1. The Emerging Importance of Non-HLA Autoantibodies in Kidney Transplant Complications.

Cardinal H, Dieudé M, Hébert MJ

J Am Soc Nephrol 28: 400–406, 2017. doi: 10.1681/ASN.2016070756

ABSTRACT

Antibodies that are specific to organ donor HLA have been involved in the majority of cases of antibody-mediated rejection in solid organ transplant recipients. However, recent data show that production of non-HLA autoantibodies can occur before transplant in the form of natural autoantibodies. In contrast to HLAs, which are constitutively expressed on the cell surface of the allograft endothelium, autoantigens are usually cryptic. Tissue damage associated with ischemia-reperfusion, vascular injury, and/or rejection creates permissive conditions for the expression of cryptic autoantigens, allowing these autoantibodies to bind antigenic targets and further enhance vascular inflammation and renal dysfunction. Antiperlecan/LG3 antibodies and antiangiotensin II type 1 receptor antibodies have been found before transplant in patients with de novo transplants and portend negative long–term outcome in patients with renal transplants. Here, we review mounting evidence suggesting an important role for autoantibodies to cryptic antigens as novel accelerators of kidney dysfunction and acute or chronic allograft rejection.

2. Not All Antibodies Are Created Equal: Factors That Influence Antibody Mediated Rejection.

Butler CL, Valenzuela NM, Thomas KA, *et al*.

Journal of Immunology Research 2017; 2017(Art. ID 7903471:1- 9.
http://dx.doi.org/10.1155/2017/7903471.

ABSTRACT

Consistent with Dr. Paul Terasaki's "humoral theory of rejection" numerous studies have shown that HLA antibodies can cause acute and chronic antibody mediated rejection (AMR) and decreased graft survival. New evidence also supports a role for antibodies to non-HLA antigens in AMR and allograft injury. Despite the remarkable efforts by leaders in the field who pioneered single antigen bead technology for detection of donor specific antibodies, a considerable amount of work is still needed to better define the antibody attributes that are associated with AMR pathology. This review highlights what is currently known about the clinical context of pre and posttransplant antibodies, antibody characteristics that influence AMR, and the paths after donor specific antibody production (no rejection, subclinical rejection, and clinical dysfunction with AMR).

3. A New Diagnostic Algorithm for Antibody-Mediated Microcirculation Inflammation in Kidney Transplants.

Sis B, Jhangric GS, Riopela J, *et al.*

American Journal of Transplantation 2012; 12: 1168–1179. doi: 10.1111/j.1600-6143.2011.03931.x.

ABSTRACT

We studied the significance of microcirculation inflammation in kidney transplants, including 329 indication biopsies from 251 renal allograft recipients, who were mostly nonpresensitized (crossmatch negative). Glomerulitis (g) and peritubular capillaritis (ptc) were often associated with antibody-mediated rejection (65% and 75%, respectively), but were also found in other diseases in the absence of donor-specific antibody (DSA): T-cell-mediated rejection (ptc, g), glomerulonephritis (g) and acute tubular necrosis (ptc). To develop rules for reducing the nonspecificity of microcirculation inflammation and defining the best grading thresholds associated with DSA, we built and validated a decision tree to predict DSA. The decision tree revealed that g + ptc sum (addition of g-score plus ptc-score) was the best predictor of DSA, followed by time posttransplant, then C4d, which had a small role. Late biopsies with g + ptc > 0 showed higher frequency of DSA compared to early biopsies with g + ptc > 0 (79% vs. 27%). Microcirculation inflammation in early biopsies was often false positive (antibody-independent). The decision tree predicted DSA with higher sensitivity and accuracy than C4d staining. Microcirculation inflammation sum score predicted graft failure independently of time, C4d and transplant glomerulopathy. Thus any degree of microcirculation inflammation in late kidney transplant biopsies strongly indicates presence of DSA and predicts progression to graft failure.

4. Supervivencia del injerto renal según la categoría de Banff 2013 en biopsia por indicación.

Arias-Cabrales C, Redondo-Pachón D, Pérez-Sáez MJ, *et al.*

Nefrologia 2016;3 6(6):660–666.

ABSTRACT

Introducción: El impacto del rechazo agudo en la supervivencia del injerto renal es bien conocido; sin embargo, el pronóstico de otras entidades es incierto. Evaluamos la frecuencia y el impacto en la supervivencia del injerto de las diferentes categorías diagnósticas según la clasificación Banff 2013 en una cohorte de trasplantados renales y su impacto en la supervivencia del injerto.

Material y métodos: Estudio retrospectivo de 495 biopsias renales por indicación, en 322 pacientes entre 1990 y 2014. Dos observadores independientes revisaron los diagnósticos histológicos y reclasificaron según Banff 2013.

Resultados: De 495 biopsias, 28 (5,7%) fueron no diagnósticas. De las 467 restantes, 10,3% fueron «normales» (categoría 1), 19,6% fueron cambios mediados por anticuerpos (categoría 2), 5,9% fueron cambios borderline (categoría 3), el 8,7% fueron rechazo mediado por células T (categoría 4), el 23,4% fue fibrosis intersticial/atrofia tubular (FIAT) (categoría 5) y el 26,5% fueron otros diagnósticos (categoría 6). Al aumentar el tiempo postrasplante, disminuyen los diagnósticos de categorías 1, 3 y 4 y aumentan los de la 5 y la 2. Observamos peor supervivencia en injertos con diagnósticos de categoría 2 (45% a 7,5 años; HR pérdida del injerto 4,29 [IC 95%: 2,39-7,73]; $p \leq 0,001$, con respecto a categoría 1). Los injertos con «histología desfavorable» (rechazo crónico mediado por anticuerpos, IFTA moderada-severa) presentan peor supervivencia que los injertos con «histología favorable» (normal, necrosis tubular aguda, FIAT leve).

Conclusiones: La clasificación de Banff 2013 permite el diagnóstico histológico en el 95% de las biopsias por indicación. La categoría 6 es la más frecuente, pero se observa una modificación en la histopatología predominante según el tiempo postrasplante. Los cambios mediados por anticuerpos se asocian con peor supervivencia del injerto.

5. Kidney Allograft Survival After Acute Rejection, the Value of Follow-Up Biopsies.

El Ters M, Grande JP, Keddis MT, *et al.*

American Journal of Transplantation 2013; 13: 2334–2341. doi: 10.1111/ajt.12370.

ABSTRACT

Kidney allografts are frequently lost due to alloimmunity. Still, the impact of early acute rejection (AR) on long-term graft survival is debated. We examined this relationship focusing on graft histology post-AR and assessing specific causes of graft loss. Included are 797 recipients without anti-donor antibodies (DSA) at transplant who had 1 year protocol biopsies. 15.2% of recipients had AR diagnosed by protocol or clinical biopsies. Compared to no-AR, all histologic types of AR led to abnormal histology in 1 and 2 years protocol

biopsies, including more fibrosis þ inflammation (6.3% vs. 21.9%), moderate/severe fibrosis (7.7% vs. 13.5%) and transplant glomerulopathy (1.4% vs. 8.3%, all $p < 0.0001$). AR were associated with reduced graft survival (HR 1⁄4 3.07 (1.92–4.94), $p < 0.0001$). However, only those AR episodes followed by abnormal histology led to reduced graft survival. Early AR related to more late alloimmune-mediated graft losses, particularly transplant glomerulopathy (31% of losses). Related to this outcome, recipients with AR were more likely to have new DSA class II 1 year posttransplant (no-AR, 11.1%; AR, 21.2%, p 1⁄4 0.039). In DSA negative recipients, early AR often leads to persistent graft inflammation and increases the risk of new DSA II production. Both of these post-AR events are associated with increased risk of graft loss.

6. The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell–mediated rejection, antibody mediated rejection, and prospects for integrative endpoints for next- generation clinical trials

Haas M, Loupy A, Lefaucheur C, *et al.*

Am J Transplant. 2018;18:293–307. DOI: 10.1111/ajt.14625

ABSTRACT

The kidney sessions of the 2017 Banff Conference focused on 2 areas: clinical implications of inflammation in areas of interstitial fibrosis and tubular atrophy (i- IFTA) and its relationship to T cell–mediated rejection (TCMR), and the continued evolution of molecular diagnostics, particularly in the diagnosis of antibody- mediated rejection (ABMR). In confirmation of previous studies, it was independently demonstrated by 2 groups that i- IFTA is associated with reduced graft survival. Furthermore, these groups presented that i- IFTA, particularly when involving >25% of sclerotic cortex in association with tubulitis, is often a sequela of acute TCMR in association with underimmunosuppression. The classification was thus revised to include moderate i- IFTA plus moderate or severe tubulitis as diagnostic of chronic active TCMR. Other studies demonstrated that certain molecular classifiers improve diagnosis of ABMR beyond what is possible with histology, C4d, and detection of donor- specific antibodies (DSAs) and that both C4d and validated molecular assays can serve as potential alternatives and/ or complements to DSAs in the diagnosis of ABMR. The Banff ABMR criteria are thus updated to include these alternatives. Finally, the present report paves the way for the Banff scheme to be part of an integrative approach for defining surrogate endpoints in next-generation clinical trials.

7. Biomarkers in renal transplantation: An updated review.

Salvadori M, Tsalouchos A.

World J Transplant 2017 June 24; 7(3): 161-178. DOI: 10.5500/wjt.v7.i3.161

ABSTRACT

Genomics, proteomics and molecular biology lead to tremendous advances in all fields of medical sciences. Among these the finding of biomarkers as non invasive indicators of biologic processes represents a useful tool in the field of transplantation. In addition to define the principal characteristics of the biomarkers, this review will examine the biomarker usefulness in the different clinical phases following renal transplantation. Biomarkers of ischemia-reperfusion injury and of delayed graft function are extremely important for an early diagnosis of these complications and for optimizing the treatment. Biomarkers predicting or diagnosing acute rejection either cell-mediated or antibody-mediated allow a risk stratification of the recipient, a prompt diagnosis in an early phase when the histology is still unremarkable. The kidney solid organ response test detects renal transplant recipients at high risk for acute rejection with a very high
sensitivity and is also able to make diagnosis of subclinical acute rejection. Other biomarkers are able to detect chronic allograft dysfunction in an early phase and to differentiate the true chronic rejection from other forms of chronic allograft nephropathies no immune related. Finally biomarkers recently discovered identify patients tolerant or almost tolerant. This fact allows to safely reduce or withdrawn the immunosuppressive therapy.

