

## Acute Antibody-Mediated Rejection in Kidney Transplantation: Clinical and Therapeutic Aspects

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### Abstract

Acute Antibody Mediated Rejection (ABMR) in kidney transplantation is a severe complication that frequently occurs after transplantation and is due either to pre-transplant Donor-Specific Antibodies (DSAs) or to de novo DSAs. New techniques to detect DSAs in the recipient serum and advances in the assessment of graft pathology have allowed us to recognize this entity in recent years.

The treatment of ABMR is a multistep process consisting of the desensitization of the patients with preformed antibodies to prevent acute ABMR: in cases of acute ABMR, the antibodies are removed from the serum and anti-B cells immunosuppressants are used.

**Keywords:** Antibody-mediated rejections; Donor specific antibodies; Complement activation, Paired exchange programs, Desensitization, Anti-B-cells therapies

### Introduction

Recent improvements in renal allograft survival relate primarily to a reduction in the incidence and consequences of T-cell mediated rejection. However, despite improvements in the outcomes of renal transplantation, the kidney allograft loss rate remains substantial and is associated with increased morbidity, mortality and costs [1,2].

Over the past two decades, our thinking has changed from considering rejection as primarily a T-cell mediated process to the realization that insufficient control of the humoral arm of a recipient's immune system by the current immunosuppressive regimens [3] is the factor primarily responsible for allograft dysfunction and loss [4-6]. In addition, the number of patients who requires re-transplantation and who are quite likely to be sensitized to Human Leukocyte Antigens (HLA) is increasing. Moreover, recent therapeutic strategies that have permitted the HLA to be crossed have created a new population at risk for antibody-mediated rejection, which has enabled these patients to be studied over an extended time period.

The emergence of sensitive techniques to detect donor specific anti-HLA antibodies (DSAs) and other HLA and non-HLA antibodies, together with advances in the assessment of graft pathology, have expanded the spectrum of what constitutes an acute Antibody Mediated Rejection (aABMR). As a consequence of this increased knowledge, at the Banff '07 and Banff '09 conferences [7,8] the concept of aABMR was further evaluated, and ABMR has been definitively included in the Banff classification. There is increasing body of evidence suggesting that patients with a high titer of anti-HLA antibodies (particularly if they are donor specific), developed either pre-transplant or post-transplant, are at high risk of developing ABMR episodes. At any given time, approximately 25% of transplant recipients have antibodies against HLA antigens as determined by the newest highly sensitive and specific techniques for DSAs monitoring [9,10]. In addition, antibodies that are not directed against HLA have also been implicated in ABMR [11]. Antibodies can mediate endothelial injury through complement dependent and independent mechanisms by transducing signals that are pro-inflammatory and proliferative [12].

### Pathophysiology

The pathophysiology of aABMR is still incompletely understood.

Studies suggest that in renal transplantation, de novo HLA-DSAs develop post-transplant in up to 25% of the unsensitized patients, often without overt clinical evidence of concurrent rejection. In addition, approximately 30% of the patients on the waiting list already have detectable HLA antibodies [13]. In both groups of patients, the presence of these antibodies increases the risk of a subsequent antibody mediated rejection [14]. The development of a histological test to identify antibody mediated complement activation on transplant biopsies (C4d staining) has provided a way of documenting the potentially deleterious interactions between the antibody and the graft endothelium. In addition, molecular techniques, such as gene expression profiling, have allowed the identification of subclinical endothelial cell damage that can be present even in the absence of complement activation or detectable DSAs [15]. In addition to antibodies reactive to the donor human leukocyte antigen molecules, antibodies directed towards minor histocompatibility antigens, endothelial cells, red blood cells, or auto-antigens can trigger or contribute to the early or late rejection after transplantation [16].

Antibody mediated injury to an allograft is initiated by DSAs binding to HLA antigens or to other targets on the allograft endothelium.

Once the endothelium is damaged by antibodies, von Willebrand factor and P-selectin are released as part of the inflammatory response. Leukocytes adhere to the glomeruli or to the dilated peritubular capillaries via cytokines (IL-1 $\alpha$ , IL-8, and chemokine ligand 2), thereby allowing complement activation.

