1. LA RESPUESTA HUMORAL EN EL ALORECONOCIMIENTO

1. Deleterious impact of C3d-binding donor-specific anti-HLA antibodies after pediatric liver transplantation.

Couchonnal E, Rivet C, Ducreux S, *et al.*

Transpl Immunol. 2017 Dec;45:8-14. doi: 10.1016/j.trim.2017.08.001. Epub 2017 Aug 3.

ABSTRACT

Background: The prevalence and clinical impact of anti-HLA donor-specific antibodies (DSA) after liver transplantation (LT) have not been extensively studied, especially in pediatric population.

Methods: The present cross-sectional study included 100 patients who underwent a first LT in childhood. Anti HLA immunization study was performed at a single time point during routine follow-up using Luminex® single antigen tests with classical anti-IgG conjugate and anti-C3d conjugate.

Results: The main indication for LT was biliary atresia (52%) and median age at LT was 4.6years. The median time between LT and DSA assessment was 7.8years (range 1-21years). DSA was identified in twenty-four patients (24%) after LT, with a prevalence of 8%, 28%, 33%, 50%, respectively 0-5years, 5-10years, 10-15years and >15years after LT. DSA were mainly class II (23/24) with a mean MFI of 9.731±5.489 and 18 (79.3%) were C3d-binding DSA. Multivariate analysis disclosed that time elapsed since LT ($p<0.01$) and history of fulminant hepatitis ($p=0.04$) were significantly associated with a higher rate of DSA. Liver function tests (at time of DSA assessment) were not different according to the presence or not of DSA (or C3d-binding DSA). Regarding histology, the DSA group had a higher rate of chronic rejection, cirrhosis and centrilobular fibrosis or cirrhosis. In addition, patients with C3d-binding DSA and high MFI (>10,000) had a significant poorer long-term graft survival ($p=0.03$).

Conclusion: In our pediatric cohort of LT, prevalence of DSA was high and increased regularly with time. Presence of C3d positive-DSA with high MFI was associated with a higher rate of graft loss.

2 . Persistent C4d and antibody-mediated rejection in pediatric renal transplant patients.

South AM, Maestretti L, Kambham N, et al.

Pediatr Transplant. 2017 Nov;21(7). doi: 10.1111/petr.13035. Epub 2017 Aug 22.

ABSTRACT

Pediatric renal transplant recipient survival continues to improve, but ABMR remains a significant contributor to graft loss. ABMR prognostic factors to guide treatment are lacking. C4d staining on biopsies, diagnostic of ABMR, is associated with graft failure. Persistent C4d+ on follow-up biopsies has unknown significance, but could be associated with worse outcomes. We evaluated a retrospective cohort of 17 pediatric renal transplant patients diagnosed with ABMR. Primary outcome at 12 months was a composite of ≥50% reduction in eGFR, transplant glomerulopathy, or graft failure. Secondary outcome was the UPCR at 12 months. We used logistic and linear regression modeling to determine whether persistent C4d+ on follow-up biopsy was associated with the outcomes. Forty-one percent reached the primary outcome at 12 months. Persistent C4d+ on follow-up biopsy occurred in 41% and was not significantly associated with the primary outcome, but was significantly associated with the secondary outcome (estimate 0.22, 95% CI 0.19-0.25, P < .001), after controlling for confounding factors. Persistent C4d+ on follow-up biopsies was associated with a higher UPCR at 12 months. Patients who remain C4d+ on follow-up biopsy may benefit from more aggressive or prolonged ABMR treatment.

3. Cellular immune profile of kidney transplant patients developing anti-HLA antibodies during childhood.

Santilli V, Cagigi A, Guzzo I, et al.

Pediatr Nephrol. 2016 Jun;31(6):1001-10. doi: 10.1007/s00467-015-3274-4. Epub 2015 Dec 21.

ABSTRACT

Background: In the field of kidney transplantation, identifying early signatures of humoral rejection is a key challenge.

Methods: We investigated the presence of anti-HLA antibodies and the distribution of lymphocyte subpopulations in 77 kidney-transplanted children and young adults compared to 23 healthy controls. Moreover, we tested whether the presence of anti-HLA antibodies could be related to modification in lymphocyte phenotype. Finally, we correlated the presence of anti-HLA antibodies and specific alteration of lymphocyte subsets with clinical outcomes.

Results: In kidney-transplanted children who developed anti-HLA antibodies, we observed an expansion of double-negative B cells (CD19 + CD27-IgD-), indicating premature aging of this compartment. Moreover, we reported signs of impaired B cell regulation, indicated by a higher IL-21R+ B cell frequency associated with an abnormal increase of follicular helper T cells. Finally, a considerable reduction in CD8+ effector T and invariant Natural killer T (NKT) cells was observed. The stability of graft function over time is significantly correlated with the frequency of peripheral effector CD4+ and CD8+ T cells and invariant NKT cells.

Conclusions: This study supports the usefulness of lymphocyte subset as one of a spectrum of early diagnostic tools required to identify patients at risk of developing donor alloimmune response.

4. The clinical impact of humoral immunity in pediatric renal transplantation.

Chaudhuri A, Ozawa M, Everly MJ, et al.

J Am Soc Nephrol. 2013 Mar;24(4):655-64. doi: 10.1681/ASN.2012070663. Epub 2013 Feb 28.

ABSTRACT

The development of anti-donor humoral responses after transplantation associates with higher risks for acute rejection and 1-year graft survival in adults, but the influence of humoral immunity on transplant outcomes in children is not well understood. Here, we studied the evolution of humoral immunity in low-risk pediatric patients during the first 2 years after renal transplantation. Using data from 130 pediatric renal transplant patients randomized to steroid-free (SF) or steroid-based (SB) immunosuppression in the NIH-SNSO1 trial, we correlated the presence of serum anti-HLA antibodies to donor HLA antigens (donor-specific antibodies) and serum MHC class 1-related chain A (MICA) antibody with both clinical outcomes and histology identified on protocol biopsies at 0, 6, 12, and 24 months. We detected de novo antibodies after transplant in 24% (23% of SF group and 25% of SB group), most often after the first year. Overall, 22% developed anti-HLA antibodies, of which 6% were donor-specific antibodies, and 6% developed anti-MICA antibody. Presence of these antibodies de novo associated with significantly higher risks for acute rejection (P=0.02), chronic graft injury (P=0.02), and decline in graft function (P=0.02). In summary, antibodies to HLA and MICA antigens appear in approximately 25% of unsensitized pediatric patients, placing them at greater risk for acute and chronic rejection with accelerated loss of graft function. Avoiding steroids does not seem to modify this incidence. Whether serial assessments of these antibodies after transplant could guide individual tailoring of immunosuppression requires additional study.

5. The role of complement in antibody-mediated rejection in kidney transplantation.

Stegall MD, Chedid MF, Cornell LD.

Nat Rev Nephrol. 2012 Nov;8(11):670-8. doi: 10.1038/nrneph.2012.212. Epub 2012 Oct 2.

ABSTRACT

Over the past decade, several studies have suggested that the complement system has an active role in both acute and chronic allograft rejection. These studies have been facilitated by improved techniques to detect antibody-mediated organ rejection, including immunohistological staining for C4d deposition in the allograft and solid-phase assays that identify donor-specific alloantibodies (DSAs) in the serum of transplant recipients. Studies with eculizumab, a humanized monoclonal antibody directed against complement component C5, have shown that activation of the terminal complement pathway is necessary for the development of acute antibody-mediated rejection in recipients of living-donor kidney allografts who have high levels of DSAs. The extent to which complement activation drives chronic antibody-mediated injury leading to organ rejection is less clear. In chronic antibody-mediated injury, early complement activation might facilitate chemotaxis of inflammatory cells into the allograft in a process that later becomes somewhat independent of DSA levels and complement factors. In this Review, we discuss the different roles that the complement system might have in antibody-mediated allograft rejection, with specific emphasis on renal transplantation.