8. Desensitization Using Bortezomib and High-dose Immunoglobulin Increases Rate of Deceased Donor Kidney Transplantation.

Jong JC, Jambaldorj E, Kwon HY, *et al.*

Medicine 2016; 95 (5), 1-10. :e2635. DOI: 10.1097/MD.0000000000002635.

ABSTRACT

Combination therapy of intravenous immunoglobulin (IVIG) and rituximab showed a good transplant rate in highly sensitized wait-listed patients for deceased donor kidney transplantation (DDKT), but carried the risk of antibody-mediated rejection. The authors investigated the impact of a new combination therapy of bortezomib, IVIG, and rituximab on transplantation rate. This study was a prospective, open-labeled clinical trial. The desensitization regimen consisted of 2 doses of IVIG (2 g/kg), a single dose of rituximab (375 mg/m^2), and 4 doses of bortezomib (1.3 mg/m^2). The transplant rate was analyzed. Anti-Human leukocyte antigen (HLA) DRB antibodies were determined by a Luminex solid-phase bead assay at baseline and after 2, 3, and 6 months in the desensitized patients. There were 19 highly sensitized patients who received desensitization and 17 patients in the control group. Baseline values of class I and II panel reactive antibody (%, peak mean fluorescence intensity) were 83±16.0 (14952±5820) and 63±36.0 (10321±7421), respectively. Deceased donor kidney transplantation was successfully performed in 8 patients (42.1%) in the desensitization group versus 4 (23.5%) in the control group. Multivariate time-varying covariate Cox regression analysis showed that desensitization increased the probability of DDKT (hazard ratio, 46.895; 95% confidence interval, 3.468–634.132; P 1⁄4 0.004). Desensitization decreased mean fluorescence intensity values of class I panel reactive antibody by 15.5% (20.8%) at 2 months. In addition, a liberal mismatch strategy in post hoc analysis increased the benefit of desensitization in donor-specific antibody reduction. Desensitization was well tolerated, and acute rejection occurred only in the control group. In conclusion, a desensitization protocol using bortezomib, high-dose IVIG, and rituximab increased the DDKT rate in highly sensitized, wait-listed patients.

9. C1 Inhibitor in Acute Antibody-Mediated Rejection Nonresponsive to Conventional Therapy in Kidney Transplant Recipients: A Pilot Study.

Viglietti D, Gosset C, Loupy A, *et al.*

American Journal of Transplantation 2016; 16: 1596–1603. doi: 10.1111/ajt.13663.

ABSTRACT

Complement inhibitors have not been thoroughly evaluated in the treatment of acute antibody-mediated rejection (ABMR). We performed a prospective, single-arm pilot study to investigate the potential effects and safety of C1 inhibitor (C1-INH) Berinert added to high-dose intravenous immunoglobulin (IVIG) for the treatment of acute ABMR that is nonresponsive to conventional therapy. Kidney recipients with nonresponsive active ABMR and acute allograft dysfunction were enrolled between April 2013 and July 2014 and received C1-INH and IVIG for 6 months (six patients). The primary end point was the change in eGFR at 6 months after inclusion (M+6). Secondary end points included the changes in histology and DSA characteristics and adverse events as evaluated at M+6. All patients showed an improvement in eGFR between inclusion and M+6: from 38.7 17.9 to 45.2 21.3 mL/min/1.73 m^2 ($p = 0.0277$). There was no change in histological features, except a decrease in the C4d deposition rate from 5/6 to 1/6 ($p = 0.0455$). There was a change in DSA C1q status from 6/6 to 1/6 positive ($p = 0.0253$). One deep venous thrombosis was observed. In a secondary analysis, C1-INH patients were compared with a similar historical control group (21 patients). C1-INH added to IVIG is safe and may improve allograft function in kidney recipients with nonresponsive acute ABMR.

10. Treatment of Acute Antibody-Mediated Renal Allograft Rejection With Cyclophosphamide.

Waiser J, Duerr M, Budde K, *et al.*

Transplantation 2017;101: 2545–2552.

ABSTRACT

Background: Antibody-mediated rejection (AMR) is a major risk for renal allograft survival. Throughout decades, cyclophosphamide treatment has been proven to be effective in patients with antibody-associated autoimmune diseases. We investigated whether cyclophosphamide combined with plasmapheresis and intravenous immunoglobulins is an option for patients with AMR.

Methods: Between March 2013 and November 2015, we initiated treatment of 13 consecutive patients with biopsy-proven acute AMR with intravenous cyclophosphamide pulses (15 mg/kg adapted to age and renal function) at 3-week intervals, PPH (6), and high-dose intravenous immunoglobulin (1.5 g/kg). Treatment was completed after 6 cyclophosphamide pulses or in case of return to baseline serum creatinine together with reduction of donor-specific HLA antibodies (DSA) below 500 mean fluorescence intensity.

Results: Eleven of 13 patients completed treatment. Median follow-up was 18 (12-44) months. At the end of follow-up, graft survival was 77% (10/13). The 3 graft losses were caused at least in part by nonadherence and premature termination of treatment. Serum creatinine increased from 1.7±0.4 mg/dL at 3 months before diagnosis to 3.7±2.4 mg/dL at diagnosis (P = 0.01), and decreased to 2.1 ± 0.7 mg/dL at 3 months after diagnosis (P = 0.01). In 7 (64%) of 11 patients, who completed treatment, DSA decreased, in 4 (36%) of 11 DSA were below 500 mean fluorescence intensity after treatment. Dose reductions had to be performed in 3 of 13 patients for leukopenia. We observed 14 hospitalizations in 9 of 13 patients.

Conclusions: To our knowledge, this is the first systematic report on cyclophosphamide-based treatment of acute AMR based on modern diagnostics. Treatment was effective and relatively safe. Future studies will show, whether cyclophosphamide proves to be a valuable alternative for the treatment of AMR.

11. Complement in Kidney Transplantation

Cernoch M & Viklicky O

Front Med 2017;4:66, 1-11. doi: 10.3389/fmed.2017.00066.

ABSTRACT

The complement system is considered to be an important part of innate immune system with a significant role in inflammation processes. The activation can occur through classical, alternative, or lectin pathway, resulting in the creation of anaphylatoxins C3a and C5a, possessing a vast spectrum of immune functions, and the assembly of terminal complement cascade, capable of direct cell lysis. The activation processes are tightly regulated; inappropriate activation of the complement cascade plays a significant role in many renal diseases including organ transplantation. Moreover, complement cascade is activated during ischemia/reperfusion injury processes and influences delayed graft function of kidney allografts. Interestingly, complement system has been found to play a role in both acute cellular and antibody-mediated rejections and thrombotic microangiopathy. Therefore, complement system may represent an interesting therapeutical target in kidney transplant pathologies.

12. Desensitization: Overcoming the Immunologic Barriers to Transplantation.

Sethi S, Choi J, Toyoda M, *et al.*

Journal of Immunology Research 2017; 2017 (Art. ID 6804678): 1-11.
http://dx.doi.org/10.1155/2017/6804678.

ABSTRACT

HLA (Human Leucocyte Antigen) sensitization is a significant barrier to successful kidney transplantation. It often translates into difficult crossmatch before transplant and increased risk of acute and chronic antibody mediated rejection after transplant. Over the last decade, several immunomodulatory therapies have emerged allowing for increased access to kidney transplantation for the immunologically disadvantaged group of HLA sensitized end stage kidney disease patients. These include IgG inactivating agents, anti-cytokine antibodies, costimulatory molecule blockers, complement inhibitors, and agents targeting plasma cells. In this review, we discuss currently available agents for desensitization and provide a brief analysis of data on novel biologics, which will likely improve desensitization outcomes, and have potential implications in treatment of antibody mediated rejection.

13. From Humoral Theory to Performant Risk Stratification in Kidney Transplantation.

Lefaucheur C, Viglietti D, Mangiola M, *et al.*

Journal of Immunology Research 2017; 2017 (Art ID 5201098):1-8.
http://dx.doi.org/10.1155/2017/5201098.

ABSTRACT

The purpose of the present review is to describe how we improve the model for risk stratification of transplant outcomes in kidney transplantation by incorporating the novel insights of donor-specific anti-HLA antibody (DSA) characteristics. The detection of anti-HLA DSA is widely used for the assessment of pre- and posttransplant risks of rejection and allograft loss; however, not all anti-HLA DSA carry the same risk for transplant outcomes. These antibodies have been shown to cause a wide spectrum of effects on allografts, ranging from the absence of injury to indolent or full-blown acute antibody-mediated rejection. Consequently, the presence of circulating anti-HLA DSA does not provide a sufficient level of accuracy for the risk stratification of allograft outcomes. Enhancing the predictive performance of anti-HLA DSA is currently one of the most pressing unmet needs for facilitating individualized treatment choices that may improve outcomes. Recent advancements in the assessment of anti-HLA DSA properties, including their strength, complement-binding capacity, and IgG subclass composition, significantly improved the risk stratification model to predict allograft injury and failure. Although risk stratification based on anti-HLA DSA properties appears promising, further specific studies that address immunological risk stratification in large and unselected populations are required to define the benefits and cost-effectiveness of such comprehensive assessment prior to clinical implementation.

14. Outcome of Kidney Transplantations Performed With Preformed Donor-Specific Antibodies of Unknown Etiology.

Sicard A, Amrouche L, Suberbielle C, *et al.*

American Journal of Transplantation 2014; 14: 193–201. doi: 10.1111/ajt.12512.

ABSTRACT

The detection of preformed donor-specific alloantibodies (DSA) with multiplex-bead arrays has led to the common observation that individuals without a history of pregnancy, transfusion or transplantation can have circulating anti-HLA antibodies of unknown etiology. We retrospectively analyzed the risk of antibody-mediated rejection (AMR) and graft outcome in 41 kidney transplant recipients with DSA of unknown etiology (DSA cause-unk) at the time of transplantation. Twenty-one patients received a post-transplantation desensitization protocol, and 20 received standard immunosuppressive therapy. The mean number of DSA was 1.4±0.8, ranging from 1 to 5. Complement-dependent cytotoxicity cross-matches were negative for all the patients. Flow cytometry crossmatches were positive in 47.6% of cases. The incidence of acute AMR was 14.6% at 1 year, regardless of the immunosuppressive regimen. No patients experienced graft loss following AMR. At month 12, across the entire population of patients with DSA cause-unk, the outcomes were favorable: the measured glomerular filtration rate was 63.8±16.4 mL/min/1.73 m^2, the screening biopsies showed low frequencies of microvascular inflammation and no transplant glomerulopathy, and graft and patient survival were 100%. In conclusion, patients with DSA cause-unk are able to mount AMR but have favorable 1-year outcomes.