If the DSAs are complement activating, the classic complement pathway is rapidly activated through the IgG binding and activation of C1q [17]. The chemo-attractants C3a and C5a are part of the complement cascade that activates C5b, allowing for the assembly of the membrane attack complex (MAC) [18]. If not treated promptly,

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Received December 11, 2013; Accepted December 24, 2013; Published December 27, 2013

Citation: Salvadori M, Bertoni E (2013) Acute Antibody-Mediated Rejection in Kidney Transplantation: Clinical and Therapeutic Aspects. J Nephrol Ther 4: 146. doi:10.4172/2161-0959.1000146

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the sequelae can include thrombotic macroangiopathy causing hemorrhage with arterial wall necrosis and, ultimately, graft loss.

Alternatively, DSAs can bind endothelial cell targets and stimulate cell proliferation or induce antibody-dependent cell-mediated cytotoxicity (ADCC) with interferon  $\gamma$  release [12]. These processes seem to be more important for the development of a type of chronic ABMR that is more dependent on Natural Killer (NK) cells than on complement [19].

The pathologic and clinical manifestations of acute ABMR constitute a spectrum of diseases normally associated with the presence of DSAs. This spectrum can vary from hyper-acute humoral rejection to acute humoral rejection, indolent or subclinical acute humoral rejection, and C4d-negative humoral rejection.

## Diagnostic and Clinical Aspects

### Hyper-acute rejection

The pathology of hyper-acute rejection is characterized by the rapid onset of edema of the kidney and thrombosis of the allograft within minutes after the graft implantation, in pre-sensitized patients who have circulating anti HLA, ABO or other allo-antibodies to donor endothelial surface antigens [20].

With improved cross-matching techniques, hyper-acute rejection has disappeared and has been dropped from the current Banff classification of kidney allograft rejection [8].

### Classical acute antibody-mediated rejection

Patients with classical acute ABMR present with an acute loss of graft function that often arises in the first weeks after the transplantation. Acute ABMR can also develop years after a transplantation and is often triggered by a decrease in immunosuppression.

Pre-sensitization is the major risk factor, but most of the patients with ABMR have a negative cross-match with the donor. This fact can be due to low level DSAs not detectable with the current techniques [21] or to the de novo generation of donor specific antibodies [22].

Renal biopsies may show acute cellular rejection, acute tubular injury, or thrombotic microangiopathy. Neutrophils in the capillaries are characteristics. Typically, the peri-tubular capillaries are dilated and fibrinoid necrosis is found in almost 20% of the cases. Microthrombi and interstitial hemorrhage also occur occasionally. The peri-tubular capillaries and glomerular endothelium show a variety of ultra structural changes, including the loss of fenestrations, detachment from the basement membrane, lysis and apoptosis [23].

Antibodies to the donor HLA class I or II antigens are present in almost 90% of the patients who also have C4d deposition in the capillaries.

Acute ABMR, even if successfully treated, has a worse prognosis in the long-term outcome as recently documented in a prospective case-control study [24]. In another recent study [25], the pre-transplant presence of class I DSAs (versus class II DSAs) predicted acute ABMR and graft loss.

A particular form of acute ABMR is verified in the case of an ABO incompatible transplantation. ABO incompatible transplantations are increasingly performed, with many centers reporting good results [26,27]. Since 2011, the outcome of ABO incompatible transplantation has been better understood, as the UK Registry data have been further analyzed and a large multicentre study in the USA has published its

results [28,29]. In the case of ABO incompatible transplantation, acute rejection may not be common. However, the rejection may be rapidly progressive and may lead to graft failure within 48 hours, despite intensive treatment. It is interesting that this rejection is quite unlike the acute antibody mediated rejection in an HLA antibody-incompatible transplantation, in which the rejection is more frequent, develops more slowly and can be reversed acutely in over 90% of the cases.

