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Update on Treatment and Prevention of Chronic Antibody Mediated Rejection in Renal Transplant Recipients

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Abstract:

Chronic antibody mediated rejection (AMR) is a major cause of allograft failure[1,2]. Chronic AMR clinically presents with proteinuria and gradual decline in renal function. The underlying mechanisms of AMR include both antibody mediated complement-dependent cytotoxicity, complement-independent cellular cytotoxicity and other mechanisms. The purpose of this review is to appraise recent literature on diagnosis, treatment and prevention of chronic AMR.

Key words: *Rejection, kidney transplant, acute rejection, chronic rejection, antibody mediated rejection, complement, plasmapheresis, Bortezomib, Rituximab, Eculizumab, Tocilizumab.*

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Introduction

Chronic antibody mediated rejection (AMR) is a major cause of allograft failure[1,2]. Chronic AMR clinically presents with proteinuria and gradual decline in renal function. The underlying mechanisms of AMR include both antibody mediated complement-dependent cytotoxicity and complement-independent cellular cytotoxicity as well as direct endothelial activation, injury and repair; the later mechanism plays an important role in pathogenesis of chronic AMR, transplant glomerulopathy and vasculopathy[2]. Despite active research, effective therapeutic options for chronic AMR remain limited and ultimate allograft survival is poor[3]. In one study of 123 patients, 76% of patients with chronic AMR lost their allografts with a median survival of 1.9 years after diagnosis. Chronicity score >8, donor specific antibody (DSA) mean florescent index (MFI) >2500, serum creatinine > 3 mg/dl and proteinuria > 1 gram/day were independently associated with higher risk of allograft failure in these patients [4].

The purpose of this review is to appraise recent literature on diagnosis, treatment and prevention of chronic AMR.

Diagnosis of Chronic AMR

The updated BANFF 2017 classification has listed two terms concerning chronic AMR; chronic active AMR and chronic AMR[5].

Chronic Active AMR

The diagnostic criteria for chronic active AMR is listed in Table 1[5]. Diagnosis of chronic active AMR requires at least 1 feature of AMR chronicity, 1 criterion of antibody interaction with tissue and at least 1 criterion of DSA or equivalents.

Table 1 – Diagnostic criteria for Chronic Active AMR based on BANFF classification 2017

At least 1 feature of AMR chronicity • Transplant glomerulopathy - Banff Lesion Score cg > 0 (by LM or EM, if available), excluding biopsies with evidence of chronic thrombotic microangiopathy • Peritubular capillary multilayering - 7 or more layers in 1 cortical peritubular capillary and 5 or more in 2 additional capillaries, avoiding portions cut tangentially by EM, if available • Arterial intimal fibrosis of new onset, excluding other causes - Leukocytes within the sclerotic intima favor chronic AMR if there is no prior history of biopsy proven TCMR but are not required
At least 1 criterion of antibody interaction with tissue • Banff Lesion Score C4d > 1 (IF on fresh frozen tissue) or C4d > 0 (IHC on paraffin-embedded tissue) • At least moderate microvascular inflammation (g + ptc > 1) in the absence of borderline, acute T cell-mediated rejection recurrent or de novo glomerulonephritis. If borderline, acute TCMR, or infection are present, (Banff Lesion Scores g + ptc) > 1 is not sufficient and Banff Lesion Score g>1 is required. • Increased expression of thoroughly validated gene transcripts/classifiers in the biopsy tissue strongly associated with AMR
At least 1 criterion of DSA or equivalents • DSA (anti-HLA or other specificity) • Banff Lesion Score C4d > 1 (IF on fresh frozen tissue) or C4d > 0 (IHC on paraffin-embedded tissue) • Increased expression of thoroughly validated gene transcripts/classifiers in the biopsy tissue strongly associated with AMR

Cg – transplant glomerulopathy, LM – Light microscopy, EM – Electron microscopy, TCMR – T cell mediated rejection, IHC – immunohistochemistry, g – glomerulitis, ptc – peritubular capillaritis, DSA – donor specific antibody

Chronic AMR

BANFF 2017 permits use of term chronic AMR for patients who meet the following criteria[5]:-

- Transplant glomerulopathy or peritubular capillary basement membrane multilayering.
- Prior documentation of active ABMR or chronic active ABMR or documented evidence of DSA.
- Criteria for antibody endothelial interaction (listed in table 1) are not met.