15. Criterios diagnósticos de rechazo mediado por anticuerpos en el trasplante renal.

Mosquera JM & Vázquez E.

Nefrologia 2011;31(4):382-91. doi:10.3265/Nefrologia.pre2011.Apr.10740

NO ABSTRACT AVAILABLE

16. Diagnosis and Management of Antibody-Mediated Rejection: Current Status and Novel Approaches.

Djamali A,. Kaufman DB, Ellis TM, *et al.*

American Journal of Transplantation 2014; 14: 255–271. doi: 10.1111/ajt.12589

ABSTRACT

Advances in multimodal immunotherapy have significantly reduced acute rejection rates and substantially improved 1-year graft survival following renal transplantation. However, long-term (10-year) survival rates have stagnated over the past decade. Recent studies indicate that antibody-mediated rejection (ABMR) is among the most important barriers to improving long-term outcomes. Improved understanding of the roles of acute and chronic ABMR has evolved in recent years following major progress in the technical ability to detect and quantify recipient anti-HLA antibody production. Additionally, new knowledge of the immunobiology of B cells and plasma cells that pertains to allograft rejection and tolerance has emerged. Still, questions regarding the classification of ABMR, the precision of diagnostic approaches, and the efficacy of various strategies for managing affected patients abound. This review article provides an overview of current thinking and research surrounding the pathophysiology and diagnosis of ABMR, ABMR-related outcomes, ABMR prevention and treatment, as well as possible future directions in treatment.

17. Eculizumab for the Treatment of Severe Antibody-Mediated Rejection: A Case Report and Review of the Literature.

Tran D, Boucher A, Collette S, *et al.*

Case Reports in Transplantation 2016; 2016 (Art ID 9874261),1-4. http://dx.doi.org/10.1155/2016/9874261.

ABSTRACT

In renal transplantation, treatment options for antibody-mediated rejection are limited. Here, we report a case of severe AMR treated with eculizumab. A 50-year-old woman known for end stage kidney disease secondary to IgA nephropathy received a kidney transplant from a 50-year-old deceased donor. At 5 months after transplantation, she presented with acute graft dysfunction and biopsy showed a severe antibody-mediated rejection associated with thrombotic microangiopathy. Despite an aggressive conventional immunosuppressive regimen, signs of rejection persisted and the patient was treated with 3 doses of eculizumab. Following the therapy, markers of TMA improved and graft function stabilized. However, ongoing signs of rejection remained in the repeated biopsy. In kidney transplantation, eculizumab is an expensive treatment and its role in the treatment of antibody-mediated rejection remains to be determined.

18. Report of the Inefficacy of Eculizumab in Two Cases of Severe Antibody-Mediated Rejection of Renal Grafts.

Burbach M, Suberbielle C, Brochériou I, *et al.*

Transplantation 2014;98: 1056-1059. DOI: 10.1097/TP.0000000000000184.

ABSTRACT

Background: Acute antibody-mediated rejection (AMR) is responsible for up to 20% to 30% of acute rejection after kidney transplantation. New therapeutic agents have recently emerged, such as eculizumab, an anticomplement protein-C5 monoclonal antibody. In the setting of renal transplantation, eculizumab has so far proved effective both for preventive and curative treatments of AMR in sensitized patients and patients diagnosed with severe AMR. Unsuccessful eculizumab treatment has only been reported once in the literature by Stegall et al. (Am J Transplant 2011; 11: 2405).

Methods and Results: We present two cases of AMR resistant to eculizumab after renal transplantation. One patient received the anti-C5 antibody curatively, and the other patient developed AMR while being treated with eculizumab after a relapse of atypical hemolytic uremic syndrome. The peculiarity of these two cases was the absence of C4d deposition in peritubular capillaries as well as the absence of C1q-binding donor-specific antiYhuman leukocyte antigen alloantibody, as determined retrospectively, suggesting that a complement-independent mechanism underlies the pathogenesis of these AMR.

Conclusion: The use of eculizumab in C4d-negative or C1q-negative AMR does not seem effective.

19. Positive Crossmatch Kidney Transplant Recipients Treated With Eculizumab: Outcomes Beyond 1 Year.

Cornell LD, Schinstock CA, Gandhi MJ, *et al.*

American Journal of Transplantation 2015; 15: 1293–1302. doi: 10.1111/ajt.13168.

ABSTRACT

This study examined outcomes beyond 1 year in eculizumab-treated (EC) positive crossmatch kidney transplants (+XMKTx) compared to a historical control group. +XMKTx received desensitization with either plasma exchange (PE) alone (N=48) or PE and EC (N=30). EC, given for at least 1 month, was continued in the setting of persistently high DSA (B flow cytometric crossmatch [BFXM] >200) including: 4 weeks (n=14); 9 weeks (n=6), 6 months (n=2), and 12months (n=8). All patients had at least 2 years follow-up. The incidence of acute clinical ABMR was lower in the EC group than controls (6.7% vs. 43.8% $p < 0.01$). Death-censored allograft survival was similar between groups. Chronic ABMR was the main cause of graft loss. On 1-year protocol biopsies, no differences were noted between EC and controls including: cg score >0, 26.7% versus 31.9% (p=0.62), ptc score 2, 60.0% versus 60.0% (p=1.00), or C4d + , 33.8% versus 13.5% (p=0.08). A persistently high BFXM in EC-treated patients was associated with cg score>0 at 1 year, while EC appeared to protect against cg if the BFXM remained low. We conclude that despite decreasing acute clinical ABMR rates, EC treatment does not prevent chronic ABMR in recipients with persistently high BFXM after +XMKTx.

20. Eculizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplant Recipients: A Pilot Randomized Controlled Trial.

Kulkarni S, Kirkiles-Smith NC, Deng YH, *et al.*

American Journal of Transplantation 2017; 17: 682–691. doi: 10.1111/ajt.14001.

ABSTRACT

We hypothesized that de novo donor-specific antibody (DSA) causes complement-dependent endothelial cell injury in kidney transplants, as assessed by expression of endothelial cell–associated transcripts (ENDATs), that may be attenuated through complement inhibition. In total, 15 participants (five control, 10 treatment) with DSA and deteriorating renal function were enrolled. The treatment group received 6-mo of eculizumab followed by 6 mo of observation, whereas controls were observed. The primary endpoint was percentage change in estimated GFR (eGFR) trajectory over the treatment period. The treatment group had an improved eGFR trajectory versus control, based on our predetermined two-sided 0.10 significance level ($p = 0.09$). Within-subject analysis of treated participants at 6-mo intervals did not show significant change ($p = 0.60$). Modeling C1q status showed that C1q-positive patients had significantly higher mean eGFR than patients with negative C1q ($p = 0.04$). Biopsies revealed elevated renal ENDATs in most participants, but ENDATs were not reduced with complement inhibition. Our data suggest that eculizumab treatment may stabilize kidney function in patients with chronic persistent DSA based on our pilot a priori significance threshold. ENDAT expression predicative of acute humoral injury is not reduced with complement inhibition in this chronic setting. Further studies will be necessary to determine which patients may benefit from eculizumab.

21. Donor-Specific HLA Antibodies in a Cohort Comparing Everolimus With Cyclosporine After Kidney Transplantation.

Liefeldt L, Brakemeiera S, Glandera P, *et al.*

American Journal of Transplantation 2012; 12: 1192–1198. doi: 10.1111/j.1600-6143.2011.03961.x.

ABSTRACT

Donor-specific HLA antibodies (DSA) have a negative impact on kidney graft survival. Therefore, we analyzed the occurrence of DSA and antibody-mediated rejection (AMR) in patients from two prospective randomized trials in our center. At 3–4.5 months post-transplant 127 patients were randomized to continue cyclosporine or converted to everolimus therapy. The presence of DSA was prospectively assessed using Luminex assays. AMR was defined according to the Banff 2009 classification. Antibody screening was available in 126 patients with a median follow-up of 1059 days. Seven out of 65 (10.8%) patients on cyclosporine developed DSA after a median of 991 days. In comparison, 14/61 patients (23.0%) randomized to everolimus developed DSA after 551 days (log-rank: p = 0.048). Eight patients on everolimus compared to two patients on cyclosporine developed AMR (log-rank: p = 0.036). Four of 10 patients with AMR—all in the everolimus group—lost their graft. A multivariate regression model revealed everolimus, >3 mismatches and living donor as significant risk factors for DSA. Acute rejection within the first year, >3 mismatches, everolimus and living donor were independent risk factors for AMR. This single center analysis demonstrates for the first time that everolimus-based immunosuppression is associated with an increased risk for the development of DSA and AMR.

22. Factors influencing long-term outcome after kidney transplantation.

Legendre C, Canaud G and Martinez F.

Transplant International 2014;27:19–27. doi:10.1111/tri.12217.

ABSTRACT

Many factors influence the long-term outcome of kidney transplantation, which is defined very schematically by patient death or renal dysfunction leading to graft loss. The most important of these factors is most likely the quality of the transplant itself, with kidneys from living donors showing a positive impact, while kidneys from expanded criteria donors show deleterious impacts. Various clinicopathological scores exist to predict mid- to long-term outcomes and avoid the transplantation of kidneys displaying inferior results. The key factors related to the recipient include their age as well as disease recurrence, HLA matching, HLA immunization, ethnic background, time on dialysis, and cardiovascular comorbidities. Renal function, defined based on estimated GFR and/or proteinuria values, is a result of all these factors. Delayed graft function has a detrimental long-term impact, as does the level of renal function impairment either in stable condition or in case of progressing dysfunction. Finally, although current immunosuppression regimes are highly efficient in preventing acute rejection, the burden of specific (diabetes, nephrotoxicity) and nonspecific (infection and cancer) side effects has significant negative long-term consequences that may well be worse in the future because of the increasing ages of both donors and recipients. The development of safer immunosuppression strategies is therefore crucial to improve long-term outcomes.

