesis that the mammalian target of rapamycin inhibitor everolimus (EVR) shows anticytomegalovirus (CMV) activity in pediatric patients, we analyzed the impact of EVRbased immunosuppressive therapy on CMV replication and disease in a large cohort (n = 301) of pediatric kidney allograft recipients. The EVR cohort (n = 59), who also received low-dose cyclosporin, was compared with a control cohort (n = 242), who was administered standard-dose cyclosporin or tacrolimus and an antimetabolite, mostly mycophenolate mofetil (91.7%). Multivariate analysis revealed an 83% lower risk of CMV replication in the EVR cohort than in the control cohort (p = 0.005). In CMV high-risk (donor+/recipient-) patients (n = 88), the EVR-based regimen was associated with a significantly lower rate of CMV disease (0% vs. 14.3%, p = 0.046) than the standard regimen. In patients who had received chemoprophylaxis with (val-) ganciclovir (n = 63), the CMV-free survival rates at 1 year and 3 years posttransplant (100%) were significantly (p = 0.015) higher in the EVR cohort (n = 15) than in the control cohort (n = 48; 1 year, 75.0%; 3 years, 63.3%). Our data suggest that in pediatric patients at high risk of CMV, an EVR-based immunosuppressive regimen is associated with a lower risk of CMV disease than a standard-dose calcineurin inhibitor–based regimen.

31. Immune function assay (ImmuKnow) as a predictor of allograft rejection and infection in kidney transplantation

Clin Transplant 2013: 27: E351–E358

He J, Li Y, Zhang H, et al.

ABSTRACT

Background: The Cylex ImmuKnow (IK) assay provides a rapid and quantitative assessment of T-cell-mediated immune function. Studies have shown correlations between ImmuKnow assay and adverse events, such as immunosuppression and low or high calcineurin inhibitor trough levels. We investigated the correlation between IK changes and rejection or infection in kidney transplant patients and studied the potential application of the IK assays in optimizing individual immunosuppressive therapy.

Methods: ImmuKnow assay was used to determine dynamic intracellular ATP changes in CD4 cells in 193 samples from 42 kidney transplant patients and 25 healthy subjects. Patients were categorized into rejection, infection, and event-free groups. The IK values were assayed and analyzed between kidney transplant patients and healthy controls.

Results: Most IK values fell between 200 and 599 ng/mL from pretransplantation to 30 months post-transplantation. The mean IK values continuously increased throughout 30 months. Incidental allograft rejection patients had significantly higher IK values compared with the event-free patients and controls. However, infection patients had significantly lower IK values. Seven days after treatment, IK values in rejection/infection patients were different compared with the values in autograft patients, and there was a significant correlation between calcineurin inhibitor (FK506) trough levels and IK values in rejection/ infection patients. Serum creatinine levels in the rejection patients were significantly higher than those in the event-free patients, and C-reactive protein levels were significantly higher in the infection patients compared with the event-free patients.

Conclusions: The IK assay combined with other biomarkers can be used to identify kidney transplant patients at high risk of rejection and infection.

32. Donor-Derived Fungal Infections in Organ Transplant Recipients: Guidelines of the American Society of Transplantation, Infectious Diseases Community of Practice

American Journal of Transplantation 2012; 12: 2414–2428

Singh N., Huprikar S., Burdette S. D. et al.

ABSTRACT

Donor-derived fungal infections can be associated with serious complications in transplant recipients. Most cases of donor-derived candidiasis have occurred in kidney transplant recipients in whom contaminated preservation fluid is a commonly proposed source. Donors with cryptococcal disease, including those with unrecognized cryptococcal meningoencephalitis may transmit the infection with the allograft. Active histoplasmosis or undiagnosed and presumably asymptomatic infection in the donor that had not resolved by the time of death can result in donor-derived histoplasmosis in the recipient. Potential donors from an endemic area with either active or occult infection can also transmit coccidioidomycosis. Rare instances of aspergillosis and other mycoses, including agents of mucormycosis may also be transmitted from infected donors. Appropriate diagnostic evaluation and prompt initiation of appropriate antifungal therapy are warranted if donor-derived fungal infections are a consideration. This document discusses the characteristics, evaluation and approach to the management of donor derived fungal infections in organ transplant recipients.

33. Multicenter Validation of Urinary CXCL9 as a Risk-Stratifying Biomarker for Kidney Transplant Injury

American Journal of Transplantation 2013; 13: 2634–2644

Hricik D. E., Nickerson P., Formica R. N. et al.

ABSTRACT

Noninvasive biomarkers are needed to assess immune risk and ultimately guide therapeutic decision-making following kidney transplantation. A requisite step toward these goals is validation of markers that diagnose and/or predict relevant transplant endpoints. The Clinical Trials in Organ Transplantation-01 protocol is a multicenter observational study of biomarkers in 280 adult and pediatric first kidney transplant recipients. We compared and validated urinary mRNAs and proteins as biomarkers to diagnose biopsy-proven acute rejection (AR) and stratify patients into groups based on risk for developing AR or progressive renal dysfunction. Among markers tested for diagnosing AR, urinary CXCL9 mRNA (odds ratio [OR] 2.77, positive predictive value [PPV] 61.5%, negative predictive value [NPV] 83%) and CXCL9 protein (OR 3.40, PPV 67.6%, NPV 92%) were the most robust. Low urinary CXCL9 protein in 6-month posttransplant urines obtained from stable allograft recipients classified individuals least likely to develop future AR or a decrement in estimated glomerular filtration rate between 6 and 24 months (92.5–99.3% NPV). Our results support using urinary CXCL9 for clinical decision-making following kidney transplantation. In the context of acute dysfunction, low values can rule out infectious/immunological causes of injury. Absent urinary CXCL9 at 6 months posttransplant defines a subgroup at low risk for incipient immune injury.

34. Single Time Point Immune Function Assay (ImmuKnow™) Testing Does Not Aid in the Prediction of Future Opportunistic Infections or Acute Rejection

Clin J Am Soc Nephrol 6: 423–429, 2011.

Huskey J., Gralla J. and Wiseman A. C.

SUMMARY

Background and objectives: Current assays and tests that are used to determine the degree of immunosuppression in renal transplant recipients are suboptimal. The ImmuKnow™ assay (Cylex™), a measure of intracellular CD4+ T cell ATP release proposed as a means to quantify cell-mediated immunity in transplant recipients, could be considered as a potential tool to identify patients at risk for opportunistic infections (OI) or acute rejection (AR).

Design, setting, participants, & measurements: We retrospectively analyzed 1330 ImmuKnow assay values in 583 renal transplant recipients at a single center from 2004 to 2009 and correlated these values with episodes of OI and AR in the subsequent 90 days. Assay values were compared with a control population matched for age, gender, and time post-transplantation.

Results: In patients with OI (*n* = 94), there were no differences in prior mean assay values compared with matched controls (386 *versus* 417 ng/ml, *P* = 0.24). In 47 patients with AR, again no differences were detected in prior assay results (390 *versus* 432 ng/ml, *P* = 0.25) when compared with controls. “Low” values (≤225 ng/ml) lacked sensitivity and specificity as a predictive test for subsequent OI, as did “strong” (≥525 ng/ml) values as a predictive test for subsequent AR.

Conclusions: Our results fail to show an association between single time point ImmuKnow assay values and the subsequent development of an adverse event in the subsequent 90 days. The optimal use of the ImmuKnow assay in kidney transplantation has yet to be determined.

35. Screening of mortality in transplant patients using an assay for immune function
Transplant Immunology 24 (2011) 246–250.
Berglund D., Bengtsson M., Biglarnia A. et al.