Treatment of Chronic AMR

In general, evidence for treatment of chronic AMR is limited and is primarily based on retrospective studies with few recently published randomized clinical trials. These studies have utilized nearly same interventions as used for acute AMR. These therapeutic options are listed in table 2.

Table 2 – Therapeutic options utilized in literature for chronic AMR[6]

Corticosteroids
Intravenous Immunoglobulins (IVIG) Neutralizes complement fixing antibodies Alter complement activity Modulates Fc receptor activation and function Regulates T and B lymphocytes
Plasmapheresis Removes antibody
Rituximab An anti-CD20 monoclonal antibody resulting in depletion of B-cells
Bortezomib A proteosome inhibitor which results in suppression and apoptosis of plasma cells
Eculizumab A humanized monoclonal antibody directed against complement protein C5, preventing formation of the membrane attack complex (C5–9)
Tociluzimab[7] A IL-6 receptor blocker which is used in treatment of rheumatoid arthritis and other rheumatological disorders

Recent evidence for treatment of chronic AMR is summarized below:-

Observational Studies

Traditional Therapies as Used for Acute AMR

Results of observational studies in patients with chronic AMR which have retrospectively compared one set of interventions (similar to those used for acute AMR) with other therapies or no treatment and found significant benefit are summarized in table 3.

Table 3 – Observational studies with historic controls showing benefit of treatment for chronic AMR

Author	Patients	Intervention	Control	Results in Intervention Group
Nair P 2019[8]	65	Steroids, IVIG, Rituximab, Plasmapheresis (n=37)	IVIG or intensified immunosuppression	Higher allograft (40.5% vs. 7.1%) and patient survival (100% vs. 82.1%) at 1 year. No difference in serum creatinine, DSA or infection rate
Larpparisuth N 2019[9]	28	IVIG, Rituximab, Plasmapheresis, Bortezomib (n=13)	IVIG, Rituximab, plasmapharesis	Lower rate of eGFR decline (-4.20 ± 4.89 mL/min/y vs -12.33 ± 10.44 mL/min/y), Higher rate of DSA resolution (69.2% vs 25%) ,lower rate of allograft loss (15.4% vs 66.7%), and better allograft survival (P = .006) at median follow up of 41.8 months
Lee 2016[10,11]	75	IVIG and Plasmapheresis (n=35, late AMR, 50% with chronic lesions)	No treatment	Better allograft survival at 10 years (73.9% vs. 35%)
Redfield 2016[4]	123	Steroids and IVIG (n=108)	Steroids or no treatment	Lower rate of allograft failure (HR 0.44, 0.2-0.96)
Chung BH 2014[12]	54	Rituximab and IVIG (n=25)	No treatment	ΔeGFR was significantly decreased after 6 months (P<0.05), better allograft survival and no serious complications
Smith RN 2012[13]	31	Rituximab (n=17)	No Rituximab	Median allograft survival 685 days vs. 439 days in control group. 8/14 patients had decline or stabilization of serum creatinine at 1 or more years of follow up
Waiser 2012[14]	19 (6 with chronic AMR)	IVIG, Plasmapheresis and Bortezomib (n=3, chronic AMR)	IVIG, Plasmapheresis and Rituximab	0/3 allograft loss compared to 3/3 allograft loss in control group at 18 months

There have been several retrospective studies which have found benefit of traditional therapies as used for acute AMR in treatment of chronic AMR but these studies have not analyzed historic controls for comparison. They can be best described as case series and are summarized in table 4.

