1. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN').

Solez K, Colvin RB, Racusen LC, *et al.*

Am J Transplant. 2007 Mar;7(3):518-26.

ABSTRACT

The 8th Banff Conference on Allograft Pathology was held in Edmonton, Canada, 15-21 July 2005. Major outcomes included the elimination of the non-specific term "chronic allograft nephropathy" (CAN) from the Banff classification for kidney allograft pathology, and the recognition of the entity of chronic antibody-mediated rejection. Participation of B cells in allograft rejection and genomics markers of rejection were also major subjects addressed by the conference.

2. Rates and determinants of progression to graft failure in kidney allograft recipients with de novo donor-specific antibody.

Wiebe C, Gibson IW, Blydt-Hansen TD, *et al.*

Am J Transplant 2015; 15: 2921–2930.

ABSTRACT

Understanding rates and determinants of clinical pathologic progression for recipients with de novo donor-specific antibody (dnDSA), especially subclinical dnDSA, may identify surrogate endpoints and inform clinical trial design. A consecutive cohort of 508 renal transplant recipients (n = 64 with dnDSA) was studied. Recipients (n = 388) without dnDSA or dysfunction had an eGFR decline of -0.65 mL/min/1.73 m(2) /year. In recipients with dnDSA, the rate eGFR decline was significantly increased prior to dnDSA onset (-2.89 vs. -0.65 mL/min/1.73 m(2) /year, $p < 0.0001$) and accelerated post-dnDSA (-3.63 vs. -2.89 mL/min/1.73 m(2) /year, $p < 0.0001$), suggesting that dnDSA is both a marker and contributor to ongoing alloimmunity. Time to 50% post-dnDSA graft loss was longer in recipients with subclinical versus a clinical dnDSA phenotype (8.3 vs. 3.3 years, $p < 0.0001$). Analysis of 1091 allograft biopsies found that dnDSA and time independently predicted chronic glomerulopathy (cg), but not interstitial fibrosis and tubular atrophy (IFTA). Early T cell-mediated rejection, nonadherence, and time were multivariate predictors of IFTA. Independent risk factors for post-dnDSA graft survival available prior to, or at the time of, dnDSA detection were delayed graft function, nonadherence, dnDSA mean fluorescence intensity sum score, tubulitis, and cg. Ultimately, dnDSA is part of a continuum of mixed alloimmune-mediated injury, which requires solutions targeting T and B cells.

3. Complement-binding anti-HLA antibodies and kidney-allograft survival.

Loupy A, Lefaucheur C, Vernerey D, *et al.*

N Engl J Med 2013; 369: 1215–1226. – role of complement binding dsa and tg

ABSTRACT

Background: Anti-HLA antibodies hamper successful transplantation, and activation of the complement cascade is involved in antibody-mediated rejection. We investigated whether the complement-binding capacity of anti-HLA antibodies plays a role in kidney-allograft failure.

Methods: We enrolled patients who received kidney allografts at two transplantation centers in Paris between January 1, 2005, and January 1, 2011, in a population-based study. Patients were screened for the presence of circulating donor-specific anti-HLA antibodies and their complement-binding capacity. Graft injury phenotype and the time to kidney-allograft loss were assessed.

Results: The primary analysis included 1016 patients. Patients with complement-binding donor-specific anti-HLA antibodies after transplantation had the lowest 5-year rate of graft survival (54%), as compared with patients with non-complement-binding donor-specific anti-HLA antibodies (93%) and patients without donor-specific anti-HLA antibodies (94%) ($P<0.001$ for both comparisons). The presence of complement-binding donor-specific anti-HLA antibodies after transplantation was associated with a risk of graft loss that was more than quadrupled (hazard ratio, 4.78; 95% confidence interval [CI], 2.69 to 8.49) when adjusted for clinical, functional, histologic, and immunologic factors. These antibodies were also associated with an increased rate of antibody-mediated rejection, a more severe graft injury phenotype with more extensive microvascular inflammation, and increased deposition of complement fraction C4d within graft capillaries. Adding complement-binding donor-specific anti-HLA antibodies to a traditional risk model improved the stratification of patients at risk for graft failure (continuous net reclassification improvement, 0.75; 95% CI, 0.54 to 0.97).

Conclusions: Assessment of the complement-binding capacity of donor-specific anti-HLA antibodies appears to be useful in identifying patients at high risk for kidney-allograft loss.

4. Banff meeting report writing committee. BANFF 2013 Banff 2013 meeting report: inclusion of c4d-negative antibody-mediated rejection and antibody-associated arterial lesions.

Haas M, Sis B, Racusen LC, Solez K, Glotz D, et al.

Am J Transplant. 2014 Feb;14(2):272-83.

ABSTRACT

The 12th Banff Conference on Allograft Pathology was held in Comandatuba, Brazil, from August 19–23, 2013, and was preceded by a 2-day Latin American Symposium on Transplant Immunobiology and Immunopathology. The meeting was highlighted by the presentation of the findings of several working groups formed at the 2009 and 2011 Banff meetings to: (1) establish consensus criteria for diagnosing antibodymediated rejection(ABMR) in the presence and absence of detectable C4d deposition; (2) develop consensus definitions and thresholds for glomerulitis (g score) and chronic glomerulopathy (cg score), associated with improved inter-observer agreement and correlation with clinical, molecular and serological data; (3) determine whether isolated lesions of intimal arteritis (''isolated v'') represent acute rejection similar to intimal arteritis in the presence of tubulointerstitial inflammation; (4) compare different methodologies for evaluating interstitial fibrosis and for performing/ evaluating implantation biopsies of renal allografts with regard to reproducibility and prediction of subsequent graft function; and (5) define clinically and prognostically significant morphologic criteria for subclassifying polyoma virus nephropathy. The key outcome of the 2013 conference is defining criteria for diagnosis of C4d-negative ABMR and respective modification of the Banff classification. In addition, three new Banff Working Groups were initiated.

5. The Revised (2013) Banff Classification for Antibody-Mediated Rejection of Renal Allografts: Update, Difficulties, and Future Considerations.

Haas, M.

Am J Transplant. 2016 May;16(5):1352-7.

ABSTRACT

The Banff 2013 classification (Banff 2013) for anti-body-mediated rejection (ABMR) in renal allografts represents the first major revision of the original Banff classification for ABMR that was published in 2003. The main impetus for this revision was the need to include C4d-negative ABMR, although this revised classification contains a number of additional features based on findings reported from 2007 to 2013. Since its publication, several studies have examined the validity of different aspects of Banff 2013 and compared it to earlier (2003, 2007) versions of the Banff ABMR classification. Recent evidence, albeit limited, indicates that Banff 2013 represents an improvement over the previous versions, enhancing our ability to accurately diagnose cases of acute/ active and chronic active ABMR on renal allograft biopsy. Molecular studies appear to justify the threshold value of glomerulitis plus peritubular capillaritis score ≥2 required by Banff 2013 for the diagnosis of C4d-negative ABMR; however, other aspects of the classification, including its overall interobserver reproducibility, the clinical significance of the category of C4d staining without evidence of rejection, and whether surrogate markers might potentially substitute for the requirement for the presence of donor-specific antibodies, require additional investigation.

6. AJKD Atlas of Renal Pathology: Chronic Antibody-Mediated Rejection.
Najafian B, Fogo AB, Lusco MA, et al.
Am J Kidney Dis. 2015 Nov;66(5):e41-2. doi: 10.1053/j.ajkd.2015.08.008.

No abstract available.

7. Impact of the Banff 2013 classification on the diagnosis of suspicious versus conclusive late antibody-mediated rejection in allografts without acute dysfunction.

Gimeno J, Redondo D, Pérez-Sáez MJ*, et al.*

Nephrol Dial Transplant. 2016 Nov;31(11):1938-1946.

ABSTRACT

Background: The Banff classification is used worldwide to characterize pathological findings in renal allograft biopsies. During the 11th Banff meeting, relevant changes were introduced in the diagnostic criteria for Category 2 antibodymediated rejection (ABMR). Here, we assess the effect of these changes on the diagnosis of late chronic ABMR.

Methods: Seventy-three indication renal graft biopsies (chronic dysfunction, proteinuria and/or the presence of *de novo* donorspecific antibodies) from 68 kidney transplant recipients initially classified following the Banff 2009 criteria were reviewed and reclassified as per the new Banff 2013 criteria.

Results: The diagnostic category changed in 18% of the study biopsies with Banff 2013. The reclassification mainly involved Category 2 cases, from which 23.5% of the biopsies from older patients with worse graft function were overlooked by Banff 2009. ABMR was ruled out in 13% of cases under the Banff 2009 criteria. A significant number of the study samples were conclusively diagnosed as ABMR (40% as per Banff 2009 and 74% as per Banff 2013; P = 0.006), because of the inclusion of microvascular inflammation and the acceptance of some ultrastructural diagnostic criteria. However, when following the criteria of the new classification, samples with histological signs of chronic ABMR, in which human leucocyte antigen donor-specific antibodies are not detected or ultrastructural studies are not performed, may be inadequately characterized.