ABSTRACT
Background: So far, the ImmuKnow Immune Cell Function Assay (Cylex, Inc., Columbia, MD, USA) has been used to assess risks of infection and rejection in transplant patients. We hypothesized that the ImmuKnow assay might be used for mortality screening in transplant patients overall.
Methods: In the period of February 2007 to December 2009, at the Uppsala University Hospital, 362 patients who received either kidney, kidney+pancreas, kidney+islet cells, liver or liver+kidney allografts were randomly screened using the ImmuKnow assay. All causes of mortality were compared between two groups: patients with at least one ImmuKnow assay below 175 ng/mL and patients with all ImmuKnow assays from 175 ng/mL and above. Subsequently, the frequency of rejection within thirty days of the ImmuKnow assay was compared between these two groups.
Results: The study included 1031 ImmuKnow assays obtained from the 362 patients. A total of 111 patients had at least one ImmuKnow below 175 ng/mL and 251 patients had all their ImmuKnow assays from 175 ng/mL and above. By January 31st 2010, 16 of 111 patients (14.4%) with at least one ImmuKnow assay below 175 ng/mL were deceased, compared to 13 of 251 patients (5.2%) with all ImmuKnow assays from 175 ng/mL and above ($p=0.0053$, Fisher's exact test). There was no difference in the frequency of rejection between the two groups (19.8% versus 17.5%, $p=0.66$).
Conclusions: In addition to assessing relative risks of infection and rejection in transplant patients, the ImmuKnow assay may be used to identify patients with increased risk of short-term mortality. Transplant patients being highly overimmunosuppressed as assessed by the ImmuKnow assay do not seem to have a lower risk of short-term rejection.

36. Cell-Mediated Immunity to Predict Cytomegalovirus Disease in High-Risk Solid Organ Transplant Recipients

American Journal of Transplantation 2009; 9: 1214–1222.

Kumara D., Chernenko S., Moussa G. et al.

ABSTRACT

Late-onset cytomegalovirus (CMV) disease commonly occurs after discontinuation of antiviral prophylaxis. We determined the utility of testing CD8+ T-cell response against CMV as a predictor of late-onset CMV disease after a standard course of antiviral prophylaxis. Transplant patients at high-risk for CMV disease were enrolled. CD8+ T-cell-mediated immunity (CMI) was tested using the QuantiFERON-CMV assay at baseline, 1, 2 and 3 months posttransplant by measurement of interferon-c response to whole blood stimulation with a 21-peptide pool. The primary outcome was the ability of CMI testing to predict CMV disease in the first 6 months posttransplant. There were 108 evaluable patients (D+/R+ n = 39; D-/R+ n = 34; D+/R- n = 35) of whom 18 (16.7%) developed symptomatic CMV disease. At the end of prophylaxis, CMI was detectable in 38/108 (35.2%) patients (cutoff 0.1 IU/mL interferon-γ). CMV disease occurred in 2/38 (5.3%) patients with a detectable interferon-c response versus 16/70 (22.9%) patients with a negative response; p = 0.038. In the subgroup of D+/R- patients, CMV disease occurred in 1/10 (10.0%) patients with a detectable interferon-γ response (cutoff 0.1 IU/mL) versus 10/25 (40.0%) patients with a negative CMI, p = 0.12. Monitoring of CMI may be useful for predicting late-onset CMV disease.

37. Immune Regulation of Human Herpesviruses and Its Implications for Human Transplantation
American Journal of Transplantation 2013; 13: 9–23.
Smith C. and Khanna R.

ABSTRACT
Human herpesviruses including cytomegalovirus, Epstein–Barr virus, HHV6, HHV7, HHV8, Herpes simplex virus (HSV)-1 and HSV-2 and varicella zoster virus (VZV) have developed an intricate relationship with the human immune system. This is characterized by the interplay between viral immune evasion mechanisms that promote the establishment of a lifelong persistent infection and the induction of a broad humoral and cellular immune response, which prevents the establishment of viral disease. Understanding the immune parameters that control herpesvirus infection, and the strategies the viruses use to evade immune recognition, has been critical in understanding why immunological dysfunction in transplant patients can lead to disease, and in the development of immunological strategies to prevent and control herpesvirus associated diseases.

38. Sequential Targeting of CD52 and TNF Allows Early Minimization Therapy in Kidney Transplantation: From a Biomarker to Targeting in a Proof-Of-Concept Trial

PLOS ONE | DOI:10.1371/journal.pone.0169624 January 13, 2017

Viklicky O., Hruba P., Tomiuk S. et al.

ABSTRACT

Background: There is high medical need for safe long-term immunosuppression monotherapy in kidney transplantation. Selective targeting of post-transplant alloantigen-(re)activated effector-T cells by anti-TNF antibodies after global T cell depletion may allow safe drug minimization, however, it is unsolved what might be the best maintenance monotherapy.

Methods: In this open, prospective observational single-centre trial, 20 primary deceased donor kidney transplant recipients received 2x20 mg Alemtuzumab (d0/d1) followed by 5 mg/kg Infliximab (d2). For 14 days all patients received only tacrolimus, then they were allocated to either receive tacrolimus (TAC, n = 13) or sirolimus (SIR, n = 7) monotherapy, respectively. Protocol biopsies and extensive immune monitoring were performed and patients were followed-up for 60 months.

Results: TAC-monotherapy resulted in excellent graft survival (5yr 92%, 95%CI: 56.6-98.9) and function, normal histology, and no proteinuria. Immune monitoring revealed low intragraft inflammation (urinary IP-10) and hints for the development of operational tolerance signature in the TAC- but not SIR-group. Remarkably, the TAC-monotherapy was successful in all five presensitized (ELISPOT+) patients. However, recruitment into SIR-arm was stopped (after n = 7) because of high incidence of proteinuria and acute/chronic rejection in biopsies. No opportunistic infections occurred during follow-up.

Conclusions: In conclusion, our novel fast-track TAC-monotherapy protocol is likely to be safe and preliminary results indicated an excellent 5-year outcome, however, a full-scale study will be needed to confirm our findings.

39. A Single Dose of Rituximab Does Not Deplete B Cells in Secondary Lymphoid Organs but Alters Phenotype and Function

American Journal of Transplantation 2013; 13: 1503–1511

Kamburova E. G., Koenen H. J. P. M., Borgman K. J. E. et al.

ABSTRACT

A single dose of the anti-CD20 monoclonal antibody rituximab induces a nearly complete B cell depletion in peripheral blood, but not in secondary lymphoid organs. Modulation of this remaining B cell population due to rituximab treatment may contribute to the therapeutic effects of rituximab. To assess the *in vivo* effects of rituximab we used lymph nodes (LNs) collected during renal transplant surgery in patients who had received rituximab 4 weeks earlier in preparation for an ABO-incompatible transplantation. Rituximab treatment resulted in a lower percentage of naïve ($IgD^{+}CD27^{-}$) and a higher percentage of switched memory ($IgD^{-}CD27^{+}$) B cells. Remarkably, transitional ($CD24^{++}CD38^{++}$) B cells were virtually lacking in the LNs of rituximab-treated patients. Moreover, LN-derived B cells from rituximab-treated patients produced different amounts of various Ig-subclasses after anti-CD40/IL-21 stimulation *ex vivo*. Finally, after stimulation of allogeneic T cells with LN-derived B cells from rituximab-treated patients, the proliferated T cells showed a decreased production of IL-17. In conclusion, after treatment with rituximab there remains a B cell population with different functional capacities. Consequently, the effect of rituximab on the immune response will not only be determined by the extent of B cell depletion, but also by the functional properties of the remaining B cells.

40. Easier Control of Late-Onset Cytomegalovirus Disease Following Universal Prophylaxis Through an Early Antiviral Immune Response in Donor-Positive, Recipient-Negative Kidney Transplants

American Journal of Transplantation 2016; 16: 2384–2394

Kaminski H., Couzi L., Garrigue I. et al.