6. Complement-activating donor-specific anti-HLA antibodies and solid organ transplant survival: A systematic review and meta-analysis.

Bouquegneau A, Loheac C, Aubert O, et al.

PLoS Med. 2018 May 25;15(5):e1002572. doi: 10.1371/journal.pmed.1002572. eCollection 2018 May.

ABSTRACT

Background: Anti-human leukocyte antigen donor-specific antibodies (anti-HLA DSAs) are recognized as a major barrier to patients' access to organ transplantation and the major cause of graft failure. The capacity of circulating anti-HLA DSAs to activate complement has been suggested as a potential biomarker for optimizing graft allocation and improving the rate of successful transplantations.

Methods and findings: To address the clinical relevance of complement-activating anti-HLA DSAs across all solid organ transplant patients, we performed a meta-analysis of their association with transplant outcome through a systematic review, from inception to January 31, 2018. The primary outcome was allograft loss, and the secondary outcome was allograft rejection. A comprehensive search strategy was conducted through several databases (Medline, Embase, Cochrane, and Scopus). A total of 5,861 eligible citations were identified. A total of 37 studies were included in the meta-analysis. Studies reported on 7,936 patients, including kidney (n = 5,991), liver (n = 1,459), heart (n = 370), and lung recipients (n = 116). Solid organ transplant recipients with circulating complement-activating anti-HLA DSAs experienced an increased risk of allograft loss (pooled HR 3.09; 95% CI 2.55-3.74, P = 0.001; I2 = 29.3%), and allograft rejection (pooled HR 3.75; 95% CI: 2.05-6.87, P = 0.001; I2 = 69.8%) compared to patients without complement-activating anti-HLA DSAs. The association between circulating complement-activating anti-HLA DSAs and allograft failure was consistent across all subgroups and sensitivity analyses. Limitations of the study are the observational and retrospective design of almost all included studies, the higher proportion of kidney recipients compared to other solid organ transplant recipients, and the inclusion of fewer studies investigating allograft rejection.

Conclusions: In this study, we found that circulating complement-activating anti-HLA DSAs had a significant deleterious impact on solid organ transplant survival and risk of rejection. The detection of complement-activating anti-HLA DSAs may add value at an individual patient level for noninvasive biomarker-guided risk stratification.

7. IGG3 anti-HLA donor-specific antibodies and graft function in pediatric kidney transplant recipients.

Hamdani G, Goebel JW, Brailey P, *et al.*

Pediatric Transplantation. 2018;e13219.

ABSTRACT

Anti-HLA DSAs are associated with ABMR and graft loss in KT recipients, yet the influence of DSA IgG subclass on outcomes in pediatric KT recipients is not completely understood. We performed a single-center retrospective chart review of pediatric KT recipients with anti-HLA DSAs, aiming to study the association between specific DSA IgG subclasses and graft outcomes, including ABMR and significant graft dysfunction (graft loss or 50% decrease in eGFR). Thirty-six patients (mean age 15.4y) with DSAs initially detected 1 month-14.3 years post-transplantation were followed for a median of 2.8 years. Rates of IgG1, 2, 3, and 4 subclass detection were 92%, 33%, 58%, and 25%, respectively. Twenty-two patients (61%) had clinical ABMR, whereas 19% had subclinical ABMR, and 13 (36%) experienced significant graft dysfunction. Patients with IgG3+ DSAs had a higher risk of graft dysfunction compared with IgG3-patients (52% vs 13%, P = .03). In a multiple Cox proportional regression analysis, the presence of IgG3+ DSA was independently associated with significant graft dysfunction (HR 10.45, 95% CI 1.97-55.55, P = .006). In conclusion, IgG3 subclass DSAs are associated with graft dysfunction and may be useful for risk stratification and treatment decisions in DSA-positive pediatric KT recipients.

8. Clinical risk stratification of paediatric renal transplant recipients using C1q and C3d fixing of de novo donor-specific antibodies.

Kim JJ, Shaw O, Martin C, *et al.*

Pediatr Nephrol (2018) 33:167–174.

ABSTRACT

Introduction: We have previously shown that children who developed de novo donor-specific human leukocyte antigen (HLA) antibodies (DSA) had greater decline in allograft function. We hypothesised that patients with complementactivating DSA would have poorer renal allograft outcomes.

Methods: A total of 75 children developed DSA in the original study. The first positive DSA sample was subsequently tested for C1q and C3d fixing. The primary event was defined as 50% reduction from baseline estimated glomerular filtration rate and was analysed using the Kaplan–Meier estimator.

Results: Of 65 patients tested, 32 (49%) and 23 (35%) tested positive for C1q and C3d fixing, respectively. Of the 32 C1qpositive (c1q+) patients, 13 (41%) did not show concomitant C3d fixing. The mean fluorescence intensity values of the original immunoglobulin G DSA correlated poorly with complement-fixing positivity (C1q: adjusted R^2 0.072; C3d: adjusted R^2 0.11; $p < 0.05$). C1q+ antibodies were associated with acute tubulitis [0.75 ± 0.18 (C1q+) vs. 0.25 ± 0.08 (C1q −) episodes per patient (mean ± standard error of the mean; $p < 0.05$] but not with worse long-term renal allograft dysfunction (median time to primary event 5.9 (C1q+) vs. 6.4 (C1q−) years; hazard ratio (HR) 0.74; 95% confidence ratio (CI) 0.30–1.81; $p = 0.58$]. C3d-positive (C3d+) antibodies were associated with positive C4d histological staining [47% (C3d+) vs. 20% (C3d−); p = 0.04] and with significantly worse long-term allograft dysfunction [median time to primary event: 5.6 (C3d+) vs. 6.5 (C3d−) years; HR 0.38; 95% CI 0.15–0.97; $p = 0.04$].

Conclusion: Assessment of C3d fixing as part of prospective HLA monitoring can potentially aid stratification of patients at the highest risk of long-term renal allograft dysfunction.

2. ASPECTOS DIAGNÓSTICOS (ANTICUERPOS HLA, HISTOLOGÍA, COMPLEMENTO, SCREENING EN POBLACION DE RIESGO, ETC)

9. Characteristics of donor-specific anti-HLA antibodies and outcome in renal transplant patients treated with a standardized induction regimen.

Zecher D, Bach C, Staudner C, *et al*.

Nephrol Dial Transplant. 2017 Apr 1;32(4):730-737. doi: 10.1093/ndt/gfw445.

ABSTRACT

Background: Pre-transplant donor-specific anti-human leukocyte antigen (HLA) antibodies (DSA) have been associated with antibody-mediated rejection (AMR) and early kidney allograft loss. Uncertainties remain regarding the general applicability of these findings and the optimal induction therapy in DSA-positive patients.

Methods: Pre-transplant sera from 174 patients receiving a crossmatch-negative kidney transplant were retrospectively analysed for DSA using Luminex technology. DSA with mean-fluorescence intensity (MFI) values above 500 were considered positive. All recipients received basiliximab induction and tacrolimus-based maintenance immunosuppression. DSA were monitored post-transplantation in patients with pre-transplant DSA. Antibody results were correlated with the incidence of rejection and graft loss.

Results: In total, 61/174 patients had pre-transplant DSA. We found a strong correlation between the presence of DSA against class I and II HLA and DSA MFI greater than 10 000. Both DSA patterns independently predicted an increased risk of early AMR (odds ratio 4.24 and 4.75, respectively, $P < 0.05$). The risk for AMR in patients with intermediate MFI (3000-10 000) gradually increased with increasing MFI but group sizes were too small to allow for final conclusions. The risk for AMR was comparable to nonsensitized patients in patients with only class I or II HLA-DSA or MFI below 3000. 5-year allograft survival was lowest in patients with simultaneous presence of class I and II HLA-DSA and MFI above 10 000 (45%) but was comparable between patients with only HLA class I or II or no DSA (90.0, 90.0 and 88.1%, respectively). AMR was the only independent predictor of graft loss. Undetectable DSA 14 days post-transplant predicted excellent long-term outcome.