8. Clinical Significance of HLA-DQ Antibodies in the Development of Chronic Antibody-Mediated Rejection and Allograft Failure in Kidney Transplant Recipients

Lee H, Min JW, Kim JI*, et al.*

Hum Immunol. 2016 Apr;77(4):346-52

ABSTRACT

With the development of the single antigen beads assay, the role of donor specific alloantibody (DSA) against human leukocyte antigens in kidney transplantation (KT) has been highlighted. This study aimed to investigate the clinical significance of DQ-DSA detected at renal allograft biopsy. We evaluated 263 KT recipients who underwent allograft biopsy and DSA detection at the same time. Among them, 155 patients who were nonsensitized before transplantation were selected to investigate the role of de-novo DQ-DSA. Both the total and nonsensitized subgroup was categorized into 4 groups each according to DSA results as: DQ only, DQ+non-DQ, non-DQ, and no DSA. In the total patient group, post-KT DSA was positive in 79 (30.0%) patients and DQ-DSA was most prevalent (64.6%). In the nonsensitized subgroup, de-novo DSAs were detected in 45 (29.0%) patients and DQ-DSA was also most prevalent (73.3%). The DQ only group showed a significantly longer post-KT duration compared to the other groups ($P<0.05$). The overall incidence of antibody-mediated rejection (AMR) was 17.9%. B-DSA, DR-DSA, and DQ-DSA were associated with AMR ($P<0.05$), but in the analysis for chronic AMR, only DQ-DSA showed significance in both the total and the nonsensitized subgroup ($P<0.05$). On comparison of Banff scores among groups, those representing humoral immunity were significantly dominant in all DSA positive groups compared to the no DSA group ($P<0.05$), and higher scores of markers representing chronic tissue injury were more frequently detected in the groups with DQ-DSA. The worst postbiopsy survival was seen in the DQ+non-DQ group of the total patient group, and patients with de-novo DQ-DSA showed poorer graft survival in the nonsensitized subgroup compared to the no DSA group ($P<0.05$). In the multivariate analysis, de-novo DQ-DSA was the only significant risk factor associated with late allograft failure ($P<0.05$). Our study is the first to demonstrate the association of DQ-DSA with detailed histological findings representing chronic AMR. These findings suggest that the detection of DQ-DSA in nonsensitized patients is significantly associated with the development of chronic AMR and late allograft failure. Therefore monitoring of DQ-DSA not only in sensitized patients, but also nonsensitized patients may be necessary to improve long-term allograft outcomes.

9. 2013 Banff Criteria for Chronic Active Antibody-Mediated Rejection: Assessment in a Real-Life Setting.

De Serres SA, Noël R, Côté I, *et al.*

Am J Transplant. 2016 May;16(5):1516-25.

ABSTRACT

Significant changes in the criteria for chronic active antibody-mediated rejection (CAABMR) were made in the Banff 2013 classification. These modifications expanded the number of patients diagnosed with CAABMR, with undetermined clinical significance. We compared the 2007 and 2013 criteria for the composite end point of death-censored graft failure or doubling of serum creatinine in 123 patients meeting the criterion related to the morphologic evidence of chronic tissue injury. In all, 18% and 36% of the patients met the 2007 and 2013 criteria, respectively. For the criterion related to antibody interaction with endothelium, only 25% were positive based on the 2007 definition compared with 82% using the 2013 definition. Cox modeling revealed that a 2013 but not a 2007 diagnosis was associated with the composite end point (adjusted hazard ratio 2.5 [95% confidence interval (CI) 1.2-5.2] vs. 1.6 [95% CI 0.7-3.8], respectively). The 2013 criterion based on both the C4d score and the glomerulitis plus peritubular capillaritis score (g+ptc) was more strongly associated with the end point than the 2007 criterion based only on C4d; however, when dissected by component, only the C4d component was significant. The association with clinical outcomes improved with the 2013 criteria. This is related to the new C4d threshold but not to the g+ptc ≥2 component.

10. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology.

Loupy A, Haas M, Solez K, *et al.*

Am J Transplant. 2017 Jan;17(1):28-41.

ABSTRACT

The XIII Banff meeting, held in conjunction the Canadian Society of Transplantation in Vancouver, Canada, reviewed the clinical impact of updates of C4d-negative antibody-mediated rejection (ABMR) from the 2013 meeting, reports from active Banff Working Groups, the relationships of donor-specific antibody tests (anti-HLA and non-HLA) with transplant histopathology, and questions of molecular transplant diagnostics. The use of transcriptome gene sets, their resultant diagnostic classifiers, or common key genes to supplement the diagnosis and classification of rejection requires further consensus agreement and validation in biopsies. Newly introduced concepts include the i-IFTA score, comprising inflammation within areas of fibrosis and atrophy and acceptance of transplant arteriolopathy within the descriptions of chronic active T cell-mediated rejection (TCMR) or chronic ABMR. The pattern of mixed TCMR and ABMR was increasingly recognized. This report also includes improved definitions of TCMR and ABMR in pancreas transplants with specification of vascular lesions and prospects for defining a vascularized composite allograft rejection classification. The goal of the Banff process is ongoing integration of advances in histologic, serologic, and molecular diagnostic techniques to produce a consensus-based reporting system that offers precise composite scores, accurate routine diagnostics, and applicability to next-generation clinical trials.

11. 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, Roufosse C, Glotz D, Seron D, et al.

Am J Transplant. 2018 Feb;18(2):293-307.

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 12. 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.

12. Evolving criteria for the diagnosis of antibody-mediated rejection in renal allografts.

Haas M.

Curr Opin Nephrol Hypertens. 2018 May;27(3):137-143.

ABSTRACT

Purpose of review: To review changes in the Banff schema for antibody-mediated renal allograft rejection over the past decade, including key revisions agreed upon during and immediately subsequent to the 2017 Banff Conference on Allograft Pathology.

Recent findings: The original Banff schema for diagnosis of acute and chronic active antibody-mediated rejection (ABMR) in renal allografts was formulated at the 2001 and 2007 Banff Conferences, and required histologic (primarily microvascular inflammation and transplant glomerulopathy), immunohistologic (C4d in peritubular capillaries), and serologic [circulating donor-specific antibodies (DSA)] evidence for a definitive diagnosis of ABMR. This schema was updated at the 2013 Banff Conference, recognizing C4d-negative ABMR, intimal arteritis as a potential manifestation of ABMR, and revising definitions and thresholds for glomerulitis and transplant glomerulopathy to improve interobserver agreement and correlation with clinical, molecular, and serologic data. Compared with the 2007 criteria, Banff 2013 improved the sensitivity of the classification for diagnosing ABMR and the correlation of ABMR diagnosis with graft outcomes. At the 2017 Banff Conference, new modifications to the classification were discussed and have subsequently been agreed upon, accepting C4d and thoroughly validated molecular classifiers as surrogate markers for DSA.

Summary: From a consensus reached at the 2017 Banff Conference, updated criteria for diagnosis of active and chronic active ABMR have been developed that recognize C4d and molecular classifiers as surrogate markers for DSA. In addition, specific recommendations for the use of molecular diagnostics in the diagnosis of ABMR were developed.

13. Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy.

Baid-Agrawal S, Farris AB 3rd, *et al.*

Kidney Int 2011; 80 (8): 879-85

ABSTRACT

Transplant glomerulopathy (TG) has received much attention in recent years as a symptom of chronic humoral rejection; however, many cases lack C4d deposition and/or circulating donor-specific antibodies (DSAs). To determine the contribution of other causes, we studied 209 consecutive renal allograft indication biopsies for chronic allograft dysfunction, of which 25 met the pathological criteria of TG. Three partially overlapping etiologies accounted for 21 (84%) cases: C4d-positive (48%), hepatitis C-positive (36%), and thrombotic microangiopathy (TMA)-positive (32%) TG. The majority of patients with confirmed TMA were also hepatitis C positive, and the majority of hepatitis C-positive patients had TMA. DSAs were significantly associated with C4d-positive but not with hepatitis C-positive TG. The prevalence of hepatitis C was significantly higher in the TG group than in 29 control patients. Within the TG cohort, those who were hepatitis C-positive developed allograft failure significantly earlier than hepatitis C-negative patients. Thus, TG is not a specific diagnosis but a pattern of pathological injury involving three major overlapping pathways. It is important to distinguish these mechanisms, as they may have different prognostic and therapeutic implications.

14. Antibodies reactive to non-HLA antigens in transplant glomerulopathy.

Dinavahi R, George A, Tretin A, *et al.*

J Am Soc Nephrol 2011; 22 (6): 1168-78.