ABSTRACT

Universal prophylaxis for cytomegalovirus (CMV) prevention is viable but, compared with a preemptive strategy, leads to higher incidence of late-onset disease (LOD) associated with poor patient and graft survival. The purpose of this study was to compare LOD with early onset disease (EOD), with a focus on the highest risk kidney transplant recipients (KTRs): CMV seronegative recipients transplanted from seropositive donors (D+R-). Since CMV control depends on both antiviral treatment and specific immune response, we also compared Vδ2-negative ($V\delta2^{neg}$) γδ T cell expansion involved in CMV infection resolution. EOD was defined as occurring <3 mo and LOD as occurring >3 mo after transplantation. Depending on the period, universal prophylaxis or preemptive treatment was used. Overall, 168 D+R- KTRs were included between 2003 and 2011. LOD was associated with a lower peak DNAemia ($p = 0.04$), fewer recurrences (odds ratio 0.16; 95% confidence interval 0.05–0.55; $p = 0.01$) and shorter anti-CMV curative treatment (40 vs. 60 days, $p < 0.0001$). As a corollary, we found that $V\delta2^{neg}$ γδ T cell expansion was faster in LOD than in EOD (31 vs. 168 days after the beginning of CMV disease, $p < 0.0001$). In D+R- KTRs, universal prophylaxis is associated with more LOD, which had better infection management and a faster immune response. These results support the use of universal prophylaxis over a preemptive strategy and reappraise outcomes of LOD.

41. De novo mTOR inhibitor-based immunosuppression in ABO-incompatible kidney transplantation

Clin Transplant 2015: 29: 1021–1028

Koch M., Wiech T., Marget M. et al.

ABSTRACT

ABO-incompatible (ABO*i*) kidney transplantation (KTx) has become an accepted therapeutic option in renal replacement therapy for patients without a blood group-compatible living donor. Using different desensitization strategies, most centers apply B-cell depletion with rituximab and maintenance immunosuppression (IS) with tacrolimus and mycophenolic acid. This high load of total IS leads to an increased rate of surgical complications and virus infections in ABO*i* patients. Our aim was to establish ABO*i* KTx using an immunosuppressive regimen, which is effective in preventing acute rejection without increasing the risk for viral infections. Therefore, we selected a *de novo* immunosuppressive protocol with low-dose calcineurin inhibitor and the mTOR inhibitor everolimus for our ABO*i* program. Here, we report the first 25 patients with a complete three-yr follow-up treated with this regimen. Three-yr patient survival and graft survival were 96% and 83%. The rate of acute T-cell-mediated rejections was low (12%). Cytomegalovirus (CMV) infection was evident in one patient only (4%). Surgical complications were common (40%), but mild in 80% of cases. We demonstrate that ABO*i* KTx with a *de novo* mTOR inhibitor-based regimen is feasible without severe surgical or immunological complications and a low rate of viral infections.

42. Posttransplantation lymphoproliferative disorder after pediatric solid organ transplantation: experiences of 20 years in a single center

Korean J Pediatr 2017;60(3):86-93

Jeong H. J., Ahn Y. H., Park E. et al.

ABSTRACT

Purpose: To evaluate the clinical spectrum of posttransplantation lymphoproliferative disorder (PTLD) after solid organ transplantation (SOT) in children.

Methods: We retrospectively reviewed the medical records of 18 patients with PTLD who underwent liver (LT) or kidney transplantation (KT) between January 1995 and December 2014 in Seoul National University Children's Hospital.

Results: Eighteen patients (3.9% of pediatric SOTs; LT:KT, 11:7; male to female, 9:9) were diagnosed as having PTLD over the last 2 decades (4.8% for LT and 2.9% for KT). PTLD usually presented with fever or gastrointestinal symptoms in a median period of 7 months after SOT. Eight cases had malignant lesions, and all the patients except one had evidence of Epstein-Barr virus (EBV) involvement, assessed by using *in situ* hybridization of tumor tissue or EBV viral load quantitation of blood. Remission was achieved in all patients with reduction of immunosuppression and/or rituximab therapy or chemotherapy, although 1 patient had allograft kidney loss and another died from complications of chemotherapy. The first case of PTLD was encountered after the introduction of tacrolimus for pediatric SOT in 2003. The recent increase in PTLD incidence in KT coincided with modification of clinical practice since 2012 to increase the tacrolimus trough level.

Conclusion: While the outcome was favorable in that all patients achieved complete remission, some patients still had allograft loss or mortality. To prevent PTLD and improve its outcome, monitoring for EBV infection is essential, which would lead to appropriate modification of immunosuppression and enhanced surveillance for PTLD.

43. Individualized immunosuppression in transplant patients: potential role of pharmacogenetics

Pharmacogenomics and Personalized Medicine 2012:5 63–72

Abboudi H. and MacPhee I. A. M.

ABSTRACT

The immunosuppressive drugs used to prevent the rejection of transplanted organs have a narrow therapeutic index. Under treatment results in episodes of rejection leading to either damage or loss of the organ. Over immunosuppression increases the risk of infection and malignancy as well as drug specific complications including diabetes mellitus and nephrotoxicity. There is wide variation in the drug dose required to achieve target blood concentrations and there is often dissociation between pharmacokinetics and pharmacodynamics. Currently, immunosuppressive drug treatment is individualized based on a clinical assessment of the risk of rejection or toxicity. Therapeutic drug monitoring is routinely employed for several immunosuppressive drugs. Pharmacogenetics has the potential to complement therapeutic drug monitoring but clinical benefit has yet to be demonstrated. Novel biomarker-based approaches to risk stratification and pharmacodynamic monitoring are under development and are ready for clinical trials.

44. Clinical Presentation and Determinants of Mortality of Invasive Pulmonary Aspergillosis in Kidney Transplant Recipients: A Multinational Cohort Study

American Journal of Transplantation 2016; 16: 3220–3234

López-Medrano F., Fernández-Ruiz M., Silva J. T. et al.

ABSTRACT

The prognostic factors and optimal therapy for invasive pulmonary aspergillosis (IPA) after kidney transplantation (KT) remain poorly studied. We included in this multinational retrospective study 112 recipients diagnosed with probable (75.0% of cases) or proven (25.0%) IPA between 2000 and 2013. The median interval from transplantation to diagnosis was 230 days. Cough, fever, and expectoration were the most common symptoms at presentation. Bilateral pulmonary involvement was observed in 63.6% of cases. Positivity rates for the galactomannan assay in serum and bronchoalveolar lavage samples were 61.3% and 57.1%, respectively. *Aspergillus fumigatus* was the most commonly identified species. Six- and 12-week survival rates were 68.8% and 60.7%, respectively, and 22.1% of survivors experienced graft loss. Occurrence of IPA within the first 6 months (hazard ratio [HR]: 2.29; p-value = 0.027) and bilateral involvement at diagnosis (HR: 3.00; p-value = 0.017) were independent predictors for 6- week all-cause mortality, whereas the initial use of a voriconazole-based regimen showed a protective effect (HR: 0.34; p-value = 0.007). The administration of antifungal combination therapy had no apparent impact on outcome. In conclusion, IPA entails a dismal prognosis among KT recipients. Maintaining a low clinical suspicion threshold is key to achieve a prompt diagnosis and to initiate voriconazole therapy.

45. Pneumocystis Pneumonia in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 272–279

Martina S. I., Fishman J. A. and the AST Infectious Diseases Community of Practice

Abstract not available

46. Mucormycosis in renal transplant recipients: review of 174 reported cases
BMC Infectious Diseases (2017) 17:283
Song Y., Qiao J., Giovanni G. et al.

ABSTRACT
Background: Mucormycosis is a highly lethal fungal infection especially in immunocompromised individuals.
Methods: In order to review the epidemiology, diagnosis, and treatment of mucormycosis in renal transplant recipients we searched publications of mucormycosis cases in renal transplant recipients in PUBMED database up to December 2015.
Results: A total of 174 cases in renal transplant recipients were included in this review. Most of the cases (76%) were male. Major underlying diseases were diabetes mellitus (43.1%). Rhinocerebral was the most common site of infection (33.3%). Rhizopus species was the most frequent fungus (59.1%) in patients with pathogen identified to species level. The mortality rates of disseminated mucormycosis (76.0%) and graft renal (55.6%) were higher than infection in other sites. The overall survival in patients received surgical debridement combined with amphotericin B/posaconazole (70.2%) was higher than those who received antifungal therapy alone (32.4%), surgery alone (36.4%) or without therapy (0%) ($p < 0.001$). The overall survivals in patients receiving posaconazole and lipid amphoterincin B were higher than that receiving deoxycholate formulation (92.3% and 73.4% vs 47.4%).
Conclusions: Mucormycosis is a severe infection in renal transplant recipients. Surgical debridement combined with antifungals, especially liposomal amphotericin B and posaconazole, can significantly improve patient's overall survival.