Conclusion: The favourable outcome in the majority of DSA-positive patients despite non-depleting antibody induction and the poor outcome in patients with class I and II HLA-DSA and high DSA strength call for a differentiated therapeutic approach in this patient population.

10. Application and interpretation of histocompatibility data in pediatric kidney transplantation

Fernández HE.

Curr Opin Organ Transplant. 2017 Aug;22(4):426-432

ABSTRACT

Purpose of review: Advances in technology to assess immunologic risk in solid organ transplant offer an opportunity to optimize the approach to pediatric deceased donor kidney transplant in the setting of a new allocation system in the United States.

Recent findings: Degree of human leukocyte antigen (HLA) mismatch, class II HLA mismatch, unacceptable antigens and donor-specific antibody (DSA) detected by solid-phase assays, and epitope matching pretransplant affect pediatric kidney transplant outcomes. Detection of de novo DSAs (*dn*DSAs) posttransplant has been associated with increased risk of acute rejection and worse allograft function. Development of dnDSA occurs in recipients with greater epitope mismatching.

Summary: Improved long-term outcomes may be anticipated in pediatric kidney transplant recipients by incorporating extended HLA mismatch information and updating the clinical approach to donor kidney matching using available technology to identify clinically relevant immunologic risk.

11. Antibody-mediated rejection in pediatric kidney transplantation: pathophysiology, diagnosis, and management.

Ng YW, Singh M, Sarwal MM.

Drugs. 2015 Apr;75(5):455-72. doi: 10.1007/s40265-015-0369-y. Review.

ABSTRACT

Kidney transplant is the preferred treatment of pediatric end-stage renal disease. One of the most challenging aspects of pediatric kidney transplant is the prevention and treatment of antibody-mediated rejection (ABMR), which is one of the main causes of graft dysfunction and early graft loss. Most challenges are similar to those faced in adult kidney transplants; however, factors unique to the pediatric realm include naivety of the immune system and the small number of studies and randomized controlled trials available when considering pharmacological treatment options. Here, we present a case of ABMR in a pediatric patient and a review of the pathophysiology, diagnosis, and management of ABMR. ABMR in pediatric kidney transplant continues to be a frustrating condition to treat because (1) there still remain many unidentified potential antigens leading to ABMR, (2) children and adults are at different stages of their immune system development, and, thus, (3) the full pathophysiology of alloimmunity is still not completely understood, and (4) the efficacy and safety of treatment in adults may not be directly translated to children. As we continue to gain a better understanding towards the precise alloimmune mechanism that drives a particular ABMR, we can also improve pharmacotherapeutic choices. With continued research, they will become more precise in treating a particular mechanism versus using a broad scope of immunosuppression such as steroids. However, there is much more to be uncovered, such as identifying more non-human leukocyte antigens and their role in alloimmunity, determining the exact mechanism of adults achieving complete operational tolerance, and understanding the difference between pediatric and adult transplant recipients. Making strides towards a better understanding of these mechanisms will lead to continued efficacy and safety in treatment of pediatric ABMR.

12. Challenges in pediatric renal transplantation.

Peruzzi L, Amore A, Coppo R.

World J Transplant. 2014 Dec 24;4(4):222-8. doi: 10.5500/wjt.v4.i4.222. Review.

ABSTRACT

Transplantation in children is the best option to treat renal failure. Over the last 25 years the improvements in therapy have dramatically reduced the risk of early acute rejection and graft loss, however the long term results in terms of graft survival and morbidity still require search for new immunosuppressive regimens. Tolerance of the graft and minimization of side effects are the challenges for improving the outcome of children with a grafted kidney. Notwithstanding the difficulties in settling in children large multicenter trials to derive statistically useful data, many important contributions in the last years brought important modifications in the immunosuppressive therapy, including minimization protocols of steroids and calcineurin inhibitors and new induction drugs. New methods for diagnosis of anti HLA antibodies and some new protocols to improve both chance and outcome of transplantation in immunized subjects represent area of ongoing research of extreme interest for children.

13. 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. doi: 10.1097/TP.0000000000000218.

No abstract available.

14. The causes, significance and consequences of inflammatory fibrosis in kidney transplantation: The Banff i-IFTA lesion.

Nankivell BJ, Shingde M, Keung KL, et al.

Am J Transplant. 2018 Feb;18(2):364-376. doi: 10.1111/ajt.14609. Epub 2018 Jan 3.

ABSTRACT

Inflammation within areas of interstitial fibrosis and tubular atrophy (i-IFTA) is associated with adverse outcomes in kidney transplantation. We evaluated i-IFTA in 429 indication- and 2052 protocol-driven biopsy samples from a longitudinal cohort of 362 kidney-pancreas recipients to determine its prevalence, time course, and relationships with T cell-mediated rejection (TCMR), immunosuppression, and outcome. Sequential histology demonstrated that i-IFTA was preceded by cellular interstitial inflammation and followed by IF/TA. The prevalence and intensity of i-IFTA increased with developing chronic fibrosis and correlated with inflammation, tubulitis, and immunosuppression era ($P < .001$). Tacrolimus era-based immunosuppression was associated with reduced histologic inflammation in unscarred and scarred i-IFTA compartments, ameliorated progression of IF, and increased conversion to inactive IF/TA (compared with cyclosporine era, $P < .001$). Prior acute (including borderline) TCMR and subclinical TCMR were followed by greater 1-year i-IFTA, remaining predictive by multivariate analysis and independent of humoral markers. One-year i-IFTA was associated with accelerated IF/TA, arterial fibrointimal hyperplasia, and chronic glomerulopathy and with reduced renal function ($P < .001$ versus no i-IFTA). In summary, i-IFTA is the histologic consequence of active T cell-mediated alloimmunity, representing the interface between inflammation and tubular injury with fibrotic healing. Uncontrolled i-IFTA is associated with adverse structural and functional outcomes.

15. Antibody-mediated vascular rejection of kidney allograft: characterization of different kidneyallograft rejection phenotypes via histology, C4d deposition and donor-specific antibodies.
Legendre C.
Clin Exp Immunol. 2014 Dec;178 Suppl 1:59-60. doi: 10.1111/cei.12512.

No abstract available

16. The Kinetics of Anti-HLA Antibodies in the First Year after Kidney Transplantation: In Whom and When Should They Be Monitored?

de Castro MCR, Barbosa EA, Souza RP, et al.

J Transplant. 2018 Apr 23;2018:8316860. doi: 10.1155/2018/8316860. eCollection 2018.

ABSTRACT

The impact of the kinetics of the anti-HLA antibodies after KTx on the occurrence of acute rejection as well as the better time-point to monitor anti-HLA Abs after transplantation is not completely defined. This prospective study followed 150 patients over 12 months after transplantation. Serum IgG anti-HLA Abs were detected by single antigen beads after typing donors and recipients for loci A, B, C, DR, and DQ. Before KTx, 89 patients did not present anti-HLA Abs and 2% developed "de novo" Abs during the 1st year, 39 patients were sensitized without DSAs, and 13% developed DSA after surgery; all of them presented ABMR. Sensitized patients presented higher acute rejection rates (36.4% versus 13.5%, $p < 0.001$), although 60% of the patients did not present ABMR. Patients, in whom DSA-MFI decreased during the first two weeks after surgery, did not develop ABMR. Those who sustained their levels presented a rate of 22% of ABMR. 85% of patients developed ABMR when MFIs increased early after transplantation (which occurred in 30% of the DSA positive patients). In the ABMR group, we observed an iDSA-MFI sharp drop on the fourth day and then an increase between the 7th and 14th POD, which suggests DSA should be monitored at this moment in sensitized patients for better ABMR prediction.

17. HLA Epitope Matching in Kidney Transplantation: An Overview for the General Nephrologist.

Sypek M, Kausman J, Holt S, et al.