23. Antibody-mediated rejection despite inhibition of terminal complement.

Bentall A, Tyan DB, Sequeira F, *et al.*

Transplant International 2014;27:1235–1243. doi:10.1111/tri.12396.

ABSTRACT

Terminal complement blockade has been shown to decrease the incidence of early acute antibody-mediated rejection (eAMR) in the first month after positive crossmatch kidney transplant recipients, yet some patients still develop eAMR. The current study investigated possible mechanisms of eAMR despite eculizumab treatment. Of the 26 patients treated with eculizumab, two developed clinical eAMR and another patient developed histologic signs of eAMR without graft dysfunction ('subclinical eAMR'). Twenty-three did not have histologic injury on early surveillance biopsies. All 26 patients had therapeutic levels of eculizumab and showed complete blockade of complement in hemolytic assays. High levels of donor-specific alloantibody (DSA) including total IgG, IgG3, and C1q+ DSA were present in patients with and without eAMR, and none correlated well with eAMR. In contrast, IgM DSA was present in only four patients after transplantation: the two patients with clinical eAMR, one patient with subclinical AMR, and one patient without eAMR (P = 0.006 correlation with eAMR). Both clinical Eamr episodes were easily treated with plasma exchange which removed IgM more completely and rapidly than IgG, resulting in normalization of function and histology. These data suggest a possible role of antidonor IgM DSA in the pathogenesis of eAMR in patients treated with terminal complement blockade.

24. A Randomized Pilot Study of Donor Stem Cell Infusion in Living-Related Kidney Transplant Recipients Receiving Alemtuzumab.

Ciancio G, Sageshima J, Akpinar E, *et al.*

Transplantation. 2013; 96(9): . doi:10.1097/TP.0b013e3182a0f68c.

ABSTRACT

Background: Transplant tolerance would remove the need for maintenance immunosuppression while improving survival and quality of life.

Methods: A prospective, randomized pilot study was undertaken to assess the safety and efficacy of donor stem cell infusion (DSCI) in living-related kidney transplant recipients treated with alemtuzumab (C1H) induction and tacrolimus and mycophenolate maintenance with switch to sirolimus and weaning over 2 years.

Results: Four patients received DSCI; 5 patients were controls. Graft failure occurred in 2 patients in the DSCI arm. Recurrence of glomerular disease occurred in 2 DSCI recipients, leading to graft loss in one. Biopsy-proven acute rejection episodes occurred in 3 patients (2 in the DSCI vs. 1 in the control). One DSCI patient, with recurrence, subsequently developed antibody-mediated rejection leading to graft failure. In the remaining 2 DSCI patients, weaning was attempted but was not successful. All (4/4) DSCI patients had biopsy-proven chronic allograft injury and/or recurrence.

Conclusion: DSCI with C1H induction and a steroid-free maintenance regimen in a small group of patients failed to induce tolerance, with suboptimal patient and graft survival. The results do not justify extension of this particular trial and underscore the importance of patient selection, specifically avoidance of patients with glomerulopathies whose recurrence may obscure potential benefit.

25. Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study.

Montgomery RA, Orandi BJ, Racusen L, *et al.*

American Journal of Transplantation 2016; 16: 3468–3478. doi: 10.1111/ajt.13871.

ABSTRACT

Antibody-mediated rejection (AMR) is typically treated with plasmapheresis (PP) and intravenous immunoglobulin (standard of care; SOC); however, there is an unmet need for more effective therapy. We report a phase 2b, multicenter double-blind randomized placebo-controlled pilot study to evaluate the use of human plasma-derived C1 esterase inhibitor (C1 INH) as add-on therapy to SOC for AMR. Eighteen patients received 20 000 units of C1 INH or placebo (C1 INH n = 9, placebo n = 9) in divided doses every other day for 2 weeks. No discontinuations, graft losses, deaths, or study drug-related serious adverse events occurred. While the study's primary end point, a difference between groups in day 20 pathology or graft survival, was not achieved, the C1 INH group demonstrated a trend toward sustained improvement in renal function. Six-month biopsies performed in 14 subjects (C1 INH = 7, placebo = 7) showed no transplant glomerulopathy (TG) (PTC+cg≥1b) in the C1 INH group, whereas 3 of 7 placebo subjects had TG. Endogenous C1 INH measured before and after PP demonstrated decreased functional C1 INH serum concentration by 43.3% ($p < 0.05$) for both cohorts (C1 INH and placebo) associated with PP, although exogenous C1 INH–treated patients achieved supraphysiological levels throughout. This new finding suggests that C1 INH replacement may be useful in the treatment of AMR.

26. Complement inhibition as potential new therapy for antibody-mediated rejection.

Eskandary F, Wahrmann M, Muhlbacher J, *et al.*

Transplant International 2016; 29: 392–402.

ABSTRACT

Antibody-mediated rejection (ABMR) is a leading cause of kidney allograft failure. While the exact mechanisms contributing to donor-specific antibody (DSA)-triggered tissue injury are still incompletely understood, complement activation via the classical pathway is believed to be one of the key players. There is now growing interest in complement blockade as an antirejection treatment. One attractive strategy may be inhibition of terminal complex formation using anti-C5 antibody eculizumab. Anecdotal reports, case series, and a unique cohort of flow crossmatch-positive live donor kidney transplant recipients subjected to eculizumab-based desensitization have demonstrated successful prevention and reversal of acute clinical ABMR. Nevertheless, maybe due to complement activation steps proximal of C5 or even complement-independent mechanisms, subclinical rejection processes that might culminate in chronic injury were found to escape inhibition. Larger studies designed to clarify the actual clinical value of terminal complement inhibition as an antirejection treatment are currently underway. In addition, alternative concepts, such as therapies that target key component C1, are currently under development, and we will see in the near future whether new strategies in the pipeline will have the potential to beneficially impact clinical practice.

27. Pharmacologic Complement Inhibition in Clinical Transplantation.

Tatapudi VS & Montgomery RA.

Curr Transpl Rep (2017) 4:91–100. DOI 10.1007/s40472-017-0148-7

ABSTRACT

Purpose of Review: Over the past two decades, significant strides made in our understanding of the etiology of antibody-mediated rejection (AMR) in transplantation have put the complement system in the spotlight. Here, we review recent progress made in the field of pharmacologic complement inhibition in clinical transplantation and aim to understand the impact of this therapeutic approach on outcomes in transplant recipients.

Recent Findings: Encouraged by the success of agents targeting the complement cascade in disorders of unrestrained complement activation like paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), investigators are testing the safety and efficacy of pharmacologic complement blockade in mitigating allograft injury in conditions ranging from AMR to recurrent post-transplant aHUS, C3 glomerulopathies and antiphospholipid anti-body syndrome (APS). A recent prospective study demonstrated the efficacy of terminal complement inhibition with eculizumab in the prevention of acute AMR in human leukocyte antigen (HLA)-incompatible living donor renal transplant recipients. C1 esterase inhibitor (C1-INH) was well tolerated in two recent studies in the treatment of AMR and was associated with improved renal allograft function.

28. Acute Antibody-Mediated Rejection in Presence of MICA-DSA and Successful Renal Re-Transplant with Negative-MICA Virtual Crossmatch.

Ming Y, Hu J, Luo Q, *et al.*

PLoS ONE 10(5): e0127861. doi:10.1371/journal.pone.0127861 2015

ABSTRACT

The presence of donor-specific alloantibodies (DSAs) against the MICA antigen results in high risk for antibody-mediated rejection (AMR) of a transplanted kidney, especially in patients receiving a re-transplant. We describe the incidence of acute C4d+ AMR in a patient who had received a first kidney transplant with a zero HLA antigen mismatch. Retrospective analysis of post-transplant T and B cell crossmatches were negative, but a high level of MICA alloantibody was detected in sera collected both before and after transplant. The DSA against the first allograft mismatched MICA*018 was in the recipient. Flow cytometry and cytotoxicity tests with five samples of freshly isolated human umbilical vein endothelial cells demonstrated the alloantibody nature of patient's MICA-DSA. Prior to the second transplant, a MICA virtual crossmatch and T and B cell crossmatches were used to identify a suitable donor. The patient received a second kidney transplant, and allograft was functioning well at one-year follow-up. Our study indicates that MICA virtual crossmatch is important in selection of a kidney donor if the recipient has been sensitized with MICA antigens.

29. Refinement of the criteria for ultrastructural peritubular capillary basement membrane multilayering in the diagnosis of chronic active/acute antibody-mediated rejection.

Go H, Shin Sung, Kim YH, *et al.*

Transplant International 2017; 30: 398–409.

ABSTRACT

Chronic active/acute antibody-mediated rejection (cABMR) is the main cause of late renal allograft loss. Severe peritubular capillary basement membrane multilayering (PTCML) assessed on electron microscopy is one diagnostic feature of cABMR according to the Banff 2013 classification. We aimed to refine the PTCML criteria for an earlier diagnosis of cABMR. We retrospectively investigated ultrastructural features of 159 consecutive renal allografts and 44 nonallografts. The presence of serum donor-specific antibodies at the time of biopsy of allografts was also examined. Forty-three patients (27.0%) fulfilled the criteria of cABMR, regardless of PTCML, and comprised the cABMR group. Forty-one patients (25.8%) did not exhibit cABMR features and comprised the non-cABMR allograft control group. In addition, 15 zero-day wedge resections and 29 native kidney biopsies comprised the nonallograft control group. When the diagnostic accuracies of various PTCML features were assessed using the cABMR and non-cABMR allograft control groups, ≥4 PTCML, either circumferential or partial, in ≥2 peritubular capillaries of the three most affected capillaries exhibited the highest AUC value (0.885), greater than the Banff 2013 classification (0.640). None of the nonallograft control groups exhibited PTCML features. We suggest that ≥4 PTCML in ≥2 peritubular capillaries of the three most affected cortical capillaries represents the proper cutoff for cABMR.

30. Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence.

Sellarés J, de Freitasa DG, Mengela M, *et al.*

American Journal of Transplantation 2012; 12: 388–399. doi: 10.1111/j.1600-6143.2011.03840.x.