### Indolent or subclinical acute ABMR

The development of the lesions associated with chronic rejection is typically preceded by the occurrence of at least one identified clinical episode of acute ABMR:

Although modern therapeutic strategies can efficiently reverse the acute renal dysfunction, they usually fail to deplete the antibody-secreting plasma cells from the spleen and bone marrow of the patients [30]. As a result, the DSAs remain detectable in the circulation and are responsible for a more indolent and slowly progressive form of antibody-mediated injury that is characterized by the persistence of glomerulitis and peri-tubular capillary C4d deposition. In contrast to the overt acute ABMR episodes, it is now recognized that kidney transplant recipients who develop de novo DSAs often show pathologic features of indolent and slowly progressive micro vascular abnormalities that occur without acute compromise of graft function or notable proteinuria, sometimes referred to as subclinical or indolent ABMR [31,32]. The appearance of de novo DSAs likely results from inadequate immunosuppression and represents a dynamic process that begins early after transplantation and continues to varying degrees thereafter.

### C4d negative acute ABMR

The first evidence for a C4d negative acute ABMR emerged in 2009 as a result of the work by the teams in Paris [33] and Edmonton [15]. The latter study demonstrated high endothelial specific gene expression in kidney transplant biopsy samples with DSAs but without C4d. In this study, the C4d negative acute ABMR was characterized by high intra-graft endothelial gene expression, allo-antibodies, histology typical of acute ABMR and poor outcomes. Most cases of C4d negative ABMR can occur more than 1 year after the transplantation and often represent an acute superimposed to a chronic ABMR. Nevertheless, cases of acute, C4d negative ABMR can occur primarily in highly sensitized patients who are transplanted after desensitization where the DSAs persist at low levels.

Several hypotheses have been suggested to explain the lack of complement deposition, despite the evidence of micro vascular inflammation and the persistence of DSAs in the circulation. The low sensitivity of C4d [7,34] could relate to technical issues, including the type of fixative and the different methods of C4d detection used (immunofluorescence versus immunochemistry). In addition, some DSAs may have a poor complement fixing ability but are nonetheless able to activate endothelial cells as documented by the Edmonton study [15].

Another possibility is that the various prophylactic strategies used for preventing ABMR may decrease the burden of complement activation within the capillaries [30]. Finally the Fc receptors on NK cells (FcRIIA) may also play a role in acute rejection, and it is possible that some examples of ABMR in the biopsies that lack C4d are due to this mechanism.

Given the concerns about the lack of sensitivity of C4d in kidney transplantation, a working group was established at the 2011 Banff

conference to refine the criteria for the diagnosis of ABMR in the kidney [35]. This work is still in progress, and at the last Banff conference held in Brazil in 2013, acute ABMR without evident complement deposition was accepted and called acute type 2 ABMR. To make a diagnosis of C4d negative ABMR the following 4 features must be present: Serologic evidence of DSAs; histological evidence of ABMR; no C4d staining on paraffin sections of the biopsy samples; and evidence of an acute graft dysfunction [36].

## Therapy for Acute ABMR

The overall therapy for acute ABMR can be divided into 2 steps: The prevention of acute ABMR and treatment of acute AMBR.

### Prevention of acute ABMR

As acute ABMR is more often due to the presence in the recipients of preexisting DSAs, the best option is to avoid such conditions. This can be achieved in three different ways.

**Implementation of acceptable mismatch programs:** Such a program is now operating in the Euro-transplant area and is in progress in countries such as France, Italy and Greece.

The Euro-transplant program is reserved for highly sensitized patients (PRA>85%).

The extensive antibody screening of all the available sera leads to the exact definition of those HLA antigens toward which the recipient candidate has never formed antibodies. In this program, the HLA antigens are defined as a string of potential epitopes (consisting of three amino acids, triplets). Some of these potential epitopes are shared between different HLA antigens and may also be present on the HLA molecules of the potential antibody producer. As a consequence, HLA mismatches that only have triplets that are shared by the different HLA antigens of the antibody producer will not lead to the induction of HLA antibodies.