There are few observational studies which have found no benefit of treatment for chronic AMR and are summarized in table 5.

Tocilizumab

Choi et al retrospectively identified 36 renal transplant recipients with transplant glomerulopathy and DSA who received rescue therapy with Tocilizumab for 6-26 months after failure to respond to Rituximab and IVIG with or without plasma exchange. Significant reduction in DSA and stabilization of renal allograft function was observed in these patients at 2 years. Patient and graft survival were 91% and 80% at 6 years respectively[25]. Tocilizumab appears to be a promising option but more studies are needed preferably in the form of prospective randomized controlled trials.

In summary, observational studies do support a role of IVIG, Rituximab, Plasmapheresis and Bortezomib in treatment of chronic AMR, but confidence in these results is low due to retrospective nature, lack of randomization, few negative studies and possible publication bias.

Table 4 – Observational studies with no control groups showing benefit of treatment for chronic AMR

AUTHOR	PATIENTS	INTERVENTION		RESULTS
Ding Y 2018[15]	11	Steroids, Rituximab, Bortezomib, Plasmapharesis (Late AMR)	No Control Group	9 patients (82%) had functioning allograft at median follow up of 50 months
Ban 2017[16]	43	Rituximab and IVIG		3 year allograft survival 60.5%, slower decline in eGFR slope
Kahwaji 2014[17]	33	Rituximab and IVIG		Stabilization of serum creatinine and DSA improvement in only patients with g+ptc > 4
Hong YA 2012[18]	6	Rituximab and IVIG		Reduction of proteinuria, improvement or stabilization of allograft function in 3 patients
Billing 2012[19]	20 pedriatric patients	Rituximab and IVIG		Loss of eGFR decreased significantly from 7.6 ml/min/1.73 m² during 6 months prior to treatment to 2.1 ml/min/1.73 m² during 6 months after treatment. Class I DSA declined by 61% class II DSA by 63% 12 months after intervention.
Rostaing 2009[20]	14	Rituximab		7 patients had stable creatinine and reduction in proteinuria at 30 months. 7 patients lost their allograft
Fehr 2009[21]	4	Rituximab and IVIG		Improvement of allograft function in all patients, reduction of DSA in 2/4 patients

Table 5 – Observational studies showing no benefit of treatment for chronic AMR

Author	Patients	Intervention	Control	Results in Intervention Group
Pineiro 2018[22]	62	IVIG, Rituximab, Plasmapheresis (n=23)	No treatment	No difference in allograft survival at 24 months (34.7% vs. 33.3%), no difference in eGFR, proteinuria, higher rate of infection (n=15 vs. 8) and higher mortality (n=4 vs. 0)
Einecke 2016[23]	71	IVIG, Rituximab, Plasmapheresis (n=39, 61% with chronic or chronic active AMR)	No treatment	No difference in allograft survival
Bachelet 2015[24]	31	IVIG, Rituximab (n=21)	No treatment	No difference in allograft survival (47% vs. 40%) at 24 months, higher rate of adverse events (p=0.03), modest reduction of DSA

Randomized Clinical Trials

In last 2 years, few randomized clinical trials have been published which addressed effectiveness of various prevailing treatment options for chronic AMR. These trials are summarized below:-

Triton Study[26]

The Triton study was a prospective, randomized, placebo-controlled, double-blind clinical trial to assess effectiveness and safety of intravenous immunoglobulins (4 doses of 0.5 g/kg) and rituximab (375 mg/m^2) in patients with transplant glomerulopathy and DSA (13 patients received treatment and 12 received wrapped saline infusion). Patients with estimated glomerular filtration rate (eGFR) <20 mL/min per 1.73m^2 and/or severe interstitial fibrosis/tubular atrophy were excluded. The primary outcome i-e eGFR decline at 1 year (-4.2 ± 14.4 vs. -6.6 ± 12.0 mL/min per 1.73 m^2;p=0.47) was not different between the two groups. Similarly secondary outcomes including Banff score, increase of proteinuria, MFI of the immune-dominant DSA and safety were similar between the groups.