47. Minimum mycophenolic acid levels are associated with donor-specific antibody formation
Pediatr Transplantation 2016: 20: 34–38
Filler G., Todorova E.K., Bax K. et al.

ABSTRACT
Although *de novo* DSA are associated with inferior graft survival, there are no effective strategies to prevent their formation. Underexposure to MPA (prodrug: MMF) also contributes to rejection rates early after transplantation, but the effect of this phenomenon on the formation of DSA long-term post-transplantation is unknown. Data are expressed as mean (standard deviation). All available data from 32 renal transplant recipients (age at transplantation 7.5 [4.5] yr) on tacrolimus and MPA immunosuppression with an average followup of 9.4 (s.d. 4.6) yr were analyzed. DSA were measured using the Luminex assay (>500 MFI was considered DSA-positive). Tacrolimus and MPA levels were measured with the Abbot Tacro II and EMIT assay, respectively. Among 1964 MPA and 3462 tacrolimus trough levels, the average MPA trough level was 3.2 (1.5) mg/L and the average tacrolimus level was 6.7 (2.8) ng/mL. At last follow-up, only 5/32 patients had undetectable DSA, with 5/32 having no class I antibodies and 6/32 having no class II antibodies. DSA formation was associated with a lower minimum MPA trough level (0.27 [0.23] vs. 0.47 [0.18] mg) and cystatin C eGFR (48 [21] vs. 70 [23] mL/min/1.73 m^2) for class I DSA formers. The average eGFR of patients without class I DSA was 70 (23) mL/min/1.73 m^2, whereas the average eGFR of patients with class I DSA was 48 (21) mL/min/1.73 m^2 ($p = 0.0071$). MPA trough levels <1.3 mg/L long-term post-transplantation are associated with the formation of DSA. The association between the formation of DSA and minimum MPA exposure may support a strategy for preventing the formation of DSA.

48. Peripheral natural killer cell and allo-stimulated T-cell function in kidney transplant recipients associate with cancer risk and immunosuppression related complications

Kidney Int. 2015 December ; 88(6): 1374–1382

Hope C. M., Fuss A., Hanf W. et al.

ABSTRACT

Reducing immunosuppression has been proposed as a means of preventing cancer in kidney transplant recipients but this can precipitate graft rejection. Here we tested whether anti-tumor natural killer (NK) cell and allo-responsive T-cell function in kidney transplant recipients may predict cancer risk and define risk of rejection. NK cell function was measured by the release of lactate dehydrogenase and T cell allo-response by interferon-γ quantification using a panel of reactive T cell Enzyme-Linked ImmunoSpot (ELISPOT) in 56 kidney transplant recipients with current or past cancer and 26 kidney transplant recipients without cancer. NK function was significantly impaired and the allo-response was significantly lower in kidney transplant recipients with cancer. With prospective follow-up, kidney transplant recipients with poor NK cell function had a hazard ratio of 2.1 [95% Confidence Interval 0.97–5.00] for the combined endpoint of metastatic cancer, cancer related death, or septic death. Kidney transplant recipients with low interferon-γ release were also more likely to reach this combined endpoint. Thus, post-transplant monitoring of allo-immunity and NK cell function is useful for assessing the risk of over immunosuppression for the development of malignancy and/or death from cancer or sepsis.

49. Low Natural Cell Counts and Risk of Invasive Fungal Disease After Solid Organ Transplantation

The Journal of Infectious Diseases 2016;213:873–4

Fernández-Ruiz M., F. López-Medrano, San Juan R. et al.

Letter to Editor

50. Therapeutic drug monitoring – Key to personalized pharmacotherapy
Clin Biochem (2017)
Oellerich M., Kanzow P., Walson P. D.

Abstract not available

51. Post-transplant Pneumocystis jirovecii pneumonia—a re-emerged public health problem?
Kidney International (2013) 84, 240–243
Chapman J. R., Marriott D. J., Chen S. C-A et al.

ABSTRACT
Pneumocystis jirovecii is a unicellular organism that in individuals with impaired immunity may cause pneumonia that can progress from minor illness to severe inflammatory pneumonia (PCP) with respiratory failure and death. Despite antimicrobial prophylaxis, which has reduced the incidence of PCP, clusters of late infections have been reported among kidney transplant recipients worldwide. A nosocomial PCP cluster was first recognized in 2010 at a Sydney hospital, but PCP clusters have since occurred in almost half of the renal transplant units on the eastern Australian seaboard, refocussing attention on optimal prophylaxis regimens and the likelihood of patient-to-patient transmission. A consensus meeting was conducted to derive the lessons from this experience for responding to PCP outbreaks. These included: (1) acting quickly—clusters of PCP in kidney transplant recipients with patient-to-patient transmission required transplant programs to act quickly to institute prophylactic and treatment measures; (2) instituting universal prophylaxis for all patients seen in the affected unit; (3) reducing patientto-patient transmission via airborne droplets in the outpatient waiting areas; (4) examining the *P. jirovecii* genotypes. The meeting also considered recommendations for the duration of prophylaxis following de novo transplant and, for the individuals in whom long term prophylaxis is required, separating units with and without clusters of PCP.

52. Cytomegalovirus-Responsive CD8⁺ T Cells Expand After Solid Organ Transplantation in the Absence of CMV Disease

American Journal of Transplantation 2017; XX: 1–10

Higdon L. E., Trofe-Clark J., Liu S. et al.

ABSTRACT

Cytomegalovirus (CMV) is a major cause of morbidity and mortality in solid organ transplant recipients. Approximately 60% of adults are CMV seropositive, indicating previous exposure. Following resolution of the primary infection, CMV remains in a latent state. Reactivation is controlled by memory T cells in healthy individuals; transplant recipients have reduced memory T cell function due to chronic immunosuppressive therapies. In this study, $CD8^+$ T cell responses to CMV polypeptides immediate-early-1 and pp65 were analyzed in 16 CMV-seropositive kidney and heart transplant recipients longitudinally pretransplantation and posttransplantation. All patients received standard of care maintenance immunosuppression, antiviral prophylaxis, and CMV viral load monitoring, with approximately half receiving T cell–depleting induction therapy. The frequency of CMV responsive $CD8^+$ T cells, defined by the production of effector molecules in response to CMV peptides, increased during the course of 1 year posttransplantation. The increase commenced after the completion of antiviral prophylaxis, and these T cells tended to be terminally differentiated effector cells. Based on this small cohort, these data suggest that even in the absence of disease, antigenic exposure may continually shape the CMV-responsive T cell population posttransplantation.

53. Clinical Usefulness of Monitoring Cytomegalovirus-Specific Immunity by Quantiferon-CMV in Pediatric Allogeneic Hematopoietic Stem Cell Transplantation Recipients

Ann Lab Med 2017;37:277-281

Lee S. M., Kim Y-J., Yoo K. H. et al.

ABSTRACT

Cytomegalovirus (CMV) is a well-established cause of morbidity and mortality in pediatric recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT). $CD8^+$ T-cells are important for controlling CMV infection. We conducted a prospective pilot study to investigate the clinical utility of measuring the CMV-specific T-cell immune response using the QuantiFERON-CMV assay (QF-CMV) in pediatric allo-HSCT recipients. Overall, 16 of 25 (64%) patients developed CMV infection. QF-CMV was evaluated in these 16 patients during the early and late phases of the first CMV infection post allo-HSCT. Whereas the initial QF-CMV results during the early phase of CMV infection did not correlate with the course of the corresponding infection, the QF-CMV results post resolution of the first CMV infection correlated with the recurrence of CMV infection until 12 months post allo-HSCT; no recurrent infections occurred in the four QF-CMV-positive patients, while recurrent infections manifested in five of eight QF-CMV-negative (62.5%) and all three QF-CMV-indeterminate patients (P=0.019). In spite of the small number of patients examined, this study supports the potential application of monitoring CMV-specific T-cell immunity using the QF-CMV assay to predict the recurrence of CMV infection in pediatric allo-HSCT recipients.