Am J Kidney Dis. 2018 May;71(5):720-731. doi: 10.1053/j.ajkd.2017.09.021. Epub 2017 Dec 12. Review.

ABSTRACT

Rapid changes in tissue-typing technology, including the widespread availability of highly specific molecular typing methods and solid-phase assays for the detection of allele-specific anti-HLA antibodies, make it increasingly challenging to remain up to date with developments in organ matching. Terms such as epitopes and eplets abound in the transplantation literature, but often it can be difficult to see what they might mean for the patient awaiting transplantation. In this review, we provide the historical context for current practice in tissue typing and explore the potential role of HLA epitopes in kidney transplantation. Despite impressive gains in preventing and managing T-cell-mediated rejection and the associated improvements in graft survival, the challenge of the humoral alloresponse remains largely unmet and is the major cause of late graft loss. Describing HLA antigens as a series of antibody targets, or epitopes, rather than based on broad seroreactivity patterns or precise amino acid sequences may provide a more practical and clinically relevant system to help avoid antibody-mediated rejection, reduce sensitization, and select the most appropriate organs in the setting of pre-existing alloantibodies. We explain the systems proposed to define HLA epitopes, summarize the evidence to date for their role in transplantation, and explore the potential benefits of incorporating HLA epitopes into clinical practice as this field continues to evolve toward everyday practice.

3. IMPACTO EN EL INJERTO (RAH, RCH, PRONÓSTICO, ETC)

18. Acute antibody-mediated rejection in pediatric kidney transplants: A single center experience

Twombley K, Thach L, Ribeiro A, *et al.*

Pediatr Transplantation 2013: 17: E149–E155

ABSTRACT

aAMR is a potentially devastating complication of kidney transplantation. The incidence of aAMR in children, while thought to be rare, is not well defined, and there is a paucity of data on treatment regimens in children. We retrospectively reviewed the outcomes of our pediatric patients that were treated for aAMR between 2007 and 2009. Three adolescent Hispanic males were found to have aAMR. All three received deceased donor transplants, and all three verbalized nonadherence. Treatment consisted of rituximab, solumedrol, PE, and IVIgG in one patient, and PE, IVIgG, and bortezomib in two patients. The only side effect of therapy noted was mild hypotension with rituximab that resolved after decreasing the infusion rate. There were no reported infections two yr after treatment, and all of the viral monitoring in these patients remained negative.

19. A multi-institutional evaluation of antibody-mediated rejection utilizing the Pediatric Heart Transplant Study database: Incidence, therapies and outcomes.

Thrush PT, Pahl E, Naftel DC, et al.

J Heart Lung Transplant. 2016 Dec;35(12):1497-1504. doi: 10.1016/j.healun.2016.06.014. Epub 2016 Jun 24.

ABSTRACT

Background: Current knowledge of antibody-mediated rejection (AMR) after heart transplantation (HT) stems largely from adult data. Using the Pediatric Heart Transplant Study (PHTS) database, we report the incidence of AMR, describe treatment, and evaluate outcomes for treated AMR in children after HT.

Methods: We queried the PHTS database for patients <18 years of age undergoing primary HT between January 2010 and December 2014. An AMR episode was defined as either a biopsy consistent with pathologic AMR or a rejection event based on immunotherapy augmentation directed against antibody production. Biopsy data, treatment strategies and survival were analyzed.

Results: An episode of AMR was identified in 179 of 1,596 (11%) HT recipients and in 246 of 705 (35%) rejection episodes. AMR was diagnosed by biopsy in 182 of 246 episodes and by immunotherapy in 64 of 179 episodes. Mixed rejection was identified in 179. Freedom from AMR was 88% and 82% at 1 and 3 years, respectively. AMR therapies included intravenous immunoglobulin (IVIg) (58%), plasmapheresis (40%), rituximab (40%), bortezomib (11%) and eculizumab (0.4%). The most commonly used combination therapies included IVIg/plasmapheresis/rituximab (13%). Thirty-three patients (16%) died after developing AMR. Patient and graft survival were lower for the AMR+ group. One- and 3-year survival after initial AMR diagnosis was 88% and 77%, respectively.

Conclusions: In his study we report the largest experience of AMR in pediatric HT recipients. AMR was common and often occurred concurrently with acute cellular rejection. There is wide variability in the treatment of AMR. Short-term patient and graft outcomes were worse for those with treated AMR.

20. Acute humoral rejection in pediatric renal transplant recipients receiving steroid minimization immunosuppression.

Butani L, Gallay BJ.

Pediatr Transplant. 2012 May;16(3):269-73. doi: 10.1111/j.1399-3046.2011.01618.x. Epub 2011 Nov 17.

ABSTRACT

SM protocols have increasingly gained acceptance owing to their favorable side effect profile with comparable cellular rejection rates. After encountering SM patients with AHR, we performed a case-control study to identify predictors associated with AHR in this cohort. Patients with (n = 4) and without (n = 19) biopsy proven AHR on a SM regimen were compared using the Student's t-tests. The median age at transplant was 13.8 yr. Compared to controls, the AHR cohort was older (15.9 vs. 12.1 yr, p = 0.01). Children with AHR had a lower mean tacrolimus trough level and were more likely to have a sub-therapeutic trough at six months (3.5 vs. 5.5 ng/mL, p = 0.05); mean MMF doses were lower at all times points except three months in the AHR group (not statistically significant). This occurred in spite of higher MPA trough levels at all study points in the AHR group (significant at 3 [p = 0.019] and 6 [p = 0.03] months). Children receiving a SM regimen have a lower safety net and may benefit from more intensive monitoring of tacrolimus exposure. MMF dose modifications based on MPA trough determinations should be resisted in the setting of SM.

21. Early subclinical rejection as a risk factor for late chronic humoral rejection.

Moreso F, Carrera M, Goma M*, et al*.

Transplantation. 2012 Jan 15;93(1):41-6.

ABSTRACT

Background: Subclinical rejection and interstitial fibrosis and tubular atrophy (IF/TA) in protocol biopsies are associated with outcome. We study the relationship between histologic lesions in early protocol biopsies and histologic diagnoses in late biopsies for cause.

Materials and methods: Renal transplants with a protocol biopsy performed within the first 6 months posttransplant between 1988 and 2006 were reviewed. Biopsies were evaluated according to Banff criteria, and C4d staining was available in biopsies for cause.

Results: Of the 517 renal transplants with a protocol biopsy, 109 had a subsequent biopsy for cause which showed the following histological diagnoses: chronic humoral rejection (CHR) (n=44), IF/TA (n=42), recurrence of the primary disease (n=11), de novo glomerulonephritis (n=7), T-cell-mediated rejection (n=4), and polyoma virus nephropathy (n=1). The proportion of retransplants (15.9% vs. 2.3%, P=0.058) and the prevalence of subclinical rejection were higher in patients with CHR than in patients with IF/TA (52.3% vs. 28.6%, P=0.0253). Demographic donor and recipient characteristics and clinical data at the time of protocol biopsy were not different between groups. Logistic regression analysis showed that subclinical rejection (relative risk, 2.52; 95% confidence interval, 1.1-6.3; P=0.047) but not retransplantation (relative risk, 6.7; 95% confidence interval, 0.8-58.8; P=0.085) was associated with CHR.

Conclusion: Subclinical rejection in early protocol biopsies is associated with late appearance of CHR.

22. Clinical and pathological analyses of chronic vascular rejection after kidney transplantation.
Shimizu T, Toma H, Shibahara R*, et al*.
Nephrology (Carlton). 2015 Jul;20 Suppl 2:20-5.