ABSTRACT

We prospectively studied kidney transplants that progressed to failure after a biopsy for clinical indications, aiming to assign a cause to every failure. We followed 315 allograft recipients who underwent indication biopsies at 6 days to 32 years posttransplant. Sixty kidneys progressed to failure in the follow-up period (median 31.4 months). Failure was rare after T-cell–mediated rejection and acute kidney injury and common after antibody-mediated rejection or glomerulonephritis. We developed rules for using biopsy diagnoses, HLA antibody and clinical data to explain each failure. Excluding four with missing information, 56 failures were attributed to four causes: rejection 36 (64%), glomerulonephritis 10 (18%), polyoma virus nephropathy 4 (7%) and intercurrent events 6 (11%). Every rejection loss had evidence of antibody-mediated rejection by the time of failure. Among rejection losses, 17 of 36 (47%) had been independently identified as nonadherent by attending clinicians. Non-adherence was more frequent in patients who progressed to failure (32%) versus those who survived (3%). Pure T-cell–mediated rejection, acute kidney injury, drug toxicity and unexplained progressive fibrosis were not causes of loss. This prospective cohort indicates that many actual failures after indication biopsies manifest phenotypic features of antibody-mediated or mixed rejection and also underscores the major role of nonadherence.

31. Comparison of Combination Plasmapheresis/IVIg/Anti-CD20 Versus High-Dose IVIg in the Treatment of Antibody-Mediated Rejection.

Lefaucheura C, Nochy D, Andradea J, *et al.*

American Journal of Transplantation 2009; 9: 1099–1107. doi: 10.1111/j.1600-6143.2009.02591.x.

ABSTRACT

Different strategies appear to improve the success in treatment of antibody-mediated rejection (AMR), although no one best method has yet emerged. The objective of this study was to compare the efficacy of the combination of Plasmapheresis/intravenous immunoglobulin (IVIg)/anti-CD20-based regimes versus high-dose IVIg alone in the treatment of AMR. Group A (12 patients) was treated with high-dose IVIg between January 2000 and December 2003; group B (12 patients) was treated by Plasmapheresis/IVIg/anti-CD20 between January 2004 and December 2005. Graft survival at 36 months was 91.7% in group B versus 50% in group A ($p = 0.02$). Donor-specific human leukocyte antigens (DSA) levels detected by Luminex single antigen (Luminex SA) and ELISA, 3 months postrejection are significantly lower in group B than in group A: DSA ELISA class 2 score 6–8 ($p = 0.02$), DSA mean intensity of fluorescence (MFI) max ($p = 0.009$) and DSA mean MFI ($p = 0.0004$). The persistence of elevated DSA levels posttreatment is more frequent in patients with graft loss as compared to those with preserved renal function: score 6–8 on ELISA ($p = 0.04$); mean MFI ($p = 0.00009$) and MFImax ($p = 0.018$). We conclude that: (1) high dose IVIg alone is inferior to Plasmapheresis/IVIg/anti-CD20 as therapy for AMR and (2)DSA postrejection can be quantified using solid phase assays, showing that 3 months after AMR, DSA levels are higher in patients with graft loss.

32. A Probabilistic Approach to Histologic Diagnosis of Antibody-Mediated Rejection in Kidney Transplant Biopsies.

Halloran PF, Famulski KS and Chang J.

American Journal of Transplantation 2017; 17: 129–139. doi: 10.1111/ajt.13934.

ABSTRACT

Histologic diagnosis of antibody-mediated rejection (ABMR) in kidney transplant biopsies uses lesion score cutoffs such as 0 versus >0 rather than actual scores and requires donor-specific antibody (DSA); however, cutoffs lose information, and DSA is not always reliable. Using microarray-derived molecular ABMR scores as a histology-independent estimate of ABMR in 703 biopsies, we reassessed criteria for ABMR to determine relative importance of various lesions, the utility of equations using actual scores rather than cutoffs, and the potential for diagnosing ABMR when DSA is unknown or negative. We confirmed that the important features for ABMR diagnosis were peritubular capillaritis (ptc), glomerulitis (g), glomerular double contours, DSA and C4d staining, but we questioned some features: arterial fibrosis, vasculitis, acute tubular injury, and sum of ptc+g scores. Regression equations using lesion scores predicted molecular ABMR more accurately than score cutoffs (area under the curve 0.85–0.86 vs. 0.75). DSA positivity improved accuracy, but regression equations predicted ABMR with moderate accuracy when DSA was unknown. Some biopsies without detectable DSA had high probability of ABMR by regression, although most had HLA antibody. We concluded that regression equations using lesion scores plus DSA maximized diagnostic accuracy and can estimate probable ABMR when DSA is unknown or undetectable.

33. Proteomics for rejection diagnosis in renal transplant patients: Where are we now?

Gwinner W, Metzger J, Husi H, *et al.*

World J Transplant 2016 March 24; 6(1): 28-41. DOI: 10.5500/wjt.v6.i1.28

ABSTRACT

Rejection is one of the key factors that determine the long-term allograft function and survival in renal transplant patients. Reliable and timely diagnosis is important to treat rejection as early as possible. Allograft biopsies are not suitable for continuous monitoring of rejection. Thus, there is an unmet need for non-invasive methods to diagnose acute and chronic rejection. Proteomics in urine and blood samples has been explored for this purpose in 29 studies conducted since 2003. This review describes the different proteomic approaches and summarizes the results from the studies that examined proteomics for the rejection diagnoses. The potential limitations and open questions in establishing proteomic markers for rejection are discussed, including ongoing trials and future challenges to this topic.

34. Quantifying Renal Allograft Loss Following Early Antibody-Mediated Rejection.

Orandi BJ, Chow EHK, Hsu A, *et al.*

American Journal of Transplantation 2015; 15: 489–498. doi: 10.1111/ajt.12982.

ABSTRACT

Unlike antibody-mediated rejection (AMR) with clinical features, it remains unclear whether subclinical AMR should be treated, as its effect on allograft loss is unknown. It is also uncertain if AMR's effect Is homogeneous across donor (deceased/live) and (HLA/ABO) antibody types. We compared 219 patients with AMR (77 subclinical, 142 clinical) to controls matched on HLA/ABO-compatibility, donor type, prior transplant, panel reactive antibody (PRA), age and year. One and 5-year graft survival in subclinical AMR was 95.9% and 75.7%, compared to 96.8% and 88.4% in matched controls (p=0.0097). Subclinical AMR was independently associated with a 2.15-fold increased risk of graft loss (95% CI: 1.19– 3.91; p=0.012) compared to matched controls, but not different from clinical AMR (p=0.13). Fifty three point two percent of subclinical AMR patients were treated with plasmapheresis within 3 days of their AMR-defining biopsy. Treated subclinical AMR patients had no difference in graft loss compared to matched controls (HR 1.73; 95% CI: 0.73–4.05; p=0.21), but untreated subclinical AMR patients did (HR 3.34; 95% CI: 1.37–8.11; p=0.008). AMR's effect on graft loss was heterogeneous when stratified by compatible deceased donor (HR=4.73; 95% CI: 1.57–14.26; p=0.006), HLA-incompatible deceased donor (HR=2.39; 95% CI: 1.10–5.19; p=0.028), compatible live donor (no AMR patients experienced graft loss), ABO-incompatible live donor (HR=6.13; 95% CI: 0.55–67.70; p=0.14) and HLA-incompatible live donor (HR=6.29; 95% CI: 3.81–10.39; p < 0.001) transplant. Subclinical AMR substantially increases graft loss, and treatment seems warranted.

35. Acute Antibody-Mediated Rejection in Renal Transplantation: Current Clinical Management.

Schinstock C & Stegall MD.

Curr Transplant Rep. 2014; 1(2): 78–85. doi:10.1007/s40472-014-0012-y.

ABSTRACT

Acute antibody mediated rejection (AMR) is recognized as a major cause of graft loss in renal transplant recipients. Early acute AMR in the first few days after transplantation occurs primarily in sensitized renal transplant recipients with donor-specific alloantibody at the time of transplant and is a relatively “pure” form of acute AMR. Late acute AMR occurs months to years after transplantation and is commonly a mixed cellular and humoral rejection. While there is no consensus regarding optimum treatment, we contend that rational therapeutic approaches are emerging and the acute episode can be managed in most instances. However, new therapies are needed to prevent ongoing chronic injury in these patients.

36. Early Versus Late Acute Antibody-Mediated Rejection in Renal Transplant Recipients.

Dörje C, Midtvedt K, Holdaas H, *et al.*

Transplantation 2013;96: 79Y84. DOI: 10.1097/TP.0b013e31829434d4.

ABSTRACT

Background: Over the last decade, the diagnostic precision for acute antibody-mediated rejection (aABMR) in kidney transplant recipients has improved significantly. The phenotypes of early and late aABMR may differ. We assessed the characteristics and outcomes of early versus late aABMR.

Methods: Between January 1, 2005 and December 31, 2010, aABMR was diagnosed in 67 grafts in 65 kidney recipients, with a median follow-up of 3.6 years (range, 61 daysY7.3 years). Recipients were stratified by early Aabmr (G3 months after transplantation; n=40) and late aABMR (93 months after transplantation; n=27). The main out-come was kidney allograft loss. Outcome of aABMR was compared with recipients with acute early (n=276) or late (n=100) non-ABMR during the same period.

Results: Recipients with late aABMR had significantly reduced graft survival compared with recipients with early aABMR (PG0.001, log-rank test; 40% vs. 75% at 4 years; hazard ratio, 3.72; 95% confidence interval, 1.65Y8.42). Graft survival in late aABMR was also inferior to late non-ABMR acute rejections (P=0.008). At transplantation, more patients were presensitized to human leukocyte antigens (22 [55%] vs. 4 [15%] in the early vs. late aABMR group). The late aABMR group was characterized by younger recipient age (37.9T12.9 vs. 50.9T11.6 years; PG0.001), increased occurrence of de novo donor-specific antibodies (52% vs. 13%; P=0.001), and nonadherence/suboptimal immuno-suppression (56% vs. 0%; PG0.001).

Conclusion: Compared with early aABMR, late aABMR had inferior graft survival and was characterized by young age, frequent nonadherence, or suboptimal immunosuppression and de novo donor-specific antibodies.

37. One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial.

Sautenet B, Blancho G, Büchler M,*et al.*

Transplantation 2016;100: 391–399.

ABSTRACT

Background: Treatment of acute antibody-mediated rejection (AMR) is based on a combination of plasma exchange (PE), IVIg, corticosteroids (CS), and rituximab, but the place of rituximab is not clearly specified in the absence of randomized trials.