54. Clinical Utility of QuantiFERON-Cytomegalovirus Test in Management of Kidney Transplant Recipients

Transplantation Proceedings, 48, 1650e1653 (2016)

Tarasewicz A., Dębska-Slizien A., and Rutkowski B.

ABSTRACT

Immune monitoring of cytomegalovirus (CMV) e specific T-cells responses has become an additional tool in the CMV risk assessment of kidney transplant recipients (KTRs). Some data demonstrated a potential use of QuantiFERON-CMV assay (QF-CMV) in stratifying CMV risk before transplantation, at the end of prophylaxis and during pre-emptive strategy. High risk for CMV disease was also reported in KTRs with indeterminate QF-CMV results in which both mitogen and CMV antigen responses were absent. Twenty-five KTRs in the first year after kidney transplantation (KT), including 17 KTRs after CMV infection treatment (CMV-KTR), were studied by QF-CMV assay.

Positive QF assay (QF+) was present in 16 of 25 (64%) of KTRs, negative (QF-) in 5 of 25 (20%), and indeterminate (QF0) in 4 of 25 (16%). The QF0 patients, in comparison to the combined group of QF+ and QF-, presented an increased incidence of CMV disease (4 of 4 [100%] vs. 7 of 21 [33.3%]; $P < .05$) and severe infectious complications such as sepsis, and systemic mycosis (4 of 4 [100%] vs. 6 of 21 [29%]; $P < .02$). Of 17 CMV-KTRs, 11 of 17 (64.7%) were QF+, 2 of 17 (11.8%) were QF-, and 4 of 17 (23.5%) were QF0. The incidence of CMV disease and severe infectious complications was not different among these groups. CMV-KTRs with interferon-γ <3.5 IU/mL vs. >3.5 IU/mL in mitogen tube, irrespective of QF-CMV status, showed an increased incidence of CMV disease (8 of 9 [88.9%] vs. 3 of 8 [37.5%]; $P < .05$) and severe infectious complications (8 of 9 [88.9%] vs. 2 of 8 [25%]; $P < .02$).

In conclusion, indeterminate result of QF-CMV or interferon-γ <3.5 IU/mL in mitogen tube seems to be related to impaired immunity. The QF-CMV assay appears to be a useful tool in clinical practice, identifying the group of KTRs with increased risk of infectious complications who may benefit from immunosuppression reduction and maintenance of antiviral prophylaxis.

55. Comparison of Cytomegalovirus (CMV) Enzyme-Linked Immunosorbent Spot and CMV Quantiferon Gamma Interferon- Releasing Assays in Assessing Risk of CMV Infection in Kidney Transplant Recipients

Journal of Clinical Microbiology p. 2501–2507

Abate D., Saldan A., Mengoli C. et al.

ABSTRACT

Assessing cytomegalovirus (CMV)-specific cell-mediated immunity (CMI) represents an appealing strategy for identifying transplant recipients at risk of infection. In this study, we compared two gamma interferon-releasing assays (IGRAs), Quantiferon- CMV and CMV enzyme-linked immunosorbent spot (ELISPOT), to determine the ability of each test to predict protective CMVspecific T-cell responses. Two hundred twenty-one Quantiferon-CMV and ELISPOT tests were conducted on 120 adult kidney transplant recipients (KTRs), including 100 CMV-seropositive transplant recipients (R+) and 20 CMV-seronegative transplant recipients of a CMV-positive donor (D^+/R^-). As a control cohort, 39 healthy adult subjects (including 33 CMV-seropositive and 6 CMV-seronegative subjects) were enrolled. CMV IgG serology was used as a reference for both tests. In the CMV-seropositive individuals, the ELISPOT and Quantiferon-CMV assays provided 46% concordance with the serology, 12% discordance, 18% disagreement between ELISPOT or Quantiferon-CMV and the serology, and 24% gray areas when one or both tests resulted in weak positives. None of the CMV-seronegative subjects showed detectable responses in the ELISPOT or the Quantiferon-CMV test. In transplant recipients, both the ELISPOT and Quantiferon-CMV assays positively correlated with each other and negatively correlated with CMV DNAemia in a significant way ($P<0.05$). During the antiviral prophylaxis, all 20 D^+/R^- KTRs we examined displayed undetectable Quantiferon-CMV and ELISPOT results, and there was no evidence of CMV seroconversion.

The receiving operator curve (ROC) statistical analysis revealed similar specificities and sensitivities in predicting detectable viremia (areas under the curve [AUC], 0.66 and 0.62 for Quantiferon-CMV and ELISPOT, respectively). ELISPOT and Quantiferon- CMV values of>150 spots/200,000 peripheral blood mononuclear cells (PBMCs) and>1 to 6 IU gamma interferon (IFN-γ) were associated with protection from CMV infection (odds ratios [OR], 5 and 8.75, respectively). In transplant recipients, the two tests displayed similar abilities for predicting CMV infection. Both the ELISPOT and Quantiferon-CMV assays require several ameliorations to avoid false-negative results.

56. Cytomegalovirus in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 93–106

Razonable R. R., Humarb A. and the AST Infectious Diseases Community of Practice

Abstract not available

57. A new strategy of delayed long-term prophylaxis could prevent cytomegalovirus disease in (D+/R-) solid organ transplant recipients

Clin Transplant 2009: 23: 666–671

San Juan R., Yebra M., Lumbreras C. et al.

ABSTRACT

Long-term prophylaxis against cytomegalovirus (CMV) started immediately after transplantation in (D+/R-) poses a higher risk of lateonset CMV disease. Delayed CMV prophylaxis could allow a transitory exposure of the immune system to CMV, which would let the immune system mount an adequate CMV-specific cytotoxic response in (D+/R-) patients and confer protection against CMV disease. We included all (D+/ R-) solid organ transplant recipients (SOT) performed at our institution (January 3/October 6) who received CMV prophylaxis (mainly with oral valganciclovir) during 100 d. In the first period (until December 4), prophylaxis was initiated immediately after transplantation (conventional prophylaxis: CP). Since January 5, it was initiated after 14 d (delayed prophylaxis: DP). Incidence and severity of CMV disease was compared between both groups. A total of 44 SOT recipients were included (CP: 26 and DP: 18). CMV disease was diagnosed in eight patients (18%), seven of 26 (27%) in the CP group, and one of 18 (5.5%) in the DP group ($p = 0.07$). CMV colitis was reported in five of 26 patients in the CP group (19%), whereas there were no cases of visceral CMV disease in the DP group ($p = 0.048$). A 14-d delay in the beginning of long-term prophylaxis against CMV in (D+/R-) is safe and could prevent the onset of late-CMV disease.

58. Effect of long-term prophylaxis in the development of cytomegalovirus-specific T-cell immunity in D+/R- solid organ transplant recipients

Transplant Infectious Disease 2015: 17: 637–646

San-Juan R., Navarro D., García-Reyne A. et al.

ABSTRACT

Background: This study aimed to characterize the dynamics of acquisition of cytomegalovirus (CMV)-specific cellmediated immunity (CMI) in CMV donor positive/recipient negative solid organ transplant (SOT) patients receiving long-term antiviral prophylaxis, and to determine whether development of CMI confers protection against CMV disease.

Methods: A prospective multicenter study was conducted in Spain from September 2009 to September 2012. Whole blood specimens were prospectively collected at 30, 90, 120, 200, and 365 days after SOT, and CMI was determined by enumeration of CMV pp65 and IE- 1-specific $CD69^+$/interferon-γ-producing $CD8^+$ and $CD4^+$ T cells by flow cytometry for intracellular cytokine staining. As part of a simultaneous clinical trial, patients received either early prophylaxis (in the first 3 days after transplantation) in the first period of the study or delayed prophylaxis (initiated at day 14) during the second period of the study. The impact of the dynamics of acquisition of CMV-specific CMI on the incidence of CMV disease was evaluated by Kaplan–Meier survival analysis.