ABSTRACT
AIM: We discuss the clinicopathological analysis of cases of chronic vascular rejection (CVR) cases after renal transplantation and clarify the mechanisms underlying the development and prognostic significance of CVR.
Patients: CVR was diagnosed in 46 renal allograft biopsy specimens (BS) obtained from 34 renal transplant patients being followed up at the Department of Urology, Tokyo Women's Medical University, between January 2009 and December 2013.
Results: CVR was diagnosed at a median of 47.4 months post-transplant. Among the 36 patients, 23 had a history of acute rejection. Among the 46 BS showing evidence of CVR, the CVR was mild (cv1 in Banff's classification) in 23, moderate (cv2) in 17, and severe (cv3) in 6. Of the 40 samples obtained at the time of the biopsy and assayed with plastic beads coated with HLA antigen, 31 (78%) showed circulating ant-HLA alloantibody, and 15 (38%) showed donor-specific antibodies. We then classified the 46 BS showing evidence of CVR by their overall histopathological features, as follows; cv alone was seen in 16 (35%) BS, cv + antibody-mediated rejection (AMR) in 26 (56%), and cv + T-cell-mediated rejection in 9 (19%). Loss of the renal allograft occurred during the observation period in nine of the patients (26%). Of the remaining patients with functioning grafts, deterioration of the renal allograft function after the biopsies occurred in 11 patients (32%).
Conclusion: The results of our study suggest that AMR may underlie CVR in many cases, while T cell-mediated rejection may play an important role in some cases.

23. The impact of C4d staining as a humoral injury marker.

Kara M, Demir F, Ata P, *et al*.

Transplant Proc. 2012 Jul-Aug;44(6):1694-6.

ABSTRACT

Purpose: Acute and chronic humoral injuries in renal transplant recipients are the main reasons for graft rejection and failure. Histological and clinical characteristics of humoral rejection and symptoms are variable and not always helpful for differential diagnosis. Clinical monitoring of the allograft, an elevated serum panel-reactive antibody (PRA), and the presence of donor-specific antibody (DSA) during immune monitoring as well as C4d staining of biopsy material can establish the differential diagnosis. Even without a cellular component, humoral rejection reaction is serious because the target tissue is the graft endothelium. Because the kidney graft has a rich vascular structure this attack causes permanent injury to the kidney in the long term. Graft dysfunction in this setting is usually more severe, requiring dialysis therapy, compared with acute cellular reactions. Positive C4d staining of peritubular capillaries in biopsy material represent a hallmark of complement-dependent cytotoxicity, supporting the diagnosis of humoral rejection. We analyzed C4d staining as a hallmark of humoral rejection.

Methods: From 2009 to 2011, we analyzed the relationship between pathological findings of C4d immunohistochemistry staining and the clinical outcomes of 45 kidney transplant recipients who underwent a kidney biopsy because of graft dysfunction due to possible humoral rejection.

Results: Biopsy specimens of 15 patients stained C4d positive; the remaining 30 showed negative results. Intravenous steroids, PP + IVIG with or without antithymocyte globulin (ATG), was administered for treatment. Sixty six percent (n = 10) of patients were C4d positive with 16% (n = 5) of those showing C4d-negative biopsy results, losing their grafts, and returning to hemodialysis.

Conclusions: C4d staining refractory humoral rejection injury was related to poor graft outcomes.

4. ESTRATEGIAS TERAPÉUTICAS (FÁRMACOS, ESTRATEGIAS, RESULTADOS, ETC..)

24. Rabbit anti-human thymocyte immunoglobulin for the rescue treatment of chronic antibody-mediated rejection after pediatric kidney transplantation.

Cihan Y, Kanzelmeyer N, Drube J, *et al.*

Pediatr Nephrol (2017) 32:2133–2142

ABSTRACT

Background: Chronic antibody-mediated rejection (cAMR) is the leading cause of late kidney graft loss, but current therapies are often ineffective. Rabbit anti-human thymocyte immunoglobulin (rATG) may be helpful, but its use is virtually undocumented.

Methods: Data were analyzed retrospectively from nine pediatric kidney transplant patients with cAMR were treated with rATG (1.5 mg/kg × 5 days) at our center after non-response to pulsed prednisolone, intravenous immunoglobulin, rituximab, and increased immunosuppressive intensity (including switching to belatacept in some cases), with or without bortezomib.

Results: The median time from diagnosis to cAMR was 179 days. rATG was started 5-741 days after diagnosis. Median estimated glomerular filtration rate (eGFR) increased from 40 mL/min/1.73 m^2 when rATG was started to 62 mL/min/1.73 m^2 9 months later ($p = 0.039$). Four patients showed substantially higher eGFR after 9 months and 2 patients showed a small improvement; eGFR continued to decline in 3 patients after starting rATG. No grafts were lost during follow-up. At last follow-up, donor-specific antibodies (DSAs) were no longer detectable in 4 out of 8 patients for whom data were available, median fluorescence intensity had decreased substantially in 1 out of 8 patients; anti-HLA DQ DSAs persisted in 2 out of 8 patients. No adverse events with a suspected relation to rATG, including allergic reactions, leukocytopenia or infections, were observed in any of the patients.

Conclusions: In this small series of patients, rATG appears a promising treatment for unresponsive cAMR. Further evaluation, including earlier introduction of rATG, is warranted.

25. Combined Posttransplant Prophylactic IVIg/Anti-CD 20/Plasmapheresis in Kidney Recipients With Preformed Donor-Specific Antibodies: A Pilot Study

Loupy A, Suberbielle-Boissel C, Zuber J*, et al.*

Transplantation. 2010 Jun 15;89(11):1403-10

ABSTRACT

Background: This study assesses the immunologic, functional, and histologic course of kidney recipients with preformed donor-specific alloantibodies (DSA) receiving deceased donor kidneys according to two prophylactic strategies that have been sequentially applied posttransplant.

Methods: The first strategy combined posttransplant quadritherapy/intravenous immunoglobulin (group 1, n=36) and the second added to the above protocol anti-CD20/plasmapheresis (group 2, n=18). All patients had a concomitant evaluation of glomerular filtration rate, protocol biopsies, and DSA mean intensity of fluorescence (MFI) at 3 month and 1 year posttransplant.

Results: Peak and day-0 class-I or II DSAmax-MFI were similar in both groups. The rate of acute antibody-mediated rejection (AMR) was similar in both groups (19.6% vs. 16.6%, respectively). At 1 year posttransplant, group 2 was characterized by lower microcirculation inflammation lesions (glomerulitis+capilaritis score of 1.8+/-0.2 vs. 2.7+/-0.2, respectively, P=0.03), a lower rate of transplant glomerulopathy (7% vs. 38%, P=0.02), and a lower rate of chronic AMR (41.3% vs. 13.3%, respectively, P=0.03). The decline in DSA-MFI from day 0 to 1 year was 44%+/-13% in group 1 compared with 80%+/-8% in group 2 (P=0.02). Finally, the 1-year glomerular filtration rate was 43+/-16 vs. 54+/-16 mL/min/1.73 m(2) in groups 1 and 2, respectively (P=0.04).

Conclusion: This study raises the possibility that a more intensive day 0 prophylactic immunosuppressive strategy combining intravenous immunoglobulin/anti-CD20/plasmapheresis in this high-risk population, despite similar rates of early acute clinical humoral rejection, is associated with significant differences in long-term function and chronic AMR rate. Future prospective randomized studies are needed to assess the best strategies to be applied in light of the pretransplant immunologic risk stratification.

26. Eculizumab to treat antibody-mediated rejection in a 7-year-old kidney transplant recipient.

Chehade H, Rotman S, Matter M, et al.

Pediatrics. 2015 Feb;135(2):e551-5. doi: 10.1542/peds.2014-2275.