ABSTRACT

Although T and B cell alloimmunity contribute to transplant injury, autoimmunity directed at kidney-expressed, non-HLA antigens may also participate. Because the specificity, prevalence, and importance of antibodies to non-HLA antigens in late allograft injury are poorly characterized, we used a protein microarray to compare antibody repertoires in pre- and post-transplant sera from several cohorts of patients with and without transplant glomerulopathy. Transplantation routinely induced changes in antibody repertoires, but we did not identify any de novo non-HLA antibodies common to patients with transplant glomerulopathy. The screening studies identified three reactivities present before transplantation that persisted after transplant and strongly associated with transplant glomerulopathy. ELISA confirmed that reactivity against peroxisomal-trans-2-enoyl-coA-reductase strongly associated with the development of transplant glomerulopathy in independent validation sets. In addition to providing insight into effects of transplantation on non-HLA antibody repertoires, these results suggest that pretransplant serum antibodies to peroxisomal-trans-2-enoyl-coA-reductase may predict prognosis in kidney transplantation.

15. Comparing transplant glomerulopathy in the absence of C4d deposition and donor-specific antibodies to chronic antibody-mediated rejection.

Torres IB, Salcedo M, Moreso F, *et al.*

Clin Transplant. 2014; 28 (10): 1148-54.

ABSTRACT

Introduction: Transplant glomerulopathy (TG) is the characteristic lesion of chronic antibody-mediated rejection (AMR). However, in some patients presents with no circulating HLA antibodies or C4d positivity.

AIM: Patients with TG accomplishing criteria for chronic AMR were compared to patients with isolated TG.

Patients and methods: We reviewed late (>6 months) graft biopsies performed between 2007 and 2010 (n = 75). Biopsies with C4d-negative TG and no circulating donor-specific antibody were called isolated TG (n = 12), and chronic AMR was defined according to Banff consensus (n = 17). HLA antibodies were evaluated by Luminex technology. Immunohistochemistry was performed to quantify graft infiltrating cells.

Results: Patients with isolated TG were older (52 ± 14 vs. 35 ± 14; p = 0.0048), received grafts from older donors (54 ± 16 vs. 41 ± 18; p = 0.0554), and displayed a lower inflammation in the glomerular (g-score: 0.5 ± 0.5 vs. 1.0 ± 0.9; p = 0.0865; CD3 positive cells/glomeruli: 1.5 ± 2.9 vs. 4.4 ± 4.1; p = 0.0147), interstitial (i-score: 1.2 ± 0.9 vs. 1.9 ± 1.0; p = 0.0685; CD45 positive cells/hpf: 18 ± 11 vs. 57 ± 68; p = 0.0132), and peritubular capillary (ptc-score 0.2 ± 0.6 vs. 1.1 ± 0.9; p = 0.0089; CD45 positive cells/hpf: 3.7 ± 3.1 vs. 10.1 ± 7.4; p = 0.0290) compartments. Fifteen grafts were lost and graft survival was significantly lower in patients with chronic AMR (p = 0.0122).

Conclusion: Isolated TG is associated with less severe allograft inflammation and with a better outcome than chronic AMR.

16. Chronic-active antibody-mediated rejection with or without donor-specific antibodies has similar histomorphology and clinical outcome - a retrospective study.

Sablik KA, Clahsen-van Groningen MC, Looman CWN, *et al.*

Transpl Int. 2018 Mar 23. doi: 10.1111/tri.13154

ABSTRACT

Chronic-active antibody-mediated rejection (c-aABMR) is defined as histological evidence of chronic endothelial injury (cg), also known as transplant glomerulopathy, and either microvascular inflammation (MVI) or positivity for C4d. Importantly, the presence of donor-specific antibodies (DSA) is currently still mandatory for the diagnosis of c-aABMR. This retrospective study of 41 c-aABMR patients investigates whether cases suspicious for c-aABMR (DSA negative, n = 24) differ from cases of c-aABMR (DSA positive, n = 17) with respect to renal histology, allograft function and long-term graft survival. All included patients had progressive loss of allograft function and were diagnosed by for cause biopsy and scored according to the Banff '15 criteria. In all DSApos cases, DSA were de novo and the majority was directed against HLA-II being mostly anti-HLA-DQ antibodies. There were no statistically significant differences in clinical characteristics, decline in allograft function and renal allograft survival in cases with or without DSAs. All cases showed chronic histomorphological damage and inflammation, irrespective of the presence of DSA. Renal histology and clinical outcome of patients suspicious for c-aABMR (DSAneg) do not significantly differ from patients with a diagnosis of c-aABMR (DSApos). We believe that our study adds to the ongoing debate regarding the need for DSAs to be present for the diagnosis of c-aABMR.

17. Donor-specific antibodies, C4d and their relationship with the prognosis of transplant glomerulopathy.

Lesage J, No.l R, Lapointe I, *et al.*

Transplantation 2015; 99 (1): 69- 76.

ABSTRACT

Background: Transplant glomerulopathy (TG) is a diagnostic criterion for chronic active antibody-mediated rejection (CAABMR), with C4d, donor-specific antibodies (DSA) and other lesions of chronic tissue injury. However, TG often presents without C4d or DSA. Until recently, such cases were termed suspicious for CAABMR, and their prognosis remains unclear.

Methods: To better understand the contribution of TG, C4d, and DSA on outcomes, we retrospectively studied 61 patients with late TG for the composite endpoint of death-censored graft failure or doubling of serum creatinine. Cases were matched to controls based on age, year and number of transplant, type of donor, and the availability of an indication biopsy during the same time after transplantation. Analyses were performed using proportional hazards models.

Results: Compared to matched controls, patients with TG had a more than fivefold increased risk of reaching the endpoint (adjusted hazard ratio (aHR), 5.3; 95% confidence interval (95% CI), 1.5-18.4). The proportion of patients with isolated TG, TG suspicious for CAABMR (C4+/DSA- or C4d-/DSA+) and TG with definite CAABMR (C4d+/DSA+) were 63%, 20%, and 17%, respectively. Suspicious and definite CAABMR showed a similar prognosis, significantly worse than isolated TG (aHR, 4.5; 95% CI, 1.1-18.9 and aHR, 5.9, 95% CI, 1.1-31.3 respectively).

Conclusion: Transplant glomerulopathy is associated with poor prognosis, independent of the level of graft dysfunction and other chronic histologic changes. This prognosis is similar whether there is evidence of tissue or peripheral alloantibody reactivity. These findings are relevant to the development of clinically meaningful criteria for CAABMR, for its clinical management, and in the future selection of population for clinical trials.

18. Identifying Subphenotypes of Antibody-Mediated Rejection in Kidney Transplants.

Halloran PF, Merino Lopez M, Barreto Pereira A.

Am J Transplant. 2016 Mar;16(3):908-20.

ABSTRACT

The key lesions in antibody-mediated kidney transplant rejection (ABMR) are microcirculation inflammation (peritubular capillaritis and/or glomerulitis lesions, abbreviated "pg") and glomerular double contours (cg lesions). We used these features to explore subphenotypes in 164 indication biopsies with ABMR-related diagnoses: 137 ABMR (109 pure and 28 mixed with T cell-mediated rejection [TCMR]) and 27 transplant glomerulopathy (TG), identified from prospective multicenter studies. The lesions indicated three ABMR subphenotypes: pgABMR, cgABMR, and pgcgABMR. Principal component analysis confirmed these subphenotypes and showed that TG can be reclassified as pgcgABMR (n = 17) or cgABMR (n = 10). ABMR-related biopsies included 45 pgABMR, 90 pgcgABMR, and 25 cgABMR, with four unclassifiable. Dominating all time intervals was the subphenotype pgcgABMR. The pgABMR subphenotype presented earliest (median <2 years), frequently mixed with TCMR, and was most associated with nonadherence. The cgABMR subphenotype presented late (median 9 years). Subphenotypes differed in their molecular changes, with pgABMR having the most histologic-molecular discrepancies (i.e. potential errors). Donor-specific antibody (DSA) was not identified in 29% of pgcgABMR and 46% of cgABMR, but failure rates and molecular findings were similar to cases where DSA was known to be positive. Thus, ABMR presents distinct subphenotypes, early pg-dominant, late cg-dominant, and combined pgcg phenotype, differing in time, molecular features, accompanying TCMR, HLA antibody, and probability of nonadherence.

19. Diagnosis and management of antibody-mediated rejection: current status and novel approaches.

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

Am J Transplant 2014; 14 (2): 255-71.

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.

20. Summary of 2017 FDA Public Workshop: Antibody-mediated Rejection in Kidney Transplantation.

Velidedeoglu E, Cavaillé-Coll MW, Bala S, *et al.*

Transplantation. 2018 Jun;102(6):e257-e264.