Methods: In this phase III, multicenter, double-blind, placebo-controlled trial, we randomly assigned patients with biopsy-proven AMR to receive rituximab (375 mg/m^2) or placebo at day 5. All patients received PE, IVIg, and CS. The primary endpoint was a composite of graft loss or no improvement in renal function at day 12.

Results: Among the 38 patients included, at 1 year, no deaths occurred, but 1 graft loss occurred in each group. The primary endpoint frequency was 52.6% (10/19) and 57.9% (11/19) in the rituximab and placebo groups, respectively (P = 0.744). Renal function improved in both groups, as soon as day 12 with no difference in serum creatinine level and proteinuria at 1, 3, 6, and 12 months. Supplementary administration of rituximab and total number of IVIg and PE treatments did not differ between the 2 groups. Both groups showed improved histological features of AMR and Banff scores at 1 and 6 months, with no significant difference between groups but with a trend in favor of the rituximab group. Both groups showed decreased mean fluorescence intensity of donor-specific antibodies as soon as day 12, with no significant difference between them but with a trend in favor of the rituximab group at 12 months.

Conclusions: After 1 year of follow-up, we observed no additional effect of rituximab in patients receiving PE, IVIg, and CS for AMR. Nevertheless, our study was underpowered and important differences between groups may have been missed. Complementary trials with long-term follow-up are needed.

38. Randomized Controlled Pilot Study of B Cell–Targeted Induction Therapy in HLA Sensitized Kidney Transplant Recipients.

Ejaz NS, Shields AR, Alloway RR, *et al.*

American Journal of Transplantation 2013; 13: 3142–3154. doi: 10.1111/ajt.12493.

ABSTRACT

Optimal induction regimens for patients at high risk for antibody and/or cell–mediated rejection have not been established. This pilot, prospective, randomized study evaluated addition of B cell/plasma cell–targeting agents to T cell–based induction with rabbit antithymocyte globulin (rATG) in high immunologic risk renal transplant recipients. Patients were randomized to induction with rATG, rATG + rituximab, rATG + bortezomib or rATG + rituximab + bortezomib. Inclusion criteria were: (1) current cytotoxic panel reactive antibody (PRA) ≥20% or peak cytotoxic PRA ≥50% or (2) T or B cell positive flow crossmatch with donor-specific antibody (DSA) or (3) historical positive serologic or cytotoxic crossmatch or DSA to donor or (4) prior allograft loss with more than one acute rejection. Median overall follow-up was 496 days: 1-year and overall acute rejection were 25% and 27.5%, and 25% of patients developed de novo DSA within 1 year. One-year and overall patient survival were 97.5% and 92.5%, and 1-year and overall death-censored allograft survival were 97.5% and 95%. Renal allograft function posttransplant was similar among all arms. Eight of nine cases of peripheral neuropathy were mild, whereas one case was moderate and required a narcotic prescription. In conclusion, addition of rituximab and/or bortezomib to rATG induction has an acceptable safety/toxicity profile in a high immunologic risk renal transplant population.

39. Immune response and histology of humoral rejection in kidney transplantation.

González-Molina M, Ruiz-Estebana P, Caballero A, *et al.*

Nefrologia. 2016; 36(4):354-67. doi: 10.1016/j.nefro.2016.

ABSTRACT

The adaptive immune response forms the basis of allograft rejection. Its weapons are direct cellular cytotoxicity, identified from the beginning of organ transplantation, and/or antibodies, limited to hyperacute rejection by preformed antibodies and not as an allogenic response. This resulted in allogenic response being thought for decades to have just a cellular origin. But the experimental studies by Gorer demonstrating tissue damage in allografts due to antibodies secreted by B lymphocytes activated against polymorphic molecules were disregarded. The special coexistence of binding and unbinding between antibodies and antigens of the endothelial cell membranes has been the cause of the delay in demonstrating the humoral allogenic response. The endothelium, the target tissue of antibodies, has a high turnover, and antigen–antibody binding is non-covalent. If endothelial cells are attacked by the humoral response, immunoglobulins are rapidly removed from their surface by shedding and/or internalization, as well as degrading the components of the complement system by the action of MCP, DAF and CD59. Thus, the presence of complement proteins in the membrane of endothelial cells is transient. In fact, the acute form of antibody-mediated rejection was not demonstrated until C4d complement fragment deposition was identified, which is the only component that binds covalently to endothelial cells. This review examines the relationship between humoral immune response and the types of acute and chronic histological lesion shown on biopsy of the transplanted organ.

40. Rituximab as Induction Therapy After Renal Transplantation: A Randomized, Double-Blind, Placebo-Controlled Study of Efficacy and Safety.

van den Hoogen MWF, Kamburova EG, Baas MC, *et al.*

American Journal of Transplantation 2015; 15: 407–416. doi: 10.1111/ajt.13052.

ABSTRACT

We evaluated the efficacy and safety of rituximab as induction therapy in renal transplant patients. In a double-blind, placebo-controlled study, 280 adult renal transplant patients were randomized between a single dose of rituximab (375mg/m^2) or placebo during transplant surgery. Patients were stratified according to panel-reactive antibody (PRA) value and rank number of transplantation. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil and steroids. The primary endpoint was the incidence of biopsy proven acute rejection (BPAR) within 6 months after transplantation. The incidence of BPAR was comparable between rituximab-treated (23/138, 16.7%) and placebo-treated patients (30/142, 21.2%, p1⁄4 0.25). Immunologically high-risk patients (PRA >6% or re-transplant) not receiving rituximab had a significantly higher incidence of rejection (13/34, 38.2%) compared to other treatment groups (rituximab-treated immunologically high-risk patients, and rituximab- or placebo-treated immunologically low-risk (PRA 6% or first transplant) patients (17.9%, 16.4% and 15.7%, p1⁄4 0.004). Neutropenia (<1.5 109/L) occurred more frequently in rituximab-treated patients (24.3% vs. 2.2%, p< 0.001). After 24 months, the cumulative incidence of infections and malignancies was comparable. A single dose of rituximab as induction therapy did not reduce the overall incidence of BPAR, but might be beneficial in immunologically high-risk patients. Treatment with rituximab was safe.

41. Molecular and Functional Noninvasive Immune Monitoring in the ESCAPE Study for Prediction of Subclinical Renal Allograft Rejection.

Crespo E, Roedder S, Sigdel S, *et al.*

Transplantation 2017; 101(6): 1400-1409. DOI: 10.1097/TP.0000000000001287.

ABSTRACT

Background: Subclinical acute rejection (sc-AR) is a main cause for functional decline and kidney graft loss and may only be assessed through surveillance biopsies.

Methods: The predictive capacity of 2 novel noninvasive blood biomarkers, the transcriptional kidney Solid Organ Response Test (kSORT), and the IFN-γ enzyme-linked immunosorbent spot assay (ELISPOT) assay were assessed in the Evaluation of Sub-Clinical Acute rejection PrEdiction (ESCAPE) Study in 75 consecutive kidney transplants who received 6-month protocol biopsies. Both assays were run individually and in combination to optimize the use of these techniques to predict sc-AR risk.

Results: Subclinical acute rejection was observed in 22 (29.3%) patients (17 T cell–mediated subclinical rejection [sc-TCMR], 5 antibody-mediated subclinical rejection [sc-ABMR]), whereas 53 (70.7%) showed a noninjured, preserved (stable [STA]) parenchyma. High-risk (HR), low-risk, and indeterminate-risk kSORT scores were observed in 15 (20%), 50 (66.7%), and 10 (13.3%) patients, respectively. The ELISPOT assay was positive in 31 (41%) and negative in 44 (58.7%) patients. The kSORT assay showed high accuracy predicting sc-AR (specificity, 98%; positive predictive value 93%) (all sc-ABMR and 58% sc-TCMR showed HR-kSORT), whereas the ELISPOT showed high precision ruling out sc-TCMR (specificity = 70%, negative predictive value = 92.5%), but could not predict sc-ABMR, unlike kSORT. The predictive probabilities for sc-AR, sc-TCMR, and sc-ABMR were significantly higher when combining both biomarkers (area under the curve > 0.85, $P < 0.001$) and independently predicted the risk of 6-month sc-AR in a multivariate regression analysis.

Conclusions: Combining a molecular and immune cell functional assay may help to identify HR patients for sc-AR, distinguishing between different driving alloimmune effector mechanisms.

42. The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis.

Susan S. Wan, Tracey D. Ying, Kate Wyburn, *et al.*

Transplantation 2018;102: 557–568. DOI: 10.1097/TP.0000000000002049.

ABSTRACT

Background: Current treatments for antibody-mediated rejection (AMR) in kidney transplantation are based on low-quality data from a small number of controlled trials. Novel agents targeting B cells, plasma cells, and the complement system have featured in recent studies of AMR.

Methods: We conducted a systematic review and meta-analysis of controlled trials in kidney transplant recipients using Medline, EMBASE, and CENTRAL from inception to February 2017.

Results: Of 14 380 citations, we identified 21 studies, including 10 randomized controlled trials, involving 751 participants. Since the last systematic review conducted in 2011, we found nine additional studies evaluating plasmapheresis + intravenous immunoglobulin (IVIG) (two), rituximab (two), bortezomib (two), C1 inhibitor (two), and eculizumab (one). Risk of bias was serious or unclear overall and evidence quality was low for the majority of treatment strategies. Sufficient RCTs for pooled analysis were available only for antibody removal, and here there was no significant difference between groups for graft survival (HR 0.76; 95% CI 0.35-1.63; P = 0.475). Studies showed important heterogeneity in treatments, definition of AMR, quality, and follow-up. Plasmapheresis and IVIG were used as standard-of-care in recent studies, and to this combination, rituximab seemed to add little or no benefit. Insufficient data are available to assess the efficacy of bortezomib and complement inhibitors.

Conclusion: Newer studies evaluating rituximab showed little or no difference to early graft survival, and the efficacy of bortezomib and complement inhibitors for the treatment of AMR remains unclear. Despite the evidence uncertainty, plasmapheresis and IVIG have become standard-of-care for the treatment of acute AMR.

43. Antibody-incompatible kidney transplantation in 2015 and beyond.

Higgins RM., Daga S and Mitchell DA.