ABSTRACT

We report on successful early eculizumab administration to treat acute antibody-mediated rejection (ABMR) in a highly sensitized kidney transplant recipient. The recipient is a 7-year-old boy who received, 6 months after a desensitization protocol with monthly intravenous immunoglobulin infusion, a second kidney transplant in the presence of low donor-specific antibodies (DSAs). Both pretransplant lymphocytotoxic and flow cytometric crossmatch were negative. Allograft function recovered promptly, with excellent initial function. On postoperative day (POD) 4, the child developed significant proteinuria with an acute rise in serum creatinine. Allograft biopsy showed severe acute ABMR. Intravenous eculizumab (600 mg), preceded by a single session of plasmapheresis, was administered on POD 5 and 12 along with a 4-day thymoglobulin course. After the first dose of eculizumab, a strikingly rapid normalization of allograft function with a decrease in proteinuria occurred. However, because circulating DSA levels remained elevated, the child received 3 doses of intravenous immunoglobulin (POD 15, 16, and 17), with a significant subsequent decrease in DSA levels. At 9 months after transplant, the child continues to maintain excellent allograft function with undetectable circulating DSA levels. This unique case highlights the potential efficacy of using early eculizumab to rapidly reverse severe ABMR in pediatric transplantation, and therefore it suggests a novel therapeutic approach to treat acute ABMR.

27. Results of early treatment for de novo donor-specific antibodies in pediatric kidney transplant recipients in a cross-sectional and longitudinal cohort.

Charnaya O, Tuchman S, Moudgil A

Pediatr Transplant. 2018 Mar;22(2). doi: 10.1111/petr.13108. Epub 2018 Jan 22.

ABSTRACT

The development of dnDSA anti-HLA antibodies has been shown to be a significant risk factor for graft failure. In 2008, we instituted a routine protocol of standardized monitoring and treatment of dnDSA in pediatric kidney transplant recipients. Of 67 first-time pediatric kidney transplant recipients, 26 (38%) developed dnDSA after 1.36 (IQ 1-2.14) years. Coefficient of variance of tacrolimus, a surrogate marker of non-adherence, was found to be the single most important risk factor for dnDSA development. Overall, there was a significant reduction in dnDSA with treatment in 19 (76%) children. No difference in graft survival and estimated glomerular filtration rate was noted between dnDSA negative and those treated for dnDSA. There was an increased risk of hospitalization in those treated for dnDSA. This study suggests that early detection and treatment of dnDSA can help to prevent graft failure and preserve graft function in the short term. Future studies and longer follow-up are needed to fully elucidate the effect of early detection and treatment of dnDSA in pediatric kidney transplant recipients.

28. Biologics in renal transplantation.

Grenda R.

Pediatr Nephrol. 2015 Jul;30(7):1087-98. doi: 10.1007/s00467-014-2886-4. Epub 2014 Jul 26.

ABSTRACT

The biologics used in transplantation clinical practice include several monoclonal and polyclonal antibodies aimed at specific cellular receptors. The effect of their mechanisms of action includes depleting or blocking specific cell subpopulations, complement system, or removing circulating preformed antibodies and blocking their production. They are used in induction, desensitization ABO-incompatible renal transplantation, rescue therapy of steroid-resistant acute rejection, treatment of posttransplant recurrence of primary disease such as nephrotic syndrome or atypical hemolytic-uremic syndrome, and in late humoral rejection. There are various indications for the use of biologic agents before and early or late after renal transplantation in both high- and low-risk recipients. In the latter situation, the biologics-based induction is used to further minimize immunosuppression maintenance. The targets of several biologic agents are present across a variety of cells, and manipulation of the immune system with biologics may be associated with significant risk of acute and late-onset adverse events; therefore, clinical risk-versus-benefit ratio must be carefully balanced in every case. Several trials on novel biologics are reported in adults but not in the pediatric population.

29. Antibody-mediated rejection and treatment in pediatric patients: one center's experience.
Gulleroglu K, Baskin E, Bayrakci US, et al.
Exp Clin Transplant. 2013 Oct;11(5):404-7.

ABSTRACT
Objectives: Antibody-mediated rejection is a rare complication that often results in the loss of the kidney graft. Treatment options include plasmapheresis, intravenous immunoglobulin, and use of rituximab.
Materials and methods: We retrospectively evaluated the data files from 86 pediatric renal transplant patients over the last 5 years. A biopsy was taken for each rejection episode.
Results: Seven patients (7.7%) developed antibody-mediated rejection. All patients with antibody-mediated rejection had histologic evidence of severe acute humoral rejection and extensive C4d staining in peritubular capillaries. Staining was diffuse (involving > 50% of peritubular capillaries) for 4 biopsies, and it was focal (involving < 50% of peritubular capillaries) for 3 biopsies. Twelve biopsies demonstrated at least 1 histologic feature associated with acute humoral rejection. Donor-specific antibodies were evaluated in recipients. The mean peak panel reactive antibody class 1 was 7.16% (range, 0%-86%). The mean time between rejection episodes and the transplant was 16.9 ± 13.5 months. All patients were treated with high-dose intravenous methylprednisolone and intravenous immunoglobulin. Three patients recovered renal function rapidly after this treatment. Donor-specific antibodies were negative in these patients. Five sessions of plasmapheresis were used simultaneously in these 4 patients. In 3 resistant patients, rituximab was prescribed after plasmapheresis and intravenous immunoglobulin. The presence of donor-specific antibodies was demonstrated in 4 patients. Two patients were refractory to antibody-mediated rejection treatment and lost their transplants. One patient had interstitial fibrosis and tubular atrophy during the 16th month after her antibody-mediated rejection. Graft survival in patients with antibody-mediated rejection at the end of 1 year was 71.4%.
CONCLUSIONS: Early diagnosis and treatment with plasmapheresis, intravenous immunoglobulin, and rituximab may resolve antibody-mediated rejection. Although effective therapy is available for acute antibody-mediated rejection, the allograft remains at risk for chronic antibody-mediated rejection and shortened survival.

30. Complement-binding anti-HLA antibodies are independent predictors of response to treatment in kidney recipients with antibody-mediated rejection.

Viglietti D, Bouatou Y, Kheav VD, et al.

Kidney Int. 2018 May 22. pii: S0085-2538(18)30255-2. doi: 10.1016/j.kint.2018.03.015

ABSTRACT

A major hurdle to improving clinical care in the field of kidney transplantation is the lack of biomarkers of the response to antibody-mediated rejection (ABMR) treatment. To discover these we investigated the value of complement-binding donor-specific anti-HLA antibodies (DSAs) for evaluating the response to treatment. The study encompassed a prospective cohort of 139 kidney recipients with ABMR receiving the standard of care treatment, including plasma exchange, intravenous immunoglobulin and rituximab. Patients were systematically assessed at the time of diagnosis and three months after treatment initiation for clinical and allograft histological characteristics and anti-HLA DSAs, including their C1q-binding ability. After adjusting for clinical and histological parameters, post-treatment C1q-binding anti-HLA DSA was an independent and significant determinant of allograft loss (adjusted hazard ratio 2.57 (95% confidence interval 1.29-5.12). In 101 patients without post-treatment C1q-binding anti-HLA DSA there was a significantly improved glomerular filtration rate with significantly reduced glomerulitis, peritubular capillaritis, interstitial inflammation, tubulitis, C4d deposition, and endarteritis compared with 38 patients with posttreatment C1q-binding anti-HLA DSA. A conditional inference tree model identified five prognostic groups at the time of post-treatment evaluation based on glomerular filtration rate, presence of cg lesion and C1q-binding anti-HLA DSA (cross-validated accuracy: 0.77). Thus, circulating complement-binding anti-HLA DSAs are strong and independent predictors of allograft outcome after standard of care treatment in kidney recipients with ABMR.

31. Efficacy of bortezomib for reducing donor-specific antibodies in children and adolescents on a steroid minimization regimen

Nguyen S, Gallay B, Butani L.

Pediatr Transplantation 2014: 18: 463–468

ABSTRACT

AMR is increasingly being recognized as an important cause of renal allograft injury, contributing to significant morbidity and graft loss. There are few controlled trials and no well-established treatment guidelines for AMR in renal transplant recipients. We retrospectively reviewed the outcome of four pediatric renal transplant recipients on a steroid minimization immunosuppression protocol treated with bortezomib for elevated DSA and acute AMR from 2012 to 2013. All patients received four doses of bortezomib 1.3 mg/m^2 given on days one, four, eight, and 11. All patients also received other treatments prior to bortezomib, which may have included rituximab, methylprednisolone, plasmapheresis, and/or IVIg. While bortezomib in addition to other therapies significantly decreased DSA titers, DSA remained very elevated months after treatment. All four patients had immediate improvement or stabilization of renal function but one eventually lost her graft. There were no adverse events related to bortezomib six months after treatment.