ABSTRACT

Despite major advances in understanding the pathophysiology of antibody-mediated rejection (AMR); prevention, diagnosis and treatment remain unmet medical needs. It appears that early T cell-mediated rejection, de novo donor-specific antibody (dnDSA) formation and AMR result from patient or physician initiated suboptimal immunosuppression, and represent landmarks in an ongoing process rather than separate events. On April 12 and 13, 2017, the Food and Drug Administration sponsored a public workshop on AMR in kidney transplantation to discuss new advances, importance of immunosuppressive medication nonadherence in dnDSA formation, associations between AMR, cellular rejection, changes in glomerular filtration rate, and challenges of clinical trial design for the prevention and treatment of AMR. Key messages from the workshop are included in this summary. Distinction between type 1 (due to preexisting DSA) and type 2 (due to dnDSA) phenotypes of AMR needs to be considered in patient management and clinical trial design. Standardization and more widespread adoption of routine posttransplant DSA monitoring may permit timely diagnosis and understanding of the natural course of type 2 and chronic AMR. Clinical trial design, especially as related to type 2 and chronic AMR, has specific challenges, including the high prevalence of nonadherence in the population at risk, indolent nature of the process until the appearance of graft dysfunction, and the absence of accepted surrogate endpoints. Other challenges include sample size and study duration, which could be mitigated by enrichment strategies.

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

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

Transpl Int. 2017 Apr;30(4):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.

22. Clinical and molecular significance of microvascular inflammation in transplant kidney biopsies.

Gupta A, O'Broin P, Bao Y, et al.

Kidney Int. 2016;89:217-225.

ABSTRACT

The diagnostic criteria for antibody-mediated rejection (AMR) are continuously evolving. Here we investigated the clinical and molecular significance of different Banff microvascular inflammation (MVI) scores in transplant kidney biopsies. A total of 356 patients with clinically indicated kidney transplant biopsies were classified into three groups based on MVI scores of 0, 1, 2, or more for Groups 1-3, respectively. Gene expression profiles were assessed using arrays on a representative subset of 93 patients. The incidence of donor-specific anti-HLA antibodies was increased from 25% in Group 1 to 36% in Group 2 and to 54% in Group 3. Acute and chronic AMR were significantly more frequent in Group 3 (15% and 35%) compared with the Group 2 (3% and 15%) and Group 1 (0% and 5%), respectively. Gene expression profiles showed increased interferon-γ and rejection-induced, cytotoxic and regulatory T-cell, natural killer cell-associated and donor-specific antibody (DSA)-selective transcripts in Group 3 compared with Groups 1 and 2. There was no significant difference in gene expression profiles between the Groups 1 and 2. Increased intragraft expression of DSA-selective transcripts was found in the biopsies of C4d- Group 3 patients. Thus, an MVI score of 2 or more was significantly associated with a histological diagnosis of acute and chronic antibody-mediated rejection. Hence, increased intragraft DSA-selective gene transcripts may be used as molecular markers for AMR, especially in C4d- biopsies.

23. 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.*

Am J Transplant. 2017 Mar;17(3):682-691. doi: 10.1111/ajt.14001. Epub 2016 Sep 16.

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 end point 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.

24. Positive crossmatch kidney transplant recipients treated with eculizumab: outcomes beyond 1 year.

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

Am J Transplant. 2015 May;15(5):1293-302.

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 12 months (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.

25. Assessment of Tocilizumab (Anti-Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients.

Choi J, Aubert O, Vo A, *et al.*

Am J Transplant. 2017 Sep;17(9):2381-2389.

ABSTRACT

Extending the functional integrity of renal allografts is the primary goal of transplant medicine. The development of donor-specific antibodies (DSAs) posttransplantation leads to chronic active antibody-mediated rejection (cAMR) and transplant glomerulopathy (TG), resulting in the majority of graft losses that occur in the United States. This reduces the quality and length of life for patients and increases cost. There are no approved treatments for cAMR. Evidence suggests the proinflammatory cytokine interleukin 6 (IL-6) may play an important role in DSA generation and cAMR. We identified 36 renal transplant patients with cAMR plus DSAs and TG who failed standard of care treatment with IVIg plus rituximab with or without plasma exchange. Patients were offered rescue therapy with the anti-IL-6 receptor monoclonal tocilizumab with monthly infusions and monitored for DSAs and long-term outcomes. Tocilizumab-treated patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years, respectively. Significant reductions in DSAs and stabilization of renal function were seen at 2 years. No significant adverse events or severe adverse events were seen. Tocilizumab provides good long-term outcomes for patients with cAMR and TG, especially compared with historical published treatments. Inhibition of the IL-6-IL-6 receptor pathway may represent a novel approach to stabilize allograft function and extend patient lives.

26. Interleukin-6, A Cytokine Critical to Mediation of Inflammation, Autoimmunity and Allograft Rejection: Therapeutic Implications of IL-6 Receptor Blockade.

Jordan SC, Choi J, Kim I*, et al.*

Transplantation. 2017 Jan;101(1):32-44. (REVIEW)

ABSTRACT

The success of kidney transplants is limited by the lack of robust improvements in long-term survival. It is now recognized that alloimmune responses are responsible for the majority of allograft failures. Development of novel therapies to decrease allosensitization is critical. The lack of new drug development in kidney transplantation necessitated repurposing drugs initially developed in oncology and autoimmunity. Among these is tocilizumab (anti-IL-6 receptor [IL-6R]) which holds promise for modulating multiple immune pathways responsible for allograft injury and loss. Interleukin-6 is a cytokine critical to proinflammatory and immune regulatory cascades. Emerging data have identified important roles for IL-6 in innate immune responses and adaptive immunity. Excessive IL-6 production is associated with activation of T-helper 17 cell and inhibition of regulatory T cell with attendant inflammation. Plasmablast production of IL-6 is critical for initiation of T follicular helper cells and production of high-affinity IgG. Tocilizumab is the first-in-class drug developed to treat diseases mediated by IL-6. Data are emerging from animal and human studies indicating a critical role for IL-6 in mediation of cell-mediated rejection, antibody-mediated rejection, and chronic allograft vasculopathy. This suggests that anti-IL-6/IL-6R blockade could be effective in modifying T- and B-cell responses to allografts. Initial data from our group suggest anti-IL-6R therapy is of value in desensitization and prevention and treatment of antibody-mediated rejection. In addition, human trials have shown benefits in treatment of graft versus host disease in matched or mismatched stem cell transplants. Here, we explore the biology of IL-6/IL-6R interactions and the evidence for an important role of IL-6 in mediating allograft rejection.

27. Bortezomib for the treatment of chronic antibody-mediated kidney allograft rejection: a case report.

Schwaiger E, Regele H, Wahrmann M, *et al.*

Clin Transpl 2010:391–396.

ABSTRACT

We report on a patient with chronic C4d-positive antibody-mediated rejection, who was subjected to treatment with bortezomib. Despite initial treatment with CD20 antibody rituximab and intravenous immunoglobulin, the patient presented with a steady increase in serum creatinine and de novo proteinuria. In an effort to directly target alloantibody-producing plasma cells and to prevent ongoing antibody-mediated graft injury, we applied treatment with a single cycle of bortezomib combined with dexamethasone. Treatment was associated with a > 50% decrease in DSA levels and disappearance of capillary C4d staining as detected in a follow-up biopsy. However, there were still profound glomerulitis, an unchanged degree of transplant glomerulopathy and a persistent discrete infiltration of the interstitium by CD138+ plasma cells. The clinical course was unfavorable: despite some decrease in urinary protein excretion, a further deterioration of kidney allograft function was noted. In summary, this case suggests distinct antihumoral efficacy of bortezomib also in the context of chronic AMR. Nevertheless, a major observation was that treatment failed to prevent deterioration of graft function. We speculate that, despite modulation of (complement-activating) DSA, advanced irreversible tissue injury in this late stage of rejection may have precluded a relevant clinical response. Together with other case studies, our results may provide a valuable basis for prospective trials designed to evaluate the efficacy of bortezomib in the prevention and treatment of earlier stages of chronic AMR, e.g. based on the results of early (protocol) biopsies and/or early post-transplant antibody monitoring.

28. Reduction in proteinuria with bortezomib based therapy for antibody mediated rejection.
Lubetzky M, Auli MJ, Walker J, *et al.*
Clin Transpl 2010:437–440.

No abstract available

29. Treatment of antibody-mediated rejection of kidney grafts with bortezomib and/or rituximab compared to standard regimen: experience of Slovene National Center.

Oblak T, Lindič J, Gubenšek J, *et al.*

Clin Nephrol. 2017 Supplement 1;88(13):91-96.

ABSTRACT

Background: The aim of our study was to determine outcomes of standard treatment of antibody-mediated rejection (ABMR) of kidney grafts as compared to the addition of bortezomib or rituximab.

Methods: The cohort of this retrospective study included patients treated for ABMR of kidney grafts at our national center in the period of 2005 - 2017, divided into two groups: standard (ST) group treated standardly with plasmapheresis or immunoadsorption, intravenous immunoglobulins, and corticosteroids, and BR group treated with the addition of bortezomib and/or rituximab. Patient and graft survival at 2 years was analyzed by Kaplan-Meier method, and predictors of graft survival were analyzed by Cox regression.