If a kidney donor with an HLA phenotype that is a combination of the patient's own HLA and 1 or more acceptable mismatches becomes available, the kidney is immediately shipped to the recipient center and transplanted [37].

In this way the hyper-immune patient can be more easily transplanted while avoiding the risk of the occurrence of an acute ABMR.

**National paired exchange programs in cases of positive cross-matches with a living donor:** The opportunity for a kidney paired donation arises when the donors in the two donor/recipient pairs are incompatible with their intended recipients. If the donors are both compatible with the recipient in the opposite pair, an exchange of kidneys can occur. This exchange procedure allows each donor to donate a kidney and each recipient to receive a transplant.

The success of paired kidney donation programs depends on the number of patients involved. The San Antonio Hospital in Texas has a well-established paired kidney donation program that has led to 83 procedures in less than 2 years. It has been calculated that if the productivity of the San Antonio Hospital program were replicated at a national level, it would potentially result in approximately 2000 additional live donor transplantations annually [38].

**Desensitization:** Patients waiting for a transplant may be highly immunized and many of them have DSAs detectable in the serum. The different desensitization protocols apply mostly to the DSAs-positive

patients with a cross-match complement dependent cytotoxicity (XM CDC) positive.

Most of the current protocols are a modification of the high dose Intravenous Immunoglobulin's (IVIG) protocol initiated at the Cedars-Sinai Medical Center or of the Plasmapheresis (PP) with low dose IVIG protocol as initiated at the John Hopkins Hospital [39].

Jordan et al. [40] initially gave high dose IVIG (2 g/kg) treatment to XM-CDC positive recipients and the patients received a kidney transplant when their XM became negative. Due to the high rate of acute ABMR, Vo et al. [41] decided to use alemtuzumab induction treatment and added rituximab to this protocol to decrease the acute rejection rates.

More recently Vo et al. [42] reported the 24-month outcomes of the aforementioned desensitization protocol, achieving a 2 years graft survival of 84% in 76 hyper immune XM positive recipients.

The other approach to desensitization consists of the use of PP and low dose anti Cytomegalovirus IVIG (CMV Ig). This approach was first adopted in 1998 at John Hopkins Hospital in XM-incompatible living donor kidney transplant candidates [43]. The patients received PP and CMV Ig at 100 mg/kg after each PP, along with tacrolimus and mycophenolate mofetil. In a recent study, Montgomery et al. successfully desensitized 211 DSA-positive recipients of living donor kidneys with PP and low dose IVIG [44].

A different approach is the use of peri-transplant Immunoabsorption (IA) instead of plasmapheresis. Bartel and colleagues, in 68 patients with deceased donors, used peri-transplant IA followed by post-transplant IA obtaining excellent transplant outcomes [45].

Overall, in the last 13 years almost 1000 patients with DSAs underwent kidney transplantation with different desensitization protocols. The patient and graft survival were 95% and 86%, respectively, at a 2-year median follow-up. The main problem is the high incidence of acute rejection rates and, in particular, of ABMR (28%) [46]. New drugs are aimed at reducing such high ABMR rates.

Stegall et al. [47] adding eculizumab treatment in the pre-post-transplant period in the DSAs-positive patients, achieved a 7.7% rate of post-transplant acute ABMR compared with the 41.2% rate in the control group. Notwithstanding, at 2 years after the transplantation the incidence of chronic ABMR was similar in the two groups. Chronic ABMR remains the major challenge in transplanting hyper immune patients.

A different option is the use of the proteasome inhibitor bortezomib. In pilot studies, bortezomib has been used in the desensitization protocols with encouraging results [48,49]. There is currently an ongoing a prospective iterative trial of proteasome inhibitor based desensitization [50]. The trial was approved by the International Review Board (IRB) and is being conducted under the aegis of FDA. The preliminary data suggest that bortezomib based desensitization regimens consisting of only two cycles (8 doses) can consistently reduce the immune-dominant HLA antibody levels, and multiple treatments with bortezomib (a two cycle regimen) can allow highly sensitized patients to undergo transplantation without IVIG use.