The major limitation of this study is the small sample size, which is lower than originally planned enrolment of 25 patients in each groups and may be the reason for observed lack of benefit. Planned enrolment couldn't be achieved due to budgetary constraints and lower participation rate.

Bortiject Trial[27]

Bortiject was a randomized, placebo-controlled trial to study effectiveness of two cycles of Bortezomib; a proteasome inhibitor (each cycle: 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11) in preventing GFR decline in patients with late DSA positive ABMR. 44 DSA-positive kidney transplant recipients with characteristic ABMR morphology (28 patients with chronic/chronic active AMR) were randomly assigned to receive Bortezomib (n=21) or placebo (n=23). The difference in eGFR slope (primary end point) was not different between Bortezomib and placebo (0.5-ml/min per 1.73 m^2 per year; p=0.86). There was no significant differences between Bortezomib and placebo-treated groups in 2-year graft survival (81% versus 96%; p=0.12), median measured GFR (33 versus 42 ml/min per 1.73 m^2; p=0.31), DSA levels, urinary protein concentration, or morphologic or molecular rejection phenotypes at 24-months follow-up. Bortezomib was associated with gastrointestinal and hematologic toxicity.

Though the study showed that Bortezomib was not effective for treatment of late AMR including patients with chronic/active AMR but it cannot rule out the effectiveness of Bortezomib in combination with other therapies like IVIG or Plasmapheresis since Bortezomib was used alone in this study.

Eculizumab Study[28]

In this pilot study, 15 renal transplant recipients > 6 months post-transplant, at least 20% decline in eGFR over preceding 12 months and de novo DSA (late AMR) were randomized in 2:1 fashion to Eculizumab (n=10) or placebo n=5). It is unclear that how many truly had chronic or chronic active AMR on biopsy based on the manuscript. An improved eGFR trajectory (primary endpoint) over 1 year was observed in treatment group versus control, based on 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). The ENDAT expression was not significantly different in follow up renal biopsies between the two groups.

Though this study showed that treatment with Eculizumab somewhat stabilized renal allograft function in patients with late AMR but it is limited by small sample size, lack of improvement on molecular markers of rejection and use of lower significance value for analysis. Further studies are needed to clarify role of Eculizumab in management of late/chronic AMR. Regardless, its high cost and limited world wide availability will impede its use for routine clinical practice.

In summary, randomized clinical trials have failed to show a convincing benefit of any intervention especially Bortezomib in treatment of chronic AMR. Other trials are limited due to inadequate sample size.

Prevention of Chronic AMR

Prevention of AMR whether acute or chronic is based on detection of DSA either before transplant (Pre formed DSA) or new DSA after transplant (De novo DSA). Sub clinical and acute AMR may also increases the risk of chronic AMR, necessitating early detection and treatment of acute AMR[1,2].

Preformed DSA

Preformed DSA is usually detected pre transplant by using combination of cross match techniques including CDC cross match, flow cytometry cross match or by employing solid phase assays for detection of anti HLA antibodies[29]. Preformed DSA can cause hyper acute AMR, acute AMR or allograft loss[2,30,31]. Even presence of low titers of DSA, as detected by sensitive solid phase assays with negative flow cytometry cross match, is associated with double the risk of AMR and increased risk of graft failure by 76% [32]. Pre-existing DSA is ideally addressed prior to transplant using various strategies depending upon intensity of DSA, results of different cross match techniques and experience of transplant center. Such strategies include avoiding a particular donor, participation in kidney paired donation program[33] or de-sensitization protocols[34]. The details of eligibility, protocols of de-sensitization, induction and maintenance immunosuppression in these high risk patients and post-transplant monitoring are beyond the scope of this review.