Results: There were 78 patients with ABMR (48 in the ST group, 30 in the BR group), 41 (53%) were men, mean age 49.5 ± 13.8 years. In ST and BR, respectively, mean serum creatinine was 267 ± 164 and 208 ± 112 µmol/L (p = 0.088), donor-specific antibodies (DSA)<bold> </bold>were positive in 75% and 97% (p = 0.022), and ABMR was acute in 50% and 33% (p = 0.149). Patient survival at 2 years was 89% in the ST and 100% in the BR group (p = 0.125). Cumulative proportion of kidney graft survival at 1 and 2 years was 67% and 53% in the ST group and 73% and 48% in the BR group, respectively, (p = 0.641). Chronic ABMR (HR 5.22, p = 0.004) was significant, while dialysis dependency at biopsy (HR 3.28, p = 0.072), serum creatinine at kidney biopsy (HR 1.003, p = 0.082), and presence of DQ-DSA (HR 3.37, p = 0.062) were borderline significant predictors of worse graft outcome. Infections were relatively common in both groups, with a trend towards more rehospitalizations due to infections in the first 6 months after treatment in the BR group (p = 0.066). In 5 patients (17%), treatment with bortezomib was discontinued prematurely due to cytopenia.

Conclusions: Bortezomib or rituximab, added to standard treatment, did not significantly improve kidney graft survival and was also not associated with significant side effects, except cytopenia in some cases. Treatment of acute ABMR resulted in better graft survival than chronic ABMR.

30. A Randomized Trial of Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection.

Eskandary F, Regele H, Baumann L, *et al.*

J Am Soc Nephrol. 2018 Feb;29(2):591-605.

ABSTRACT

Late antibody-mediated rejection (ABMR) is a leading cause of kidney allograft failure. Uncontrolled studies have suggested efficacy of the proteasome inhibitor bortezomib, but no systematic trial has been undertaken to support its use in ABMR. In this randomized, placebo-controlled trial (the Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection [BORTEJECT] Trial), we investigated whether two cycles of bortezomib (each cycle: 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11) prevent GFR decline by halting the progression of late donor-specific antibody (DSA)-positive ABMR. Forty-four DSA-positive kidney transplant recipients with characteristic ABMR morphology (median time after transplant, 5.0 years; pretransplant DSA documented in 19 recipients), who were identified on cross-sectional screening of 741 patients, were randomly assigned to receive bortezomib (n=21) or placebo (n=23). The 0.5-ml/min per 1.73 m^2 per year (95% confidence interval, -4.8 to 5.8) difference detected between bortezomib and placebo in eGFR slope (primary end point) was not significant (P=0.86). We detected no significant differences between bortezomib- and placebo-treated groups in median measured GFR at 24 months (33 versus 42 ml/min per 1.73 m^2; P=0.31), 2-year graft survival (81% versus 96%; P=0.12), urinary protein concentration, DSA levels, or morphologic or molecular rejection phenotypes in 24-month follow-up biopsy specimens. Bortezomib, however, associated with gastrointestinal and hematologic toxicity. In conclusion, our trial failed to show that bortezomib prevents GFR loss, improves histologic or molecular disease features, or reduces DSA, despite significant toxicity. Our results reinforce the need for systematic trials to dissect the efficiency and safety of new treatments for late ABMR.

31. Bortezomib in late antibody-mediated kidney transplant rejection (BORTEJECT Study): study protocol for a randomized controlled trial.

Eskandary F, Bond G, Schwaiger E, *et al.*

Trials. 2014 Apr 3;15:107.

ABSTRACT

Background: Despite major advances in transplant medicine, improvements in long-term kidney allograft survival have not been commensurate with those observed shortly after transplantation. The formation of donor-specific antibodies (DSA) and ongoing antibody-mediated rejection (AMR) processes may critically contribute to late graft loss. However, appropriate treatment for late AMR has not yet been defined. There is accumulating evidence that the proteasome inhibitor bortezomib may substantially affect the function and integrity of alloantibody-secreting plasma cells. The impact of this agent on the course of late AMR has not so far been systematically investigated.

Methods/design: The BORTEJECT Study is a randomized controlled trial designed to clarify the impact of intravenous bortezomib on the course of late AMR. In this single-center study (nephrological outpatient service, Medical University Vienna) we plan an initial cross-sectional DSA screening of 1,000 kidney transplant recipients (functioning graft at ≥180 days; estimated glomerular filtration rate (eGFR) >20 ml/minute/1.73 m2). DSA-positive recipients will be subjected to kidney allograft biopsy to detect morphological features consistent with AMR. Forty-four patients with biopsy-proven AMR will then be included in a double-blind placebo-controlled intervention trial (1:1 randomization stratified for eGFR and the presence of T-cell-mediated rejection). Patients in the active group will receive two cycles of bortezomib (4 × 1.3 mg/m2 over 2 weeks; 3-month interval between cycles). The primary end point will be the course of eGFR over 24 months (intention-to-treat analysis). The sample size was calculated according to the assumption of a 5 ml/minute/1.73 m2 difference in eGFR slope (per year) between the two groups (alpha: 0.05; power: 0.8). Secondary endpoints will be DSA levels, protein excretion, measured glomerular filtration rate, transplant and patient survival, and the development of acute and chronic morphological lesions in 24-month protocol biopsies.

Discussion: The impact of anti-humoral treatment on the course of late AMR has not yet been systematically investigated. Based on the hypothesis that proteasome inhibition improves the outcome of DSA-positive late AMR, we suggest that our trial has the potential to provide solid evidence towards the treatment of this type of rejection.

32. Differential effect of bortezomib on HLA class I and class II antibody.

Philogene MC, Sikorski P, Montgomery RA, *et al.*

Transplantation. 2014 Sep 27;98(6):660-5.

ABSTRACT

Background: Bortezomib has been used to reduce HLA antibody in patients either before transplantation or as treatment for antibody-mediated rejection (AMR). Reports on its efficacy show mixed results. The mechanism of action of this agent is via proteasome inhibition. The primary route of synthesis of HLA class I molecules is dependent on peptide generation by the proteasome, whereas that of class II is not. We observed a differential effect of bortezomib on class I versus class II antibody and hypothesized that this was related to a reduced expression of class I HLA antigens.

Methods: The effect of bortezomib on HLA antibody levels was evaluated in 13 patients who were desensitized for incompatible renal transplantation. We calculated the percent difference in HLA antibody level before and after bortezomib treatment and the impact of bortezomib on HLA expression in lymphocytes of healthy control subjects.

Results: On average, the level of HLA class I donor-specific antibody (DSA) decreased by 32%, whereas that of class II DSA increased by 29%. In vitro bortezomib treatment of lymphocytes resulted in a mean decrease of 23% in MHC class I expression on B lymphocytes and no change (+1.08%) in MHC class II expression (P=0.0003). The amount of intracellular class I molecules was reduced by a mean of 29% with bortezomib.

Conclusion: These data indicate that bortezomib reduces HLA class I antibody more effectively than class II antibody. This difference may be due to the reduced expression of class I molecules resulting from treatment with this proteasome inhibitor.

33. Late antibody-mediated rejection in renal allografts: outcome after conventional and novel therapies.

Gupta G, Abu Jawdeh BG, Racusen LC, *et al.*

Transplantation. 2014 Jun 27;97(12):1240-6.

ABSTRACT

Background: Although several strategies for treating early antibody-mediated rejection (AMR) in kidney transplants have been investigated, evidence on treatment of late AMR manifesting after 6 months is sparse. In this single-center series, we present data on 23 consecutive patients treated for late AMR.

Methods: Late AMR was diagnosed using Banff 2007 criteria along with presence of donor-specific antibodies (DSA) and acute rise in serum creatinine (SCr). Response to therapy was assessed by improvement in SCr, histologic improvement, and decline in DSA strength.

Results: Overall, 17% (4/23) had documented nonadherence while 69% (16/23) had physician-recommended reduction in immunosuppression before AMR. Eighteen patients (78%) were treated with plasmapheresis or low-dose IVIg+rituximab; 11 (49%) with refractory AMR also received one to three cycles of bortezomib. While there was an improvement (P=0.02) in mean SCr (2.4 mg/dL) at the end of therapy compared with SCr at the time of diagnosis (2.9 mg/dL), this improvement was not sustained at most recent follow-up. Eleven (48%) patients had no histologic resolution on follow-up biopsy. Lack of histologic response was associated with older patients (odds ratio [OR]=3.17; P=0.04), presence of cytotoxic DSA at time of diagnosis (OR=200; P=0.04), and severe chronic vasculopathy (cv≥2) on index biopsy (OR=50; P=0.06).