Nephrol Dial Transplant (2015) 30: 1972–1978. doi: 10.1093/ndt/gfu375

ABSTRACT

Rejection caused by donor-specific antibodies (principally ABO and HLA antibodies) has become one of the major barriers to successful long-term transplantation. This review focuses on clinical outcomes in antibody-incompatible transplantation, the current state of the science underpinning clinical observations, and how these may be translated into further novel therapies. The clinical outcomes for allografts facing donor-specific antibodies are at present determined largely by the use of agents developed in the 20th century for the treatment of T-lymphocyte-mediated cellular rejection, such as interleukin-2 agents and anti-thymocyte globulin. These treatments are partially effective, because acute antibody-mediated rejection is mediated to a considerable extent by T lymphocytes. However these treatments are essentially ineffective in chronic antibody-mediated rejection. Future therapies for the prevention and treatment of antibody-mediated rejection are likely to fall into the categories of those that reduce antibody production, extracorporeal antibody removal and disruption of the effector arms of antibody-mediated tissue damage.

44. The emerging role of complement inhibitors in transplantation.

Frameaux-Bacchi V, Legendre CM.

Kidney Int. 2015; 88(5):967-73. doi: 10.1038/ki.2015.253.

ABSTRACT

The role of complement in the biology of kidney transplantation is becoming more and more significant, especially but not only because we now have access to drugs inhibiting complement. After describing the main characteristics of complement biology, both activation of the complement cascade and the many regulatory factors, we will review the precise role of complement in kidney transplant biology. Complement activation has been involved in ischemia-reperfusion injury, in the recurrence of several diseases such as atypical hemolytic uremic syndrome, C3 glomerulopathies, and antiphospholipid syndrome, as well as the process of antibody-mediated rejection, either acute or chronic. There are many potentially interesting drugs interfering with complement inhibition that have been or may be studied in kidney transplantation. Currently, the bulk of data concerns eculizumab, a monoclonal antibody blocking the complement cascade at the C5. Its efficacy has been demonstrated in the treatment and prevention of recurrence of atypical hemolytic uremic syndrome with an overall good safety profile. Although it has been reported to be efficacious to prevent antibody-mediated rejection, properly designed trials are currently being performed to state this efficacy. In addition, randomized trials are, in the process, regarding the prevention of ischemia-reperfusion injury after kidney transplantation.

45. A systematic review of the role of C4d in the diagnosis of acute antibody-mediated rejection.

Sapir-Pichhadze R, Curran SP, John R *et al.*

Kidney Int. 2015; 87(1):182-94. doi: 10.1038/ki.2014.166.

ABSTRACT

In this study, we conducted a systematic review of the literature to re-evaluate the role of C4d in the diagnosis of acute antibody-mediated rejection of kidney allografts. Electronic databases were searched until September 2013. Eligible studies allowed derivation of diagnostic tables for the performance of C4d by immunofluorescence or immunohistochemistry with comparison to histopathological features of acute antibody-mediated rejection and/or donor-specific antibody (DSA) assays. Of 3492 unique abstracts, 29 studies encompassing 3485 indication and 868 surveillance biopsies were identified. Assessment of C4d by immunofluorescence and immunohistochemistry exhibited slight to moderate agreement with glomerulitis, peritubular capillaritis, solid-phase DSA assays, DSA with glomerulitis, and DSA with peritubular capillaritis. The sensitivity and specificity of C4d varied as a function of C4d and comparator test thresholds. Prognostically, the presence of C4d was associated with inferior allograft survival compared with DSA or histopathology alone. Thus, our findings support the presence of complement-dependent and -independent phenotypes of acute antibody-mediated rejection. Whether the presence of C4d in combination with histopathology or DSA should be considered for the diagnosis of acute antibody-mediated rejection warrants further study.

46. Clinical relevance of pretransplant anti-HLA donor-specific antibodies: does C1q-fixation matter?

Crespo M, Torio A, Mas V *et al.*

Transpl Immunol. 2013; 29(1-4):28-33. doi: 10.1016/j.trim.2013.07.002.

ABSTRACT

Anti-HLA donor-specific antibodies (DSA) identified by single antigen bead array (SAB) are questioned for their excess in sensitivity and lack of event prediction after transplantation.

Population and methods: We retrospectively evaluated specific types of preformed DSA (class I, class II or C1q-fixing) and their impact on graft survival. Kidney transplantations performed across negative CDC-crossmatch were included (n=355). Anti-HLA antibodies were tested using SAB to identify DSA and their capacity to fix C1q.

Results: Twenty-eight patients with pretransplant DSA(+) with MFI>2000 were selected to assess C1q fixation. DSA were C1q+ in 15 patients and C1q- in 13, without significant differences in demographics, acute rejection, graft loss or renal function. The maximum MFI of DSA in patients with C1q-fixing DSA was significantly higher (p=0.008). Patients with DSA class-I suffered more antibody-mediated rejection (AMR) and had worse graft survival than class-II. The capacity of DSA I to fix C1q did not correlate with rejection, graft function or graft loss.

Conclusions: C1q testing in pretransplant sera with DSA was unable to predict acute antibody-mediated rejection or early graft loss, but the presence of DSA class I compared to DSA only class II did. Despite non-fixing complement in vitro, pretransplant C1q-negative DSA I can mediate rejection and graft loss.

47. A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection.

Macklin PS, Morris PJ, Knight SR.

Transplant Rev (Orlando). 2017; 31(2):87-95. doi: 10.1016/j.trre.2017.01.002.

ABSTRACT

Rituximab is a B-lymphocyte depleting agent that is used to treat hematological malignancies and autoimmune diseases. Recently, it has gained interest as an immunomodulatory agent in renal transplantation. This systematic review evaluates the evidence for its use in the treatment of acute and chronic antibody-mediated renal transplant rejection (AAMR; CAMR). A systematic search of four databases and three trial registries was conducted. The small number and heterogeneous nature of included studies precluded meta-analysis and thus a narrative review was conducted. A total of 28 records met the inclusion criteria (AAMR, 18 records relating to 9 studies; CAMR, 10 records relating to 7 studies). Two systematic reviews were identified that had differing inclusion criteria to this current review. Of seven primary studies in the setting of AAMR, four reported increased graft survival and one reported improved graft function with rituximab. This contrasts with CAMR in which only one of seven studies reported improved graft outcomes with a rituximab-based regimen; three studies reported inferior outcomes and three reported no difference. Only one study reported that rituximab was associated with an increase in adverse effects. The included studies suggest that rituximab may be of some benefit in the setting of AAMR but a lack of high quality evidence precludes firm conclusions from being drawn. Rituximab does not appear to reliably improve outcomes in CAMR. Further well-conducted studies are required to better define the effects and long-term safety profile of rituximab in the treatment of antibody-mediated renal transplant rejection.

48. Intravenous immunoglobulin in kidney transplantation.

Tedla FM, Roche-Recinos A, Brar A.

Curr Opin Organ Transplant. 2015; 20(6):630-7. doi:10.1097/MOT.0000000000000250.

ABSTRACT

Purpose of review: Antibody-mediated injury of renal allografts has assumed increasing importance with the availability of potent immunosuppressants directed against T-lymphocytes. Intravenous immunoglobulin (IVIG) has been used for prevention and treatment of antibody-mediated rejection. The review summarizes recent advances that shed light on mechanisms of action of IVIG and outlines current roles of IVIG in kidney transplantation.

Recent findings: Observational studies support the use of IVIG for desensitization and treatment of acute rejection. Most studies are small and uncontrolled, but a matched case-control study reported a better survival with incompatible live-donor kidney transplant after desensitization using IVIG-containing regimens compared with dialysis or waiting for compatible transplant. Recent data indicate that variations in glycosylation and amino acid sequence cause the crystallizable fragment of immunoglobulin G to assume specific conformations that have high affinity for canonical crystallizable fragment receptors (FcR) or a newly discovered class of FcRs, labelled type II FcRs. Signaling through type II FcRs appears to trigger anti-inflammatory pathways.

Summary: Recent discoveries expand our understanding of the mechanism of action of IVIG. Future research is expected to clarify the relevance of these findings to humans and could lead to the development of novel immunomodulatory agents.

49. Clinical efficacy of rituximab for acute rejection in kidney transplantation: a meta-analysis.

Zhao YG, Shi BY, Qian YY, Bai HW, Xiao L, He XY.

Int Urol Nephrol. 2014 Jun;46(6):1225-30. doi: 10.1007/s11255-013-0599-4.

ABSTRACT

Objectives: This meta-analysis was undertaken to compare the efficacy and safety of pretransplant treatment with rituximab in sensitized patients receiving kidney transplantation.

Methods: PubMed, EMBASE, and Cochrane databases were searched to identify studies that used pretransplantation rituximab in eligible patients. The major outcomes included antibody-mediated rejections (AMR) after kidney transplantation and one-year graft survival rate. The meta-analysis was performed using fixed-effects model.

Results: Seven studies were identified including a total of 589 patients, of whom 312 were treated without rituximab, while 277 were treated with rituximab. In our meta-analysis, patients treated with rituximab had significantly fewer AMR after kidney transplantation [odds ratio (OR) 0.52, 95 % CI 0.28, 0.98, P = 0.04] and higher rate of one-year graft survival rates (OR 3.02, 95 % CI 1.14, 8.02, P = 0.03), indicating that rituximab is effective against acute rejection and enhances graft survival in kidney transplantation. No differences were noted in other efficacy and safety parameters in these two patient groups.

Conclusions: We demonstrated that preinduction with rituximab could significantly improve AMR and graft survival rates in sensitized patients undergoing kidney transplantation. Future prospective controlled studies are warranted to further understand rituximab's role in kidney transplantation.

50. Does tubulitis without interstitial inflammation represent borderline acute T cell mediated rejection?

Nankivell BJ, P'Ng CH, Chapman JR.

Am J Transplant. 2018 Apr 24. doi: 10.1111/ajt.14888.