De Novo DSA

De novo DSA formation after kidney transplant is associated with late acute AMR, chronic AMR, T cell mediated rejection and reduced allograft survival[2,30,35 – 37]. The incidence of de novo DSA was found to be 7-30%[2,38] and as high as 60% in non-compliant patients[31] in various studies with majority being class II especially DR and DQ antibodies[2,39]. A pragmatic approach to post transplant de novo DSA screening

and subsequent intervention is illustrated in Figure 1. It is important to understand that this approach has not been validated in high quality randomized clinical trials. Various components of this algorithm are discussed below.

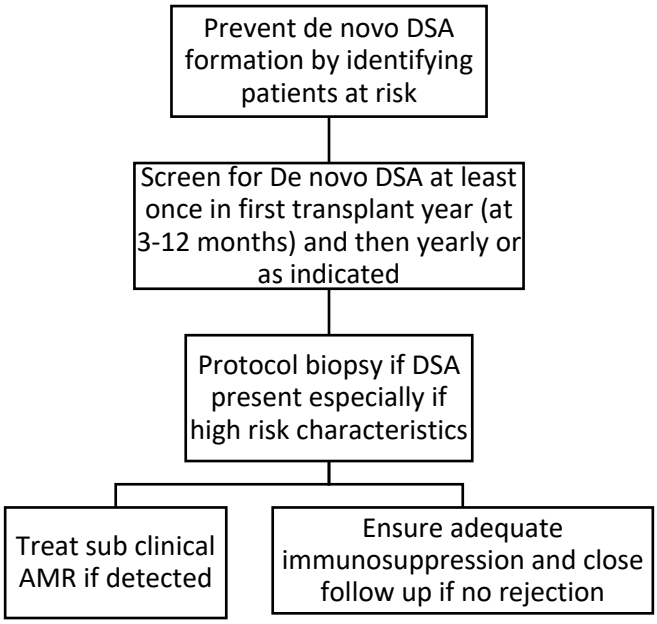

Figure 1 – Approach to post transplant de novo DSA surveillance and subsequent intervention

Which patients are at risk of developing de novo DSA?

Renal transplant recipients with HLA-DR mismatch[31] and non-compliance[31,36] appear to be at high risk of developing de novo DSA. Other associated risk factors include young age, male sex, African American race, presence of pre-formed non-HLA DSA, acute rejection episodes, sensitization events like pregnancy, re-transplant or blood transfusion[40].

Effect of immunosuppressive therapy either for induction or maintenance on de novo DSA formation has been the subject of two excellent reviews[40,41]. In general, the existing literature is limited, varied and evolving. Of note, early calcineurin (CNI) inhibitor switch to mammalian target of rapamycin (mTOR) inhibitor was found to be associated with increased risk of de novo DSA formation but late switch or continuation of mTOR inhibitor with low dose CNI does not appear to increase the risk. Benefit of tacrolimus over cyclosporine in reducing de novo DSA formation is not consistent. Interestingly, Belatacept was associated with extremely low rate of de novo DSA formation[40,41]. Early steroid withdrawal was not associated with increased risk of DSA formation even after 5 years of follow up of 37 renal transplant recipients[42].

In practice, prevention of de novo DSA formation should be focused on ensuring adherence, maintaining adequate immunosuppression based on patients' risk profile and avoidance of preventable sensitization events like blood transfusions.

How often should patients be monitored for de novo DSA after transplant?

In patients without preformed DSA or history of DSA, consensus guidelines recommend screening for de novo DSA at least once 3-12 months post-transplant and at any time if there is allograft dysfunction, significant change in maintenance immunosuppression is planned or suspected non-adherence[39]. Some transplant centers monitor it more frequently while others monitor it yearly. A protocol biopsy with an aim to treat sub-clinical rejection if present is recommended if DSA is detected.

Do all DSA predict adverse allograft outcomes?

Many DSA are benign and do not impact allograft outcome. In one study only 25% of DSA detected in 1st post transplant year persisted 12 months later[43]. This makes it difficult to formulate interventional approach based on routine post-transplant DSA monitoring [2]. In recent years, several studies have identified DSA characteristics which are associated with increased risk of adverse allograft outcomes. Examples of such characteristics are shown in table 6.