Conclusions: A major setting in which late AMR occurred in our cohort was reduction or change in immunosuppression. Our data demonstrate an inadequate response of late AMR to current and novel (bortezomib) therapies. The benefits of therapy need to be counterweighed with potential adverse effects especially in older patients, large antibody loads, and chronic allograft vasculopathy.

34. Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial.

Moreso F, Crespo M, Ruiz JC, Torres A, Gutierrez-Dalmau A, Osuna A, Perelló M, Pascual J, Torres IB, Redondo-Pachón D, Rodrigo E, Lopez-Hoyos M, Seron D.

Am J Transplant. 2018 Apr;18(4):927-935.

ABSTRACT

There are no approved treatments for chronic antibody mediated rejection (ABMR). We conducted a multicenter, prospective, randomized, placebo-controlled, double-blind clinical trial to evaluate efficacy and safety of intravenous immunoglobulins (IVIG) combined with rituximab (RTX) (EudraCT 2010-023746-67). Patients with transplant glomerulopathy and anti-HLA donor-specific antibodies (DSA) were eligible. Patients with estimated glomerular filtration rate (eGFR) <20 mL/min per 1.73m^2 and/or severe interstitial fibrosis/tubular atrophy were excluded. Patients were randomized to receive IVIG (4 doses of 0.5 g/kg) and RTX (375 mg/m^2) or a wrapped isovolumetric saline infusion. Primary efficacy variable was the decline of eGFR at one year. Secondary efficacy variables included evolution of proteinuria, renal lesions, and DSA at 1 year. The planned sample size was 25 patients per group. During 2012-2015, 25 patients were randomized (13 to the treatment and 12 to the placebo group). The planned patient enrollment was not achieved because of budgetary constraints and slow patient recruitment. There were no differences between the treatment and placebo groups in eGFR decline (-4.2 ± 14.4 vs. -6.6 ± 12.0 mL/min per 1.73 m^2 , P-value = .475), increase of proteinuria (+0.9 ± 2.1 vs. +0.9 ± 2.1 g/day, P-value = .378), Banff scores at one year and MFI of the immunodominant DSA. Safety was similar between groups. These data suggest that the combination of IVIG and RTX is not useful in patients displaying transplant glomerulopathy and DSA.

35. A systematic review of the use of rituximab for the treatment of antibody-mediated renal transplant rejection (REVIEW).

Macklin PS, Morris PJ, Knight SR.

Transplant Rev (Orlando). 2017 Apr;31(2):87-95.

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.

36. Current outcomes of chronic active antibody mediated rejection—a large single center retrospective review using the updated BANFF 2013 criteria.

Redfield RR, Ellis TM, Zhong W, *et al.*

Hum Immunol 2016;77:346–52.

ABSTRACT

Background: The updated BANFF 2013 criteria has enabled a more standardized and complete serologic and histopathologic diagnosis of chronic active antibody mediated rejection (cAMR). Little data exists on the outcomes of cAMR since the initiation of this updated criteria.

Methods: 123 consecutive patients with biopsy proven cAMR (BANFF 2013) between 2006 and 2012 were identified.

Results: Patients identified with cAMR were followed for a median of 9.5 (2.7-20.3) years after transplant and 4.3 (0-8.8) years after cAMR. Ninety-four (76%) recipients lost their grafts with a median survival of 1.9 years after diagnosis with cAMR. Mean C4d and allograft glomerulopathy scores were 2.6 ± 0.7 and 2.2 ± 0.8, respectively. 53.2% had class II DSA, 32.2% had both class I and II, and 14.5% had class I DSA only. Chronicity score >8 (HR 2.9, 95% CI 1-8.4, p=0.05), DSA >2500 MFI (HR 2.8, 95% CI 1.1-6.8, p=0.03), Scr >3mg/dL (HR 3.2, 95% CI 1.6-6.3, p=0.001) and UPC >1g/g (HR 2.5, 95% CI 1.4-4.5, p=0.003) were associated with a higher risk of graft loss.

Conclusions: cAMR was associated with poor graft survival after diagnosis. Improved therapies and earlier detection strategies are likely needed to improve outcomes of cAMR in kidney transplant recipients.

37. Clinical outcome in patients with chronic antibody mediated-rejection treated with and without rituximab and intravenous immunoglobulin combination therapy.

Chung BH, KimY, Jeong HS, *et al.*

Transpl Immunol 2014;31:140–4.

ABSTRACT

We previously reported that rituximab (RTX) and intravenous immunoglobulin (IVIg) combination therapy (RIT) is effective in treating patients with chronic active antibody-mediated rejection (CAMR), and the proteinuria level can determine the response to RIT. However, the results were not compared to those of patients who did not receive RIT. Fifty-nine patients with CAMR were divided into 2 groups: an RIT treated group (n = 25) and a historic control (HC) group who had not received RIT (n = 29). The RIT group was treated with RTX (375 mg/m(2)) and IVIg (0.4 g/kg) for 4 days. We compared the decline in glomerular filtration rate/month (ΔeGFR), RIT-related complications, and allograft survival rate in both groups. We also compared the allograft survival rate between patients with high proteinuria (spot urine protein/creatinine [PC] ratio > 3.5 g/g) and low proteinuria (PC ratio < 3.5 g/g). ΔeGFR was significantly decreased in the RIT group compared with the HC group after 6 months ($P < 0.05$). No serious complications were associated with RIT, and only one case of herpes zoster infection developed. The overall allograft survival rate in the RIT group was significantly higher than in the HC group. In both groups, patients with low proteinuria survived better than patients with heavy proteinuria ($P < 0.05$). The allograft survival rate was greater in the high proteinuria RIT group than that in the HC group. RIT treatment is recommended for delaying the progression of CAMR without serious complications, and is not limited by the presence of heavy proteinuria.

38. Intravenous immunoglobulins and rituximab therapy for severe transplant glomerulopathy in chronic antibody-mediated rejection: a pilot study.

Bachelet T, Nodimar C, Taupin J-L, *et al.*

Clin Transplant 2015;29:439–46.

ABSTRACT

Outcome of patients with transplant glomerulopathy (TG) is poor. Using B-cell targeting molecules represent a rational strategy to treat TG during chronic antibody-mediated rejection. In this pilot study, 21 patients with this diagnosis received four doses of intravenous immunoglobulins and two doses of rituximab (IVIG/RTX group). They were retrospectively compared with a untreated control group of 10 patients. At 24 months post-biopsy, graft survival was similar and poor between the treated and the untreated group, 47% vs. 40%, respectively, p = 0.69. This absence of response of IVIG/RTX treatment was observed, regardless the phenotype of TG. Baseline estimated glomerular filtration rate (eGFR) and decline in eGFR during the first six months after the treatment were risk factors associated with 24-month graft survival. The IVIG/RTX therapy had a modest effect on the kinetics of donor-specific alloantibodies at M24, compared to the untreated group, not associated with an improvement in graft survival. The mean number of adverse events per patient was higher in the IVIG/RTX group than in the control group (p = 0.03). Taken together, IVIG/RTX treatment for severe TG during chronic antibody-mediated rejection does not seem to change the natural history of TG and is associated with a high incidence of adverse events.

39. Partial therapeutic response to rituximab for the treatment of chronic alloantibody mediated rejection of kidney allografts.

Smith RN, Malik F, Goes N, *et al.*

Transpl Immunol 2012;27:107–13.

ABSTRACT

Background and objectives: Chronic rejection leads to kidney allograft failure and develops in many kidney transplant recipients. One cause of chronic rejection, chronic antibody mediated rejection (CAMR), is attributed to alloantibodies. Maintenance immunosuppression including prednisone, mycophenolate mofetil (MMF) and calcineurin inhibitors may limit alloantibody production in some patients, but many maintain or develop alloantibody production, leading to CAMR. Therefore, no efficacious therapy to treat CAMR is presently available to prevent the progression of CAMR to kidney allograft failure.

Design, setting, participants, and measurements: We performed a retrospective review of 31 subjects with CAMR, of which 14 received Rituximab and 17 subjects did not. Response to Rituximab was defined as decline or stabilization of serum creatinine for at least one year. Data reviewed included demographic, clinical, allograft, post-transplant, and pathological variables. Pathological variables in the diagnostic allograft biopsy were scored according to Banff criteria.

Results: The median survival time (MST) for allografts in the control group was 439 days, and for the Rituximab treated group was 685 days. The Rituximab group was dichotomous with 8 subjects showing a medial survival time of 1180 days, and 6 subjects having a median survival time of 431 days. The MST for the responders was statistically significant from the non-responders and controls. No pathological parameter distinguished any subset of subjects.

Conclusions: These data show that Rituximab followed by standard maintenance immunosuppression shows a therapeutic effect in the treatment of CAMR, which is confined to a subset of treated subjects, not identifiable a priori.