32. C3 glomerulopathy and eculizumab: a report on four paediatric cases.

Lebreton C, Bacchetta J, Dijoud F, *et al*.

Pediatr Nephrol. 2017 Jun;32(6):1023-1028. doi: 10.1007/s00467-017-3619-2. Epub 2017 Feb 24.

ABSTRACT

Background: Eculizumab may be used to treat C3-glomerulopathy (C3G), a rare but severe glomerular disease.

Diagnosis and treatment: Patients 1, 2 and 3 were diagnosed with nephritic syndrome with alternative complement pathway activation (low C3, C3Nef-positive) and C3G at the age of 9, 13 and 12 years, respectively. Treatment with eculizumab normalized proteinuria within 1, 2 and 7 months, respectively. Proteinuria relapsed when eculizumab was withdrawn, but the re-introduction of eculizumab normalized proteinuria. Patient 4 was diagnosed with C3G at 9 years of age, with progression to end-stage renal disease within 2 years, followed by a first renal transplantation (R-Tx) with early disease recurrence and graft loss within 39 months. After a second R-Tx, she rapidly presented with biological and histological recurrence: therapy with eculizumab was started, with no effect on proteinuria after 5 months, in a complex clinical setting (i.e. association of C3G recurrence, humoral rejection and BK nephritis). Eculizumab was withdrawn due to multiple viral reactivations, but the re-introduction of the drug a few months later enabled a moderate decrease in proteinuria.

Conclusion: These cases illustrate the efficacy of eculizumab, at least on native kidneys, in paediatric C3G. However, larger international studies are warranted to confirm the benefit and safety of eculizumab therapy.

5. ESTRATEGIAS DE PREVENCIÓN (ADHERENCIA, PAUTAS DE IS EN MANTENIMIENTO, TRATAMIENTOS DE DESENSIBILIZACIÓN, ETC…)

33. Lymphocyte-depleting induction therapy lowers the risk of acute rejection in African American pediatric kidney transplant recipients.

Crowson CN, Reed RD, Shelton BA, *et al*.

Pediatr Transplant. 2017 Feb;21(1). doi: 10.1111/petr.12823. Epub 2016 Oct 3.

ABSTRACT

The use of lymphocyte-depleting induction immunosuppression has been associated with a reduction in risk of AR after KT among adult recipients, particularly among high-risk subgroups such as AAs. However, data on induction regimen and AR risk are lacking among pediatric KT recipients. We examined outcomes among 7884 first-time pediatric KT recipients using SRTR data (2000-2014). Characteristics were compared across race using Wilcoxon rank-sum tests for continuous and chi-square tests for categorical variables. Risk of AR was estimated using modified Poisson regression, stratified by recipient race, adjusting for recipient age, gender, BMI, primary diagnosis, number of HLA mismatches, maintenance immunosuppression, and donor type. Risk of AR within 1 year was lower in AA recipients receiving lymphocyte-depleting induction (ATG or alemtuzumab; RR, 0.66; 95% CI, 0.52-0.83 P < .001) compared to AA recipients receiving anti-IL-2 receptor antibody induction. This difference was not seen in non-AA recipients receiving lymphocyte-depleting induction (RR, 0.93; 95% CI, 0.81-1.06, P = .26) compared to IL-2 induction. These findings support a role for lymphocyte-depleting induction agents in AA pediatric patients undergoing KT and continued use of IL-2 inhibitor induction in non-AA pediatric KT recipients.

34. Desensitization protocol enabling pediatric crossmatch-positive renal transplantation: successful HLA-antibody-incompatible renal transplantation of two highly sensitized children.

Adamusiak AM, Stojanovic J, Shaw O, *et al.*

Pediatr Nephrol. 2017 Feb;32(2):359-364. doi: 10.1007/s00467-016-3489-z. Epub 2016 Sep 1.

ABSTRACT

Background: Renal transplantation improves quality of life (QoL) and survival in children requiring renal replacement therapy (RRT). Sensitization with development of a broad-spectrum of anti-HLA antibodies as a result of previous transplantation or after receiving blood products is an increasing problem. There are no published reports of desensitization protocols in children allowing renal transplantation from HLA-antibody-incompatible living donors.

Methods: We adopted our well-established adult desensitization protocol for this purpose and undertook HLA antibody-incompatible living donor renal transplants in two children: a 14-year-old girl and a 13-year-old boy.

Results: After 2 and 1.5 years of follow-up, respectively, both patients have stable renal allograft function despite a rise in donor-specific antibodies in one case.

Conclusions: HLA-incompatible transplantation should be considered in selected cases for sensitized children.

35. Safety and Efficacy of Alemtuzumab Induction in Highly Sensitized Pediatric Renal Transplant Recipients.

Kim IK, Choi J, Vo AA, *et al*.

Transplantation. 2017 Apr;101(4):883-889. doi: 10.1097/TP.0000000000001416

ABSTRACT

Background: Studies show that alemtuzumab, a potent lymphocyte-depleting agent, is well tolerated in pediatric renal transplantation. We report on the use of alemtuzumab induction in highly HLA sensitized (HS) pediatric kidney transplant patients.

Methods: Fifty pediatric renal transplants were performed from 1/2009-12/2014. 15 HS patients received IVIG (2 g/kg ×2 doses)/rituximab (375 mg/m ×1) for desensitization with alemtuzumab induction (15-30 mg, 1 dose, subcutaneous), whereas 35 nonsensitized patients received anti-IL-2R. Graft survival and infections were compared between 2 groups.

Results: All HS patients had received a prior transplant and were older with lower risk for viral infections due to serostatus. Patient survival was 100%, and graft outcomes were similar with mean 1-year creatinine of 1.03 ± 0.45 versus 0.99 ± 0.6 (P = 0.48). Although a higher incidence of acute cellular rejection was seen in HS patients receiving alemtuzumab (P = 0.001), there was a nonsignificant difference in antibody-mediated rejection. White blood cell and absolute lymphocyte count were significantly lower in alemtuzumab group at 30 days (P < 0.0001) and at 1 year (P = 0.026 and P = 0.001), respectively. There was no significant difference in bacterial, viral, or fungal infections after transplant.

Conclusions: Alemtuzumab induction with desensitization led to nearly equivalent graft survival and functional outcomes in HS pediatric patients as nonsensitized patients receiving anti-IL-2R induction. With this small sample size, we observed significant reduction of white blood cell and absolute lymphocyte count up to 1 year posttransplant. The risk of infection was comparable between the 2 groups; however, patients who received alemtuzumab were older and at lower risk of viral infection due to serostatus.

36. IVIG and rituximab for treatment of chronic antibody-mediated rejection: a prospective study in paediatric renal transplantation with a 2-year follow-up

Billing H, Rieger S, Süsal C *et al.*

Transpl Int. 2012 Nov;25(11):1165-73.

SUMMARY

Chronic antibody-mediated rejection (AMR) is the major cause of late renal allograft loss. There is, however, no established treatment for this condition. We report the results of a prospective pilot study on an antihumoral therapy (AHT) consisting of high-dose intravenous immunoglobulin G (IVIG) and rituximab in 20 paediatric renal transplant recipients. Donor-specific HLA antibodies (HLA DSA) were quantified by Luminex-based bead array technology. Loss of eGFR decreased significantly from 7.6 ml/min/1.73 m^2 during 6 months prior to AHT to 2.1 ml/min/1.73 m^2 (P = 0.0013) during 6 months after AHT. Fourteen patients (70%) responded: nine of nine patients (100%) without and five of 11 (45%) with transplant glomerulopathy (P = 0.014). C4d positivity in PTC decreased from 40 ± 18.5% in the index biopsy to 11.6 ± 12.2% (P = 0.002) in the follow-up biopsy. In four of nine biopsies (44%) C4d staining turned negative. During 2 years of follow-up, the median loss of eGFR in each of the four 6-month periods remained significantly lower compared with prior to AHT. Class I DSA declined in response to AHT by 61% (p = 0.044), class II DSA by 63% (p = 0.033) 12 months after intervention. AHT with IVIG and rituximab significantly reduces or stabilizes the progressive loss of transplant function in paediatric patients with chronic AMR over an observation period of 2 years, apparently by lowering circulating DSA and reducing intrarenal complement activation.