Table 6 – Characteristics of DSA associated with adverse allograft outcomes

High mean florescent intensity (MFI) – Different thresh hold identified in various studies >3000 associated with poor allograft survival[44] >6000 associated with > 100 times risk of AMR[44] >3000 associated with risk of AMR[43,45], >6000 associated with inferior allograft survival in association with acute rejection episode[46]
C1q binding DSA[2,47–49]
C3d binding DSA[50,51]
IgG3 subclass of DSA - associated with shorter time to rejection[49] and inferior allograft survival[49,52]
IgG4 subclass of DSA -associated with chronic AMR/late AMR[49]
De novo DSA compared to preformed DSA[53]
HLA-DQ DSA[54]

C1q/C3d binding DSA or IgG DSA subclass assays may be helpful in identifying patients at increased risk of AMR and/or allograft loss. Early intervention in the form of protocol biopsy and treatment may eventually improve allograft survival in these patients. However, lack of routine availability and interventional studies based on these assays limit their current application in clinical practice.

Does treatment of sub clinical ABMR improve allograft outcome?

Sub clinical ABMR is detected in 25-53% of protocol renal biopsies after detection of DSA[38,43,55 – 57]. In a study of 1001 renal transplant protocol biopsies, patients with sub clinical AMR (n=142) had the poorest graft survival at 8 years post-transplant (56%) compared with subclinical TCMR (n=132) (88%) and no rejection (n=727) (90%) groups (P<0.001). At 1 year, sub clinical AMR was independently associated with a 3.5-fold increase in graft loss (95% confidence interval, 2.1 to 5.7)[58].

Potential benefit of treating sub clinical AMR was evaluated in a retrospective study of 220 renal transplant recipients, who underwent indication vs. DSA surveillance based protocol biopsies and afterwards treated for sub clinical and clinical AMR if detected. The allograft survival was comparable and superior in patients with no rejection and sub clinical rejection compared to those with clinical rejection (3% and 8% vs. 46%, p<0.001)[59]. This suggests that early detection and treatment of sub clinical rejection by DSA monitoring may improve allograft outcome.

What should be done if de novo DSA is present and allograft biopsy does not reveal rejection?

Consensus guidelines recommend close monitoring of these patients for clinical rejection[39]. In a recent study by Parajuli et al , allograft survival of de novo DSA positive but biopsy negative patients was comparable to DSA negative patients, though 18% of these patients developed active AMR during follow up[60], which emphasizes that these patients should be evaluated for adequacy of immunosuppression and monitored closely.

Summary and Recommendations

Chronic AMR is a major cause of long term allograft failure. Diagnosis of chronic active AMR requires at least 1 criterion each for AMR chronicity, antibody endothelial interaction and DSA or equivalent. Evidence for treatment of chronic AMR is limited due to retrospective nature, somewhat conflicting results and lack of randomization. Few recent randomized clinical trials with limited sample size have failed to show any significant benefit of Rituximab, IVIG, Bortezomib or Eculizumab. Further studies are needed to elucidate role of Tocilizumab in treatment of chronic AMR.

In clinical practice, chronic AMR is best prevented by detecting and addressing preformed DSA (including low intensity) prior to transplant and preventing de novo DSA by ensuring compliance and adequate immunosuppression post-transplant. Screening for de novo DSA in the first year post transplant and perhaps yearly followed by protocol biopsy and treatment of sub clinical rejection if indicated seems to be a rational approach, though needs confirmation in a prospective randomized clinical trial. Due to lack of definite proven effective treatment options for chronic AMR, a patient should be clearly explained the prognosis, cost, side effects and uncertainty of benefit if any further intervention is planned in the form of IVIG, Rituximab or Plasmapheresis. Treatment with Bortezomib alone is not recommended. Further studies are needed to improve current practice of treatment and prevention of chronic AMR.

Conflict of Interest: None Declared

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