Results: A total of 95 SOT recipients were recruited. CMV infection and disease occurred in 38 (40%) and 26 (27.4%) patients, respectively. The proportion of patients achieving any detectable CMV-specific CMI response at each of the different monitoring points was higher in liver transplant recipients, as compared to kidney or heart transplant recipients. The presence of any detectable response at day 120 or 200 was protective against the development of CMV disease (positive predictive values 92% and 93%, respectively).

Conclusions: The rate of acquisition of CMV-specific CMI in SOT recipients undergoing antiviral prophylaxis differed significantly between different SOT populations. Patients developing any detectable CMI response were protected against the occurrence of CMV disease.

59. ABO desensitization affects cellular immunity and infection control after renal transplantation

Transplant International ESOT 28 (2015) 1179–1194

Schachtner T., Stein M. and Reinke P.

ABSTRACT

The impact of ABO desensitization on overall immunity, infectious control, and alloreactivity remains unknown. We compared 35 ABO-incompatible kidney transplant recipients (KTRs) to a control of 62 ABO compatible KTRs. Samples were collected before, at +1, +2, +3, +6, and +12 months post-transplantation. CMV-, BKV-specific, and alloreactive T cells were measured using an interferon-γ ELISPOT assay. The extent of immunosuppression was quantified by enumeration of lymphocyte subpopulations and cytokines. No differences were observed for 5-year allograft survival and function between both groups ($P > 0.05$). However, ABO-incompatible KTRs were more likely to develop CMV infection, BKV-associated nephropathy, and severe sepsis ($P = 0.001$). Interestingly, ABO-incompatible KTRs with poor HLA-match showed the highest rates of infections and inferior allograft function ($P < 0.05$). $CD3^+$, $CD4^+$ T-cell counts, interferon-γ and IL-10 levels were lower in ABO-incompatible KTRs early post-transplantation ($P < 0.05$). Likewise, ABO-incompatible KTRs showed impaired BKV- and CMV-specific T-cell immunity ($P < 0.05$). ABO-incompatible KTRs showed lower frequencies of alloreactive T cells ($P < 0.05$). Our data suggest T-cell depletion due to ABO desensitization, which may contribute to the increased risk of T-cell-dependent infections. Elimination of B cells serving as antigen-presenting cells, thereby causing impaired T-cell activation, plays a significant role in both impaired infection control and reduced alloreactive T-cell activation.

60. Parasitic Infections in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 280–303

Schwartza B. S., Mawhorter S. D. and the AST Infectious Diseases Community of Practice

Abstract not available

61. Sequential Targeting of CD52 and TNF Allows Early Minimization Therapy in Kidney Transplantation: From a Biomarker to Targeting in a Proof-Of-Concept Trial

PLOS ONE | DOI:10.1371/journal.pone.0169624 January 13, 2017

Viklicky O., Hruba P., Tomiuk S. et al.

ABSTRACT

Background: There is high medical need for safe long-term immunosuppression monotherapy in kidney transplantation. Selective targeting of post-transplant alloantigen-(re)activated effector-T cells by anti-TNF antibodies after global T cell depletion may allow safe drug minimization, however, it is unsolved what might be the best maintenance monotherapy.

Methods: In this open, prospective observational single-centre trial, 20 primary deceased donor kidney transplant recipients received 2x20 mg Alemtuzumab (d0/d1) followed by 5 mg/kg Infliximab (d2). For 14 days all patients received only tacrolimus, then they were allocated to either receive tacrolimus (TAC, n = 13) or sirolimus (SIR, n = 7) monotherapy, respectively. Protocol biopsies and extensive immune monitoring were performed and patients were followed-up for 60 months.

Results: TAC-monotherapy resulted in excellent graft survival (5yr 92%, 95%CI: 56.6-98.9) and function, normal histology, and no proteinuria. Immune monitoring revealed low intragraft PLOS ONE inflammation (urinary IP-10) and hints for the development of operational tolerance signature in the TAC- but not SIR-group. Remarkably, the TAC-monotherapy was successful in all five presensitized (ELISPOT+) patients. However, recruitment into SIR-arm was stopped (after n = 7) because of high incidence of proteinuria and acute/chronic rejection in biopsies. No opportunistic infections occurred during follow-up.

Conclusions: In conclusion, our novel fast-track TAC-monotherapy protocol is likely to be safe and preliminary results indicated an excellent 5-year outcome, however, a full-scale study will be needed to confirm our findings.

62. Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus

American Journal of Transplantation 2015; 15: 2655–2664

Tedesco-Silva H., Felipe C., Ferreira A. et al.

ABSTRACT

This study compared the incidence of CMV infection/disease in de novo kidney transplant recipients receiving everolimus ormycophenolate and no CMV pharmacological prophylaxis. We randomized 288 patients to receive a single 3mg/kg dose of antithymocyte globulin, tacrolimus, everolimus, and prednisone (r-ATG/ EVR, n=85); basiliximab, tacrolimus, everolimus, and prednisone (BAS/EVR, n=102); or basiliximab, tacrolimus, mycophenolate, and prednisone (BAS/MPS, n=101). The primary end-point was the incidence of first CMV infection/disease in the intention-to-treat population at 12 months. Patients treated with r-ATG/ EVR showed a 90% proportional reduction (4.7% vs. 37.6%, HR 0.10, 95% CI 0.037–0.29; p<0.001), while those treated with BAS/EVR showed a 75%proportional reduction (10.8% vs. 37.6%, HR 0.25, 95%CI 0.13–0.48; p<0.001) in the incidence of CMV infection/disease compared to BAS/MPS. There were no differences in the incidence of acute rejection (9.4 vs. 18.6 vs. 15.8%, p=0.403), wound-healing complications, delayed graft function, and proteinuria. Mean estimated glomerular filtration rate was lower in BAS/EVR (65.7±21.8 vs. 60.6±20.9 vs. 69.5±21.5ml/min, p¼0.021). In *de novo* kidney transplant recipients receiving no pharmacological CMV prophylaxis, reduced-dose tacrolimus and everolimus was associated with a significant reduction in the incidence of CMV infection/disease compared to standard tacrolimus dose and mycophenolate (Clinical- Trials.gov NCT01354301).

63. *Candida* Infections in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 220–227

Silveira F. P., Kusne S. and the AST Infectious Diseases Community of Practice

Abstract not available

64. Aspergillosis in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 228–241

Singh N. M., Husain S. and the AST Infectious Diseases Community of Practice

Abstract not available

65. Everolimus Versus Mycophenolate Mofetil *De Novo* After Lung Transplantation: A Prospective, Randomized, Open-Label Trial

American Journal of Transplantation 2016; 16: 3171–3180

Strueber M., Warnecke G., Fuge J. et al.

ABSTRACT

The role of mammalian target of rapamycin (mTOR) inhibitors in de novo immunosuppression after lung transplantation is not well defined. We compared Everolimus versus mycophenolate mofetil in an investigator-initiated single-center trial in Hannover, Germany. A total of 190 patients were randomly assigned 1:1 on day 28 posttransplantation to mycophenolate mofetil (MMF) or Everolimus combined with cyclosporine A (CsA) and steroids. Patients were followed up for 2 years. The primary endpoint was freedom from bronchiolitis obliterans syndrome (BOS). The secondary endpoints were incidence of acute rejections, infections, treatment failure and kidney function. BOS-free survival in intention-to-treat (ITT) analysis was similar in both groups (p = 0.174). The study protocol was completed by 51% of enrolled patients. The per-protocol analysis shows incidence of bronchiolitis obliterans syndrome (BOS): 1/43 in the Everolimus group and 8/54 in the MMF group (p = 0.041). Less biopsy-proven acute rejection (AR) (p = 0.005), cytomegalovirus (CMV) antigenemia (p = 0.005) and lower respiratory tract infection (p = 0.003) and no leucopenia were seen in the Everolimus group. The glomerular filtration rate (GFR) decreased in both groups about 50% within 6 months. Due to a high withdrawal rate, the study was underpowered to prove a difference in BOS-free survival. The dropout rate was more pronounced in the Everolimus group. Secondary endpoints indicate potential advantages of Everolimus-based protocols but also a potentially higher rate of drug-related serious adverse events.