37. Three-yr safety and efficacy of everolimus and low-dose cyclosporine in de novo pediatric kidneytransplant patients.

Ferraresso M, Belingheri M, Ginevri F, et al.

Pediatr Transplant. 2014 Jun;18(4):350-6. doi: 10.1111/petr.12261.

ABSTRACT

The three yr results of a multicenter trial in de novo pediatric KT treated with a proliferative signal inhibitor and low dose CNI are presented. Thirty-seven children (9.1 ± 5 yr old) received basiliximab, cyclosporine A (CyA C2:1400 ng/mL), (MMF C0:1.5-3 μg/mL), and prednisone. Three wk later everolimus was started (C0:5-10 ng/mL), CyA was reduced (C2:600 ng/mL after 90 days 300 ng/mL), and MMF discontinued. During the three-yr period patient and graft survivals were 96%. One patient died for causes unrelated to the immunosuppression. Cumulative acute rejection rate including protocol and indication biopsies was 21.9%. None of the patients had signs of chronic humoral rejection. Incidence of dnDSA was 5%, 11%, and 22% at one, two, and three yr post-transplant, respectively. Mean glomerular filtration rate measured at one yr and three yr post-transplant was 105.5 ± 31 and 110.7 ± 27 mL/min/1.73 m(2), respectively. A growth velocity of 7.7 ± 6.7 cm/yr was achieved with positive catch-up growth. No malignancy or post-transplant lymphoproliferative diseases were diagnosed. In conclusion, the treatment based on basiliximab induction, everolimus, low-dose cyclosporine, and low-dose prednisone leads to good long-term efficacy in de novo pediatric KT recipients.

38. Rapid Reduction in Donor-Specific Anti-Human Leukocyte Antigen Antibodies and Reversal of Antibody-Mediated Rejection With Bortezomib in Pediatric Heart Transplant Patients

Morrow WR, Frazier EA, Mahle WT *et al.*

Transplantation. 2012 Feb 15;93(3):319-24

ABSTRACT

Background: High titer donor-specific antibodies (DSA) and positive crossmatch in cardiac transplant recipients is associated with increased mortality from antibody-mediated rejection (AMR). Although treatment to reduce antihuman leukocyte antigen antibodies using plasmapheresis, intravenous immunoglobulin, and rituximab has been reported to be beneficial, in practice these are often ineffective. Moreover, these interventions do not affect the mature antibody producing plasma cell. Bortezomib, a proteasome inhibitor active against plasma cells, has been shown to reduce DSA in renal transplant patients with AMR. We report here the first use of bortezomib for cardiac transplant recipients in four pediatric heart recipients with biopsyproven AMR, hemodynamic compromise, positive crossmatch, and high titer class I DSA.

Methods: Patients received four intravenous dose of bortezomib (1.3 mg/m^2) over 2 weeks with plasmapheresis and rituximab. DSA specificity and strength (mean fluorescence intensity) was determined with Luminex. All had received previous treatment with plasmapheresis, intravenous immunoglobulin, and rituximab that was ineffective.

Results: AMR resolved in all patients treated with bortezomib with improvement in systolic function, conversion of biopsy to C4d negative in three patients and IgG negative in one patient, and a prompt, precipitous reduction in DSAs. In three patients who received plasmapheresis before bortezomib, plasmapheresis failed to reduce DSA. In one case, DSA increased after bortezomib but decreased after retreatment.

Conclusions: Bortezomib reduces DSA and may be an important adjunct to treatment of AMR in cardiac transplant recipients. Bortezomib may also be useful in desensitization protocols and in prevention of AMR in sensitized patients with positive crossmatch and elevated DSA.

39. Renal transplantation in sensitized children and young adults: a nationwide approach.

Dello Strologo L, Murer L, Guzzo I, et al.

Nephrol Dial Transplant. 2017 Jan 1;32(1):191-195. doi: 10.1093/ndt/gfw369.

ABSTRACT

Background: High levels of preformed anti-HLA antibodies dramatically diminish renal transplant outcomes. Most desensitization programmes guarantee good intermediate outcomes but quite disappointing long-term prognosis. The search for a fully compatible kidney increases time on the waiting list.

Methods: In February 2011, a nationwide hyperimmune programme (NHP) was begun in Italy: all available kidneys are primarily proposed to highly sensitized patients with a panel reactive antibody above 80%. In this manuscript, we evaluate the outcome of paediatric patients transplanted with this approach.

Results: Twenty-one patients were transplanted. Complete data are available for 20 patients. Mean age at transplantation was 14.5 years [standard deviation (SD) ± 5.5)]. Mean time on the waiting list was 29.3 months (SD ± 27.5). Median follow-up was 29.2 months (range: 11.2-59.3). The average number of HLA mismatches in these patients was 2.3 versus 3.7 in 48 standard patients transplanted in the same period ($P < 0.001$). Only one graft was lost. Two cases of humoral rejection occurred and were successfully treated. No cellular rejection was reported. Median creatinine clearance was 84, 88, 77 and 77 mL/min/1.73 m 2 respectively 1, 6, 12 and 24 months after transplant.

Conclusions: Transplantation of sensitized patients avoiding prohibited antigens is feasible, at least in a selected cohort of patients. In order to be able to further improve this approach, which in our opinion is very successful, it would be necessary to expand the donor pool, possibly increasing the number of countries participating in the programme. In this series, time on the waiting list did not increase significantly. This allocation policy should ideally lead to an outcome comparable to that expected in standard patients, which is particularly desirable in young patients who have the longest life expectancy. Since long-term results of desensitization programmes are not (yet) convincing, we suggest that these programmes should be reserved for selected cases where compatible organs cannot be found within a reasonable time span.

40. Maintaining calcineurin inhibition after the diagnosis of post-transplant lymphoproliferative disorder improves renal graft survival.

Serre JE, Michonneau D, Bachy E, et al.

Kidney Int. 2014 Jan;85(1):182-90. doi: 10.1038/ki.2013.253. Epub 2013 Jun 26.

ABSTRACT

Post-transplant lymphoproliferative disorder (PTLD) is an uncontrolled proliferation of transformed lymphocytes fostered by immunosuppression. In addition to chemotherapy, treatment of PTLD includes a reduction of maintenance immunosuppression. Patients with PTLD have an increased risk of graft loss, suggesting that reduced immunosuppression strategy needs to be optimized with regard to graft outcome. Here we retrospectively reviewed 101 cases involving PTLD to identify the risks associated with graft loss. During a median follow-up of 70 months, 39 patients died and 21 lost their graft. Multivariate analysis found that an eGFR under 30 ml/min per 1.73 m(2) at PTLD diagnosis, a biopsy-proven acute rejection episode following reduction of immunosuppression, and the absence of calcineurin inhibition in maintenance immunosuppression are independent risk factors for allograft loss. Neither the type of PTLD nor the chemotherapy regimen was predictive of allograft failure. Histological analysis of graft biopsies showed that maintaining calcineurin inhibition after the diagnosis of PTLD reduced the risk of developing de novo anti-HLA antibodies and humoral rejection. Remarkably, calcineurin inhibitor maintenance was neither associated with higher mortality nor with worse progression-free survival. Thus, maintaining calcineurin inhibition at a reduced dose after the diagnosis of PTLD seems safe and may improve renal graft outcome, possibly through better control of the recipient's humoral immune response.