40. Rituximab and Intravenous Immunoglobulin Treatment of Chronic Antibody-Mediated Kidney Allograft Rejection.

Fehr T, Rusi B, Fischer A*, et al.*

Transplantation. 2009 Jun 27;87(12):1837-41

ABSTRACT

Kidney transplant rejections are classified into T-cell-mediated and antibody-mediated rejections (AMR). C4d staining on allograft biopsies and solid-phase assays to measure donor-specific alloantibodies have helped to precisely define the latter. Although for acute AMRs, therapy mainly relies on plasmapheresis or immunoadsorption, no studies for treatment of chronic AMR are available. Here, we report on four kidney allograft recipients suffering from chronic AMR 1 to 27 years posttransplant, who were treated with a combination of rituximab and intravenous immunoglobulin (IVIG). Rituximab/IVIG improved kidney allograft function in all four patients, whereas donor-specific antibodies were reduced in 2 of 4 patients. However, in one patient an acute rejection episode occurred 12 months after this treatment, and another patient had severe, possibly rituximab-associated lung toxicity. Thus, rituximab/IVIG may be a useful strategy for the treatment of chronic AMR, but further randomized multicenter studies are necessary to establish its efficacy and safety profile.

41. Histopathologic features of transplant glomerulopathy associated with response to therapy with intravenous immune globulin and rituximab.

Kahwaji J, Najjar R, Kancherla D, *et al.*

Clin Transplant. 2014;28: 546–553.

ABSTRACT

Transplant glomerulopathy (TG) is associated with poor long-term allograft survival and is often accompanied by microcirculation inflammation. Histopathologic scoring may inform prognosis and help guide therapy. We retrospectively assessed 33 patients with biopsy-proven TG. All biopsies were given a glomerulitis (g) and peritubular capillaritis (ptc) score. We determined allograft survival and serum creatinine stability in three different score groups: g < 2 and ≥ 2, ptc < 2 and ≥ 2, and (g + ptc) < 4 and ≥ 4. We assessed the impact of treatment with intravenous immune globulin (IVIG) and rituximab on outcomes. Graft survival and serum creatinine stability did not differ in each of the histopathologic score groups. Higher-score groups were associated with the presence of concomitant antibody-mediated rejection and were more likely to receive IVIG and rituximab. Treatment with IVIG and rituximab resulted in stability of serum creatinine within the higher-score groups, but not in the lower-score groups. Stabilization of serum creatinine was associated with an improvement in donor-specific antibody. Histopathologic scoring in kidney allograft biopsies with TG may help guide treatment. The combination of IVIG and rituximab appears to be beneficial in patients whose biopsies have moderate or severe microvascular injury.

42. Successful treatment of chronic antibody-mediated rejection with IVIG and rituximab in pediatric renal transplant recipients.

Billing H, Rieger S, Ovens J, *et al.*

Transplantation 2008, 86:1214–1221.

ABSTRACT

Background: Chronic antibody-mediated rejection (CAMR) of renal allografts has recently been recognized as a defined nosologic entity. The outcome of CAMR is poor; there is no established treatment protocol for this condition. We therefore initiated a pilot study on treatment of CAMR with an antihumoral regimen consisting of high-dose intravenous immunoglobulin (IVIG) and the chimeric anti-CD20 antibody rituximab.

Methods: Six pediatric renal transplant recipients with CAMR received four weekly doses of IVIG (1 g/kg body weight per dose), followed by a single dose of rituximab (375 mg/m2 body surface area) 1 week after the last IVIG infusion. Renal allograft biopsies were evaluated using the Banff '05 classification. Human leukocyte antigen-specific antibodies were detected by panel-reactive lymphocytotoxicity and solid phase ELISA assays.

Results: Median glomerular filtration rate during 6 months before intervention dropped by 25 (range, 11-26) mL/min/1.73 m2 ($P<0.05$) and increased in response to antihumoral therapy by 21 (-14 to +30) 6 months ($P<0.05$) and by 19 (-14 to +23) mL/min/1.73 m2 12 months ($P=0.063$) after start of treatment. Glomerular filtration rate improved or stabilized in 4 patients; the two nonresponders had the highest degree of transplant glomerulopathy, the highest degree of C4d deposition in peritubular capillaries and pronounced interstitial inflammation. The treatment regimen was well tolerated.

Conclusion: This pilot study demonstrates that CAMR in pediatric renal transplant recipients can be treated successfully and safely with a combination of IVIG and rituximab. This observation should encourage more extensive studies to evaluate this new treatment strategy.

43. 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, Susal C*, et al.*

Transpl Int 2012, 25:1165–1173.

ABSTRACT

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 m² during 6 months prior to AHT to 2.1 ml/min/1.73 m² (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.

44. Indicators of Treatment Responsiveness to Rituximab and Plasmapheresis in Antibody-Mediated Rejection After Kidney Transplantation.

Immenschuh S, Zilian E, Dämmrich ME, *et al.*

Transplantation. 2015 Jan;99(1):56-62

ABSTRACT

Background: Treatment of patients with antibody-mediated rejection (AMR) after kidney transplantation by rituximab and plasmapheresis is ambiguous. Because of its unknown efficiency and serious side effects, biomarkers, which are predictive for responsiveness to this treatment in AMR patients, are required.

Methods: Twenty renal transplant patients were included in this retrospective study. Selection was based on Renal Index Biopsies, classified according to Banff within 3 months before treatment. Patients were categorized into responders (R) and nonresponders (NR) depending on whether they returned to dialysis within 6 months after initiation of rituximab treatment. Clinical, histopathologic (Banff classification) and serologic parameters were compared between both groups by t test, Mann-Whitney U test, or likelihood ratio chi-square test.

Results: In comparisons between the groups, the R group showed a 1.5-fold higher level of estimated glomerular filtration rate and a fourfold lower level of proteinuria. By contrast, there were no differences in the histologic scores for chronic transplant lesions between the groups. The t and i scores were higher in NRs, whereas Banff-C4d scores of peritubular capillaries were increased in the Rs. Transplant biopsies in the Rs exhibited more CD138+ cell infiltrates. Serologic determination of human leukocyte antigen antibodies showed higher positivity for human leukocyte antigen class II donor-specific antibodies in the R group. No significant differences in other clinical criteria were found.

Conclusion: Increased proteinuria, decreased graft function, and a higher grade of tubulitis and inflammation in AMR are negative predictors for responsiveness to rituximab therapy. Rituximab therapy therefore should be initiated in an early phase of AMR.

45. Rituximab and Monitoring Strategies for Late Antibody-Mediated Rejection After Kidney Transplantation.

Parajuli S, Mandelbrot DA, Muth B, *et al.*

Transplant Direct. 2017 Oct 27;3(12):e227.

ABSTRACT

Background: There is limited information on treatment strategies and monitoring strategies for late antibody-mediated rejection (ABMR) after kidney transplantation.

Methods: In this observational and nonrandomized study, we compared 78 patients diagnosed with late ABMR (>3 months after transplant) who were treated with standard of care steroids/IVIG (n = 38) ± rituximab (n = 40) at our center between March 1, 2013 and December 31, 2016. All patients had follow-up biopsy and donor-specific antibodies (DSA) monitoring within 3 to 12 weeks.

Results: Patients had biopsy 7.3 ± 7 years after transplant and were followed for 15.9 ± 9.6 months after ABMR was diagnosed. Both treatment strategies were associated with a significant decline in DSA, microvascular inflammation (peritubular capillaritis + glomerulitis), and C4d Banff scores. In univariate regression analyses, rituximab, estimated glomerular filtration rate (eGFR), Banff i, t, v, chronicity (interstitial fibrosis + tubular atrophy + fibrous intimal thickening + allograft glomerulopathy) scores on the first biopsy, and eGFR and Banff v score on follow-up biopsy were associated with graft loss. Multivariate analyses retained only rituximab (hazard ratio, 0.23; 95% confidence interval, 0.06-0.84; P = 0.03) and eGFR at follow-up biopsy (0.84; 95% confidence interval, 0.76-0.92; P < 0.001) as significant predictors of graft loss. Kaplan-Meier analyses demonstrated that the benefit associated with rituximab was apparent after 1 year (15% vs 32% graft loss, P = 0.02).

Conclusion: Treatment of late ABMR with steroids/IVIG ± rituximab was effective in reducing DSA and microcirculation inflammation. The addition of rituximab was associated with better graft survival. Follow-up biopsies could be considered in the management of acute rejection to monitor the effect of therapy. Randomized studies on the best therapeutic options for ABMR are needed.

46. Clinical Outcome of Rituximab and Intravenous Immunoglobulin Combination Therapy in KidneyTransplant Recipients with Chronic Active Antibody-Mediated Rejection.

Ban TH, Yu JH, Chung BH, *et al.*

Ann Transplant. 2017 Aug 4;22:468-474.

ABSTRACT

Background: We previously reported that rituximab (RIT) and intravenous immunoglobulin (IVIg) combination therapy is effective in deterring the progression of chronic active antibody-mediated rejection (CAMR), but that report was based on the assessment of a small number of cases for a short period.