66. CMV-specific T-cell immunity, viral load, and clinical outcome in seropositive renal transplant recipients: a pilot study

Clin Transplant 2010: 24: 401–409

Sund F., Lidehäll A-K., Claesson K. et al.

ABSTRACT

Background: Cytomegalovirus (CMV) infection is still the leading opportunistic infection following solid organ transplantation. The aim of this prospective study of renal transplant recipients was to evaluate the dynamics of CMV-specific T-cells, viral load, and clinical symptoms of CMV infection.

Methods: Levels of tetramer-selected $CD8^+$ T-cells (TetraCD8), CMV-specific interferon-γ producing $CD8^+$ T-cells (IFNγCD8), and $CD4^+$ T-cells (IFNγCD4), measured using major histocompatibility complex-tetramer and cytokine flow cytometry techniques, and CMV DNA were monitored monthly in 17 CMV-seropositive patients up to one yr (median 12 months, range 3–12) after transplantation and correlated to clinical outcome.

Results: CMV DNAemia was detected in 94% of the patients, but only one patient developed CMV disease. CMV DNAemia >1 million copies/mL was seen in asymptomatic patients. CMV-specific T-cells decreased rapidly after transplantation. TetraCD8 and IFNγCD8 regenerated within three months, whereas IFNγCD4 recovery was impaired up to one yr after transplantation. The proportion of IFNγCD4 at two months posttransplantation as compared with baseline, correlated strongly with the magnitude of the CMV DNAemia.

Conclusions: Monitoring the reduction of IFNγCD4 compared with baseline during the first months after transplantation could be considered in predicting risk for high-grade CMV DNAemia and in deciding strategic approaches for pre-emptive and prophylactic therapy.

67. Validation of T-Track® CMV to assess the functionality of cytomegalovirus-reactive cell-mediated immunity in hemodialysis patients

BMC Immunology (2017) 18:15

Banas B., Böger C. A., Lückhoff G. et al.

ABSTRACT

Background: Uncontrolled cytomegalovirus (CMV) replication in immunocompromised solid-organ transplant recipients is a clinically relevant issue and an indication of impaired CMV-specific cell-mediated immunity (CMI). Primary aim of this study was to assess the suitability of the immune monitoring tool T-Track® CMV to determine CMV-reactive CMI in a cohort of hemodialysis patients representative of patients eligible for renal transplantation. Positive and negative agreement of T-Track® CMV with CMV serology was examined in 124 hemodialysis patients, of whom 67 (54%) revealed a positive CMV serostatus. Secondary aim of the study was to evaluate T-Track® CMV performance against two unrelated CMV-specific CMI monitoring assays, QuantiFERON®-CMV and a cocktail of six class I iTAg™ MHC Tetramers.

Results: Positive T-Track® CMV results were obtained in 90% (60/67) of CMV-seropositive hemodialysis patients. In comparison, 73% (45/62) and 77% (40/52) positive agreement with CMV serology was achieved using QuantiFERON®-CMV and iTAg™ MHC Tetramer. Positive T-Track® CMV responses in CMV-seropositive patients were dominated by pp65-reactive cells (58/67 [87%]), while IE-1-responsive cells contributed to an improved (87% to 90%) positive agreement of T-Track® CMV with CMV serology. Interestingly, T-Track® CMV, QuantiFERON®-CMV and iTAg™ MHC Tetramers showed 79% (45/57), 87% (48/55) and 93% (42/45) negative agreement with serology, respectively, and a strong inter-assay variability. Notably, T-Track® CMV was able to detect IE-1-reactive cells in blood samples of patients with a negative CMV serology, suggesting either a previous exposure to CMV that yielded a cellular but no humoral immune response, or TCR cross-reactivity with foreign antigens, both suggesting a possible protective immunity against CMV in these patients.

Conclusion: T-Track® CMV is a highly sensitive assay, enabling the functional assessment of CMV-responsive cells in hemodialysis patients prior to renal transplantation. T-Track® CMV thus represents a valuable immune monitoring tool to identify candidate transplant recipients potentially at increased risk for CMV-related clinical complications.

68. Fingerprints of transplant tolerance suggest opportunities for immunosuppression minimization

Clinical Biochemistry 49 (2016) 404–410

Sarwal M. M.

ABSTRACT

HLA incompatible organ transplant tolerance is the holy grail of transplantation. Stable engraftment of an HLA mismatched allograft and life-long tolerance induction, though feasible in highly selected cohorts with depletional protocols, is not ready for generalized application to the entire transplant recipient pool. It has thus been important to harness biomarkers that can uncover mechanisms and tools for monitoring HLA mismatched recipients that develop a state of operational tolerance, during accidental immunosuppression withdrawal secondary to problems of over-immunosuppression (infection or malignancy) or toxicity (mostly cosmetic or cardiovascular). A restricted and unpredictable group of patients can demonstrate a clinical state of operational tolerance, manifested by state of stable graft function of a graft with HLA mismatches between recipient and donor, intact immune responses to third party antigens and no measurable immunosuppression. These patients have served as the basis for the discovery of clinically correlative biomarkers, in distal biofluids (mainly blood), that can define the existing state of operational clinical tolerance. Operationally tolerant patients are rare, as withdrawal of immunosuppression most often results in rejection and graft loss. Nevertheless, operationally tolerant kidney, liver and heart allograft recipients have been reported. The presence of similar biomarker signature profiles in HLA mismatched transplant recipients on immunosuppression, suggests the feasibility of utilizing these biomarkers for educated immunosuppression minimization with a view to retaining immunological quiescence, while reducing the maintenance immunosuppression burden to a “safe” alloimmune threshold. Though clinical operational tolerance is rare, as immunosuppression cessation most often results in increased alloimmunity and rejection, the biomarker profile studies that have harnessed whole genome profiling suggest that the frequency of this state may be ~8% in kidney allograft recipients, and even more frequent in pediatric recipients and in liver transplantation: 25% in adult liver allograft recipients and ~60% in pediatric liver allograft recipients. In this review we discuss putative molecular mechanisms, cellular players and correlative biomarkers that have been developed through clinically associative studies of tolerant and non-tolerant patients. Through mechanisms of carefully constructed and monitored randomized, prospective clinical trials, the transplant community stands at the cusp of improved quality of recipient life through educated immunosuppression minimization.

69. *Aspergillus* Tracheobronchitis

Medicine 2012;91: 261Y273

Fernández-Ruiz M., Tiago Silva J., San-Juan R. et al.

ABSTRACT

Aspergillus tracheobronchitis (AT) is an infrequent but severe form of invasive pulmonary aspergillosis in which the fungal infection is entirely or predominantly confined to the tracheobronchial tree. We reviewed 8 cases of AT diagnosed in our tertiary care center during an 18-year period, as well as 148 cases previously reported in the English literature from 1985 to July 2011. The demographic, clinical, imaging, bronchoscopic, and outcome characteristics of every eligible patient were excerpted, and predictors of inhospital mortality were identified by logistic regression. Solid organ transplantation (SOT) (44.2%), hematologic malignancy (21.2%), neutropenia (18.7%), and chronic obstructive pulmonary disease (15.4%) were the most common underlying conditions reported. Most cases occurred in patients receiving long-term corticosteroid treatment (71.8%) or chemotherapy (25.0%). Fever and respiratory complaints (cough, dyspnea, stridor, or wheezing) were the most frequent symptoms; one-third of patients developed acute respiratory distress at presentation, and 15.1% were asymptomatic at the time of diagnosis. Initial imaging studies were not informative in 47.4% of the cases. *Aspergillus fumigatus* was the predominant species (74.4%). The pseudomembranous form was the most commonly observed (31.9% of cases) and was more frequent in neutropenic patients ($p = 0.007$), whereas ulcerative AT (31.2%) was associated with SOT ($p = 0.001$). The most frequent antifungal monotherapy regimens were amphotericin B deoxycholate (23.1%) and itraconazole (18.6%), whereas combined therapy was administered in 35.9% of the cases. Overall in hospital mortality was 39.1%, with neutropenia (odds ratio [OR], 20.47; $p < 0.001$) and acute respiratory distress at presentation (OR, 9.54; $p = 0.002$) as independent prognostic factors. Our pooled analysis of the literature shows that AT remains a rare opportunistic infection with a nonspecific presentation and a variable course depending on the nature of the predisposing factor.