ABSTRACT

Tubulitis without interstitial inflammation (Banff i0), termed "isolated tubulitis" (ISO-T), has been controversially included within the Banff "borderline" category of acute T cell mediated rejection (TCMR). This single-center, retrospective, observational study of 2055 consecutive biopsies from 775 recipients, determined the clinical significance of ISO-T. ISO-T prevalence was 19.1%, comprising mild tubulitis (i0t1) in 97.2%. Independent clinical predictors of tubulitis were HLA mismatch, prior TCMR and antibody-mediated rejection, pulse corticosteroids, and BKVAN (P = .006 to P < .001 by multivariable analysis). Histological associations of tubulitis included interstitial inflammation, peritubular capillaritis, tubular atrophy, and SV40T (P = .005 to <.001). The dominant pathological diagnoses in ISO-T (n = 393) were interstitial fibrosis/tubular atrophy (IF/TA, 44.5%) or normal/minimal (31.8%). Subanalysis of ISO-T from indication biopsies (n = 107) found acute tubular injury (37.4%), IF/TA (28.0%), normal/minimal (12.1%), acute rejection (9.3%, vascular or antibody), chronic-active TCMR (2.8%), and BKVAN (5.6%). Allograft function of ISO-T frequently improved, affected by early biopsy timing and underlying disease diagnosis. Subsequent histology of 1197 ISO-T biopsy-pairs was generally benign. The 1- and 5-year death-censored graft survivals of ISO-T were 98.8% and 92.7%. In summary, tubulitis without inflammation does not represent borderline TCMR. We suggest its removal from the borderline category, and reinstatement of i1 as the diagnostic threshold.

51. La patología del trasplante renal.

Vazquez Martul E.

Rev Esp Patol. 2018; 51(2):110-123. doi: 10.1016/j.patol.2017.10.001

ABSTRACT

In order to make an objective assessment of the histopathology of a renal biopsy during a kidney transplant, all the various elements involved in the process must be understood. It is important to know the characteristics of the donor organ, especially if the donor is older than 65. The histopathological features of the donor biopsy, especially its vascular status, are often related to an initial poor function of the transplanted kidney. The T lymphocyte inflammatory response is characteristic in acute cellular rejection; the degree of tubulitis, together with the amount of affected parenchyme, are important factors. The proportion of cellular sub-populations, such as plasma cells and macrophages, is also important, as they can be related to antibody-mediated humoral rejection. Immunofluorescent or immunohistochemical studies are necessary to rule out C4d deposits or immunogloblulins. The presence of abundant deposits of C4d in tubular basement membranes supports a diagnosis of humoral rejection, as does the presence of capillaritis, glomerulitis which, together with vasculitis, are typical diagnostic findings in C4d negative cases. Interstitial fibrosis, tubular atrophy and glomerular sclerosis, although non-specific, imply a chronic phase. Transplant glomerulopathy and multilamination in more than 6 layers of the tubular and glomerular basement membranes are quasi-specific characteristics of chronic humoral rejection. Electron microscopy is essential to identify of these pathologies as well as to demonstrate the presence of other glomerular renal diseases.

52. IgG Endopeptidase in Highly Sensitized Patients Undergoing Transplantation

Jordan S.C., Lorant T., Choi J., *et al.*

N Engl J Med 2017;377:442-53.

ABSTRACT

Background: Donor-specific antibodies create an immunologic barrier to transplantation. Current therapies to modify donor-specific antibodies are limited and ineffective in the most highly HLA-sensitized patients. The IgG-degrading enzyme derived from Streptococcus pyogenes (IdeS), an endopeptidase, cleaves human IgG into F(ab')2 and Fc fragments inhibiting complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, which suggests that IdeS might be useful for desensitization. We report on the combined experience of two independently performed open-label, phase 1–2 trials (conducted in Sweden and the United States) that assessed the efficacy of IdeS with regard to desensitization and transplantation of a kidney from an HLA-incompatible donor.

Methods: We administered IdeS to 25 highly HLA-sensitized patients (11 patients in Uppsala or Stockholm, Sweden, and 14 in Los Angeles) before the transplantation of a kidney from an HLA-incompatible donor. Frequent monitoring for adverse events, outcomes, donor-specific antibodies, and renal function was performed, as were renal biopsies. Immunosuppression after transplantation consisted of tacrolimus, mycophenolate mofetil, and glucocorticoids. Patients in the U.S. study also received intravenous immune globulin and rituximab after transplantation to prevent antibody rebound.

Results: Recipients in the U.S. study had a significantly longer cold ischemia time (the time elapsed between procurement of the organ and transplantation), a significantly higher rate of delayed graft function, and significantly higher levels of class I donorspecific antibodies than those in the Swedish study. A total of 38 serious adverse events occurred in 15 patients (5 events were adjudicated as being possibly related to IdeS). At transplantation, total IgG and HLA antibodies were eliminated. A total of 24 of 25 patients had perfusion of allografts after transplantation. Antibodymediated rejection occurred in 10 patients (7 patients in the U.S. study and 3 in the Swedish study) at 2 weeks to 5 months after transplantation; all these patients had a response to treatment. One graft loss, mediated by non-HLA IgM and IgA antibodies, occurred.

Conclusions: IdeS reduced or eliminated donor-specific antibodies and permitted HLA-incompatible transplantation in 24 of 25 patients. (Funded by Hansa Medical; ClinicalTrials
.gov numbers, NCT02224820, NCT02426684, and NCT02475551.)

53. Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors

Orandi B.J., Luo X., Massie A.B., *et al.*

Engl J Med 2016;374:940-50.

ABSTRACT

Background: A report from a high-volume single center indicated a survival benefit of receiving a kidney transplant from an HLA-incompatible live donor as compared with remaining on the waiting list, whether or not a kidney from a deceased donor was received. The generalizability of that finding is unclear.

Methods: In a 22-center study, we estimated the survival benefit for 1025 recipients of kidney transplants from HLA-incompatible live donors who were matched with controls who remained on the waiting list or received a transplant from a deceased donor (waitinglist- or-transplant control group) and controls who remained on the waiting list but did not receive a transplant (waiting-list-only control group). We analyzed the data with and without patients from the highest-volume center in the study.

Results: Recipients of kidney transplants from incompatible live donors had a higher survival rate than either control group at 1 year (95.0%, vs. 94.0% for the waiting-list-ortransplant control group and 89.6% for the waiting-list-only control group), 3 years (91.7% vs. 83.6% and 72.7%, respectively), 5 years (86.0% vs. 74.4% and 59.2%), and 8 years (76.5% vs. 62.9% and 43.9%) (P<0.001 for all comparisons with the two control groups). The survival benefit was significant at 8 years across all levels of donorspecific antibody: 89.2% for recipients of kidney transplants from incompatible live donors who had a positive Luminex assay for anti-HLA antibody but a negative flowcytometric cross-match versus 65.0% for the waiting-list-or-transplant control group and 47.1% for the waiting-list-only control group; 76.3% for recipients with a positive flow-cytometric cross-match but a negative cytotoxic cross-match versus 63.3% and 43.0% in the two control groups, respectively; and 71.0% for recipients with a positive cytotoxic cross-match versus 61.5% and 43.7%, respectively. The findings did not change when patients from the highest-volume center were excluded.

Conclusions: This multicenter study validated single-center evidence that patients who received kidney transplants from HLA-incompatible live donors had a substantial survival benefit as compared with patients who did not undergo transplantation and those who waited for transplants from deceased donors. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases.)

54. Antibody-Mediated Rejection: Analyzing the Risk, Proposing Solutions

Arias M, Rush DN, Wiebe C, *et al.*

Transplantation. 2014 Aug 15;98 Suppl 3:S3-21.

NO ABSTRACT AVAILABLE

55. Dynamic Prognostic Score to Predict Kidney Allograft Survival in Patients with Antibody-Mediated Rejection

Viglietti D, Loupy A, Aubert O, *et al.*

J Am Soc Nephrol. 2018 Feb;29(2):606-619.

ABSTRACT

No tool is available for the early assessment of response to antibody-mediated rejection (ABMR) therapies in kidney allograft recipients. This study was designed to define a dynamic composite prognostic ABMR score to predict kidney allograft survival, integrating the disease characteristics at diagnosis and the response to treatment. Among 1978 kidney recipients who underwent transplant between 2008 and 2014, we included 278 patients diagnosed with active ABMR and receiving standard treatment, including plasma exchange, intravenous Ig, and rituximab. Patients were prospectively assessed at diagnosis and after treatment for clinical data, histologic characteristics (allograft biopsy specimen), and donor-specific anti-HLA antibodies (DSA). The dynamic ABMR prediction model included GFR (P<0.001) and presence of interstitial fibrosis/tubular atrophy (P=0.003) at diagnosis and changes in GFR (P<0.001), peritubular capillaritis Banff score (P=0.002), and DSA mean fluorescence intensity (P<0.001) after treatment. Overall, this model showed good calibration and discrimination (C-statistic=0.84). The ABMR prognostic score derived from the prediction model identified three risk strata with 6-year kidney allograft survival rates of 6.0% (high-risk group, n=40), 44.9% (intermediate-risk group, n=36), and 84.4% (low-risk group, n=202), and it provided greater net clinical benefit to patients than did considering them all to have the same level of risk of allograft loss. The performance of the ABMR prognostic score was validated in an independent cohort of 202 kidney recipients with ABMR (C-statistic=0.79). The ABMR prognostic score could be used to inform therapeutic decisions in clinical practice and for the design of clinical trials.

56. Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

Stegall MD, Diwan T, Raghavaiah S, *et al.*

Am J Transplant. 2013 Jan;13(1):241.

ABSTRACT

Sensitized renal transplant recipients with high levels of donor-specific alloantibody (DSA) commonly develop antibody-mediated rejection (AMR), which may cause acute graft loss or shorten allograft survival. We examined the efficacy of terminal complement inhibition with the humanized anti-C5 antibody, eculizumab, in the prevention AMR in renal transplant recipients with a positive crossmatch against their living donor. The incidence of biopsy-proven AMR in the first 3 months posttransplant in 26 highly sensitized recipients of living donor renal transplants who received eculizumab posttransplant was compared to a historical control group of 51 sensitized patients treated with a similar plasma exchange (PE)-based protocol without eculizumab. The incidence of AMR was 7.7% (2/26) in the eculizumab group compared to 41.2% (21/51) in the control group ($p = 0.0031$). Eculizumab also decreased AMR in patients who developed high levels of DSA early after transplantation that caused proximal complement activation. With eculizumab, AMR episodes were easily treated with PE reducing the need for splenectomy. On 1-year protocol biopsy, transplant glomerulopathy was found to be present in 6.7% (1/15) eculizumab-treated recipients and in 35.7% (15/42) of control patients ($p = 0.044$). Inhibition of terminal complement activation with eculizumab decreases the incidence of early AMR in sensitized renal transplant recipients.