Material and methods: Forty-three patients with CAMR were recruited during the study period after 2010. The patients were divided into high (n=17, 39.5%) and low proteinuria groups (n=26, 60.5%) based on spot urine protein-to-creatinine ratio of > or <3.5 g/g. We compared clinical outcomes between the two groups in terms of allograft survival rate, decrease in estimated glomerular filtration rate (ΔeGFR), change in proteinuria level, and infectious complications. We also evaluated the risk factors of allograft failure.

Results: The 3-year allograft survival rate after combination treatment was 60.5% overall, but was higher in the low proteinuria group than in the high proteinuria group (69.2% versus 47.1%; log rank $p<0.05$). The combination treatment reduced the eGFR slope in both groups, and this effect was more definite in the low proteinuria group. No significant differences in the amount of proteinuria and infectious complication rate were found between the two groups. Proteinuria and eGFR at treatment were independent predictive factors of allograft failure ($p<0.01$ and $p<0.001$, respectively).

Conclusions: RIT and IVIg combination therapy was effective in reducing the progression of CAMR, and this effect was more definite in the patients with low proteinuria.

47. Differential modulation of donor-specific antibodies after B-cell depleting therapies to cure chronicantibody mediated rejection.

Touzot M, Couvrat-Desvergnes G, Castagnet S*, et al.*

Transplantation. 2015 Jan;99(1):63-8.

ABSTRACT

Background: Donor-specific antibodies (DSA) are considered as reliable biomarkers for antibody-mediated rejection (ABMR) diagnosis. However, it is unclear whether DSA monitoring is necessary and could predict graft outcome after antirejection treatment.

Methods: We analyzed 28 non-sensitized kidney transplant patients with ABMR associated with de novo anti-human leukocyte antigen (HLA) DSA. Donor-specific antibody levels were measured by single antigen bead assays 12 months after antirejection therapy onset. Patients were placed in three groups according to their antirejection treatment: group I (n = 10), plasma exchange-Rituximab; group II (n = 8), Bortezomib; and group III (n = 10), optimization of maintenance immunosuppression. Half of the patients in group I demonstrated concomitant acute cellular rejection (ACR+).

Results: De novo DSA were mainly anti-DQ (60%). Anti-class I and anti-DR DSA disappeared after treatment in group I and remained negative during follow-up, whereas anti-DQ DSA persisted without any modulation. In contrast, class I-II HLA-DSA mean fluorescence intensity remained unchanged in groups II and III. Graft loss was observed in 80% and 20% of patients from group I (ACR+) and group III, respectively. One year after the ABMR treatment, a 16-mL/min decline in estimated glomerular filtration rate was observed in patients from group I (ACR-) and group III. Group II showed better outcomes with a mean estimated glomerular filtration rate decline of 6.4 mL/min.

Conclusion: Modulation of DSA at and after treatment of ABMR did not correlate with graft outcome over a 12-month period.

48. Better understanding of transplant glomerulopathy secondary to chronic antibody-mediated rejection.

Remport A, Ivanyi B, Mathe Z, *et al.*

Nephrol Dial Transplant. 2015 Nov;30(11):1825-33. Review

ABSTRACT

Transplant glomerulopathy (TG) is generally accepted to result from repeated episodes of endothelial activation, injury and repair, leading to pathological abnormalities of double contouring or multi-layering of the glomerular basement membrane. TG is a major sequel of chronic active antibody-mediated rejection (cABMR), from pre-existing or de novo anti-HLA antibodies. Hepatitis C infection, thrombotic microangiopathy or other factors may also contribute to TG development. TG prevalence is 5-20% in most series, reaching 55%, in some high-risk cohorts, and is associated with worse allograft outcomes. Despite its prevalence and clinical significance, few well-studied treatment options have been proposed. Similar to desensitization protocols, plasmapheresis with or without immunoabsorption, high-dose intravenous immunoglobulin, rituximab, bortezomib and eculizumab have been proposed in the treatment of TG due to cABMR individually or in various combinations. Robust clinical trials are urgently needed to address this major cause of allograft loss. This review summarizes the current knowledge of the epidemiology, etiology, pathology, and the preventive and treatment options for TG secondary to cABMR.

49. The effect of combination therapy with rituximab and intravenous immunoglobulin on the progression of chronic antibody mediated rejection in renal transplant recipients.

An GH, Yun J, Hong YA, *et al.*

J Immunol Res. 2014;2014:828732.

ABSTRACT

The treatment for chronic active antibody-mediated rejection (CAMR) remains controversial. We investigated the efficacy of rituximab (RTX) and intravenous immunoglobulin (IVIg) for CAMR. Eighteen patients with CAMR were treated with RTX (375 mg/m(2)) and IVIg (0.4 g/kg) for 4 days. The efficacy of RTX/IVIg combination therapy (RIT) was assessed by decline in estimated glomerular filtration rate per month (ΔeGFR) before and after RIT. Patients were divided into responder and nonresponder groups based on decrease and no decrease in ΔeGFR, respectively, and their clinical and histological characteristics were compared. Response rate to RIT was 66.7% (12/18), and overall ΔeGFR decreased significantly to 0.4 ± 1.7 mL·min(-1) ·1.73 m(-2) per month 6 months after RIT compared to that observed 6 months before RIT (1.8 ± 1.0, $P < 0.05$). Clinical and histological features between the 12 responders and the 6 nonresponders were not significantly different, but nonresponders had a significantly higher proteinuria levels at the time of RIT (2.5 ± 2.5 versus 7.0 ± 3.5 protein/creatinine (g/g), $P < 0.001$). The effect of the RIT on ΔeGFR had dissipated in all patients by 1 year post-RIT. Thus, RIT delayed CAMR progression, and baseline proteinuria level was a prognostic factor for response to RIT.

50. 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 Nov;32(11):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.

51. Long-term graft survival in patients with chronic antibody-mediated rejection with persistent peritubular capillaritis treated with intravenous immunoglobulin and rituximab.

Mulley WR, Huang LL, Ramessur Chandran S, *et al.*

Clin Transplant. 2017 Sep;31(9).

ABSTRACT

Chronic antibody-mediated rejection (cAMR) is the major cause of premature renal allograft loss and is resistant to therapy with 12-month graft failure of up to 50% reported. We examined the duration of graft survival and associates of graft failure in patients with donor-specific antibody-positive cAMR and treatment-resistant peritubular capillaritis between June 2007 and October 2010. Those with advanced interstitial fibrosis (n=5) were excluded. Included patients (n=24) received treatment with high-dose intravenous immunoglobulin and fixed-dose rituximab (500 mg). Compared with previous reports, the study group experienced prolonged graft survival (median 82.1 months). Graft loss was predicted by eGFR and degree of proteinuria at diagnosis but not by donor-specific HLA antibody class or intensity, nor individual or summed Banff scores. Allograft biopsies were further examined for infiltrating leukocyte subtypes and location with high numbers of glomerular leukocytes, particularly macrophages, independently associated with an increased risk of graft failure. This study suggests that patients with cAMR and persistent microcirculatory inflammation, excluding those with advanced histological damage, can expect prolonged graft survival when treated with IVIg and rituximab. Trial level evidence is required to validate this observation. Further examination of the role of macrophages in cAMR is warranted.

52. Antibody-mediated rejection: New approaches in prevention and management.

Montgomery RA, Loupy A, Segev DL.

Am J Transplant. 2018 Jan;18 Suppl 3:3-17

ABSTRACT

Despite the success of desensitization protocols, antibody-mediated rejection (AMR) remains a significant contributor to renal allograft failure in patients with donor-specific antibodies. Plasmapheresis and high-dose intravenous immunoglobulin have proved to be effective treatments to prevent and treat AMR, but irreversible injury in the form of transplant glomerulopathy can commonly manifest months to years later. There is an unmet need to improve the outcomes for patients at risk for AMR. Updated Banff criteria now take into account the increasing understanding of the complex and heterogeneous nature of AMR phenotypes, including the timing of rejection, subclinical and chronic AMR, C4d-negative AMR, and antibody-mediated vascular rejection. Treatment for AMR is not standardized, and there is little in the way of evidence-based treatment guidelines. Refining more precisely the mechanisms of injury responsible for different AMR phenotypes and establishing relevant surrogate endpoints to facilitate more informative studies will likely allow for more accurate determination of prognosis and efficacious intervention using new therapeutic approaches. In addition to plasma exchange and intravenous immunoglobulin, a number of other add-on therapies have been tried in small studies without consistent benefit, including anti-CD20, proteasome inhibitors, complement inhibitors, anti-interleukin-6 receptor blockers, and immunoglobulin G-degrading enzyme of Streptococcus pyogenes (called IdeS).

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

Wan SS, Ying TD, Wyburn K, *et al.*

Transplantation. 2018 Apr;102(4):557-568.

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.