70. Number of Peripheral Blood Regulatory T Cells and Lymphocyte Activation at 3 Months After Conversion to mTOR Inhibitor Therapy

Transplantation Proceedings, 42, 2871–2873 (2010)

San Segundo D., Fernández-Fresnedo G., Gago M. et al.

ABSTRACT

Background. Mammalian target of rapamycin (mTOR) inhibitors are effective for induction and maintenance of regulatory T cells (Tregs).

Objective. To assess the effects of conversion from calcineurin inhibitors (CNIs) to mTOR on the number of circulating Tregs and lymphocyte activation.

Patients and Methods. In 18 renal transplant recipients receiving CNI therapy (cyclosporine in 9, and tacrolimus in 9), treatment was converted to mTOR inhibitors (everolimus in 14, and rapamycin in 4). Peripheral blood samples were obtained before and 3 months after conversion. The number of circulating Tregs was measured using flow cytometry, and defined as CD4+/CD25high/CD127low/CD27+/CD62L+/CD45RO+/ Foxp3+. Lymphocyte activation was assessed indirectly according to production of intracellular adenosine triphosphate (iATP) on polyclonal activation using a phytohemaglutinin assay (Immuknow; Cylex, Inc, Columbia, Maryland).

Results. In 15 patients (83.3%), the absolute number of Tregs increased significantly (P=.001) after conversion (median, 16.35 cells/mm^3; 95% confidence interval [CI], 13.97–21.94) vs 3 months after conversion (32.03 cells/mm^3; 95% CI, 26.25–41.66). The iATP production decreased from 326 ng/mL (95% CI, 302–419) to 248 ng/mL (95% CI, 196–318; P = .02), and increased in 4 patients (22.22%). No significant correlation was demonstrated between Treg concentration and change in iATP production. No rejection episodes were reported during follow-up.

Conclusions. Despite the small number of patients in whom therapy was converted from CNI inhibitors to mTOR inhibitors, the data suggest an increase in the absolute number of Tregs after conversion. In addition, the concentration of activated peripheral $CD4^+$ T cells decreased to nearly that associated with risk of infection due to overimmunosuppression.

71. Interactions Between Anti-Infective Agents and Immunosuppressants in Solid Organ Transplantation

American Journal of Transplantation 2013; 13: 318–326

Trofe-Clark J., Lemonovich T.L. and the AST Infectious Diseases Community of Practice

Abstract not available

72. CMV and BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor–Based Regimen Versus a CNI-Based Regimen: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

Clin J Am Soc Nephrol 12: 2017

Mallat S. G., Tanios B. Y., Itani H. S. et al.

ABSTRACT

Background and objectives: The objective of this meta-analysis is to compare the incidences of cytomegalovirus and BK polyoma virus infections in renal transplant recipients receiving a mammalian target of rapamycin inhibitor (mTOR)–based regimen compared with a calcineurin inhibitor–based regimen.

Design, setting, participants, & measurements: We conducted a comprehensive search for randomized, controlled trials up to January of 2016 addressing our objective. Other outcomes included acute rejection, graft loss, serious adverse events, proteinuria, wound-healing complications, and eGFR. Two review authors selected eligible studies, abstracted data, and assessed risk of bias. We assessed quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation methodology.

Results: We included 28 randomized, controlled trials with 6211 participants classified into comparison 1: mTOR inhibitor versus calcineurin inhibitor and comparison 2: mTOR inhibitor plus reduced dose of calcineurin inhibitor versus regular dose of calcineurin inhibitor. Results showed decreased incidence of cytomegalovirus infection in mTOR inhibitor–based group in both comparison 1 (risk ratio, 0.54; 95% confidence interval, 0.41 to 0.72), with high quality of evidence, and comparison 2 (risk ratio, 0.43; 95% confidence interval, 0.24 to 0.80), with moderate quality of evidence. The available evidence neither confirmed nor ruled out a reduction of BK polyoma virus infection in mTOR inhibitor–based group in both comparisons. Secondary outcomes revealed more serious adverse events and acute rejections in mTOR inhibitor–based group in comparison 1 and no difference in comparison 2. There was no difference in graft loss in both comparisons. eGFR was higher in the mTOR inhibitor–based group in comparison 1 (mean difference =4.07 ml/min per 1.73 m2; 95% confidence interval, 1.34 to 6.80) and similar to the calcineurin inhibitor–based group in comparison 2. More proteinuria and wound-healing complications occurred in the mTOR inhibitor–based groups.

Conclusions: We found moderate- to high-quality evidence of reduced risk of cytomegalovirus infection in renal transplant recipients in the mTOR inhibitor–based compared with the calcineurin inhibitor–based regimen. Our review also suggested that a combination of a mTOR inhibitor and a reduced dose of calcineurin inhibitor may be associated with similar eGFR and rates of acute rejections and serious adverse events compared with a standard calcineurin inhibitor–based regimen at the expense of higher incidence of proteinuria and wound-healing complications.

73. Biomarkers of Over-Immunosuppression

Clinical pharmacology & Therapeutics, volume 90 number 2, august 2011

Budde K, Matz M, Dürr M and Glander P.

SUMMARY

An important goal in transplantation is to tailor immunosuppression to the individual needs of the patient, avoiding both rejection and over-immunosuppression. Opportunistic infections and malignancies remain a significant cause of death after transplantation and are obvious consequences of over-immunosuppression. Currently, monitoring of immunosuppression is conducted mainly on the basis of pharmacokinetic characteristics, which do not necessarily predict clinical outcome in the individual. This review focuses on the potential of using biomarkers as a monitoring tool to prevent over-immunosuppression after transplantation.

74. Immunologic monitoring in kidney transplant recipients

Kidney Res Clin Pract 32(2013)52–61

Townamchai N., Safa K., Chandraker A.

ABSTRACT

Transplant biopsy has always been the gold standard for assessing the immune response to a kidney allograft (Chandraker A: Diagnostic techniques in the work-up of renal allograft dysfunction—an update. *Curr Opin Nephrol Hypertens* 8:723–728,1999). A biopsy is not without risk and is unable to predict rejection and is only diagnostic once rejection has already occurred. However, in the past two decades, we have seen an expansion in assays that can potentially put an end to the “drug level” era, which until now has been one of the few tools available to clinicians for monitoring the immune response. A better understanding of the mechanisms of rejection and tolerance, and technological advances has led to the development of new noninvasive methods to monitor the immune response. In this article, we discuss these new methods and their potential uses in renal transplant recipients.

75. Management of cytomegalovirus infection in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations

Transplantation Reviews xxx (2016) xxx–xxx

Torre-Cisneros J., Aguado J.M., Casto J.J. et al.

ABSTRACT

Cytomegalovirus (CMV) infection remains a major complication of solid organ transplantation. Because of management of CMV is variable among transplant centers, in 2011 the Spanish Transplantation Infection Study Group (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) developed consensus guidelines for the prevention and treatment of CMV infection in solid organ transplant recipients. Since then, new publications have clarified or questioned the aspects covered in the previous document. For that reason, a panel of experts revised the evidence on CMV management, including immunological monitoring, diagnostics, prevention, vaccines, indirect effects, treatment, drug resistance, immunotherapy, investigational drugs, and pediatric issues. This document summarizes the recommendations.