### Treatment of acute ABMR

Antibody mediated rejection in kidney recipients responds poorly to corticosteroids and anti-thymocyte agents alone, which are the standard treatments for acute cellular rejection.

The international guidelines do not define an evidence-based treatment for acute ABMR, and the Kidney Disease Improving Global Outcomes Guidelines (KDIGO) recommend the use of one or more of the following: corticosteroids, PP, IVIG, anti-CD20 antibodies or lymphocyte-depleting antibodies [51].

Two studies have reviewed the current approach to the treatment of acute ABMR [52] and the randomized controlled trials to treat acute ABMR [53].

While the literature suggests that plasmapheresis with or without low-dose IVIG and high dose IVIG alone, show evidence for the efficacy of the treatment of acute ABMR and could be considered as a Standard of Care (SOC), the treatment regimens have not been standardized or optimized.

Approaches vary with regards to the amount of replacement volume, type of replacement fluids, number of PP sessions, and the dose, timing and formulation of the IVIG used.

Other agents such as rituximab, bortezomib and eculizumab have sometimes been used in conjunction with the above mentioned therapies.

Rituximab is the most commonly used agent and two studies in particular evaluated rituximab as part of a combination treatment approach [54,55]. The latter study included 54 patients and compared a historical group treated with plasma exchange and IVIG with a later group receiving an additional single dose of 500 mg/m<sup>2</sup> rituximab. The use of rituximab was associated with a 90% 2-year graft survival, compared with 60% in the control group. Notwithstanding, the benefit of adding rituximab remains doubtful in light of all the published patient series.

Several case reports and series have been published regarding the use of bortezomib in the treatment of acute AMBR.

The largest series of 20 patients treated by bortezomib has been reported by Flechner et al. [56]. With this treatment regimen, a graft survival rate of 85% at 10 months post-transplant was achieved. The mean decrease of the dominant DSA in the Mean Fluorescence Index (MFI) values was 50%. However, the side effects of the treatment were considerable. One of the most recent studies compared 10 bortezomib treated patients with a historical group of 9 rituximab treated patients and achieved a graft survival of 60% with bortezomib compared with only 11% with rituximab at 18 months [57].

Taken together, these preliminary results for bortezomib in acute ABMR are promising, but carefully performed controlled studies will be necessary to prove its benefit.

In the setting of kidney transplantation, there is emerging, but still limited, evidence that eculizumab is efficient for the treatment acute ABMR [58]. Thus far there are only a few reports in the literature on the use of eculizumab in refractory acute ABMR [59,60].

One last option to salvage a graft with acute therapy-resistant ABMR is a rescue splenectomy, as has been reported by at least three groups [61-63]. Most patients underwent this operation before the advent of eculizumab and it may well be that in the future a splenectomy may be avoided by using eculizumab instead. A splenectomy is recommended only in resistant cases of acute ABMR in which bortezomib or eculizumab have already failed.

In summary the first step therapy for acute ABMR includes steroid pulses, antibody removal with PP or IA and IVIG. The second step

in patients with persistent allograft dysfunction includes the use of bortezomib and/or rituximab. The third step in resistant acute ABMR includes eculizumab and a rescue splenectomy.

## Conclusions

Acute ABMR is a severe complication of kidney transplantation, often occurring in recipients with preformed or de novo DSAs. This entity is now well identified due to new techniques for the identification of DSA in patient sera or to new techniques applied to renal biopsy samples. The mechanism of ABMR is an endothelial injury whether mediated by complement or not. Acute AMBR may occur early or even late after the transplantation; the latter case is generally ascribed to a reduction in immunosuppression or to non-compliance. The clinical manifestations often consist of a rapid decline of renal function. Treatment is difficult. The prevention by desensitization in sensitized patients is mandatory. When acute AMBR is identified, the classic anti T cell treatments have a poor efficacy. The removal of antibodies by PP or IA is mandatory. Such removal should be associated with an anti B-cell therapy. New immunosuppressants that act on B cells or plasma cells are aimed at achieving better results.

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