

# Current Issues in the Treatment of Chronic Antibody-Mediated Rejection in Kidney Transplantation

Byung Ha Chung<sup>1,2</sup>, Chul Woo Yang<sup>1,2</sup>

<sup>1</sup>Transplant Research Center, <sup>2</sup>Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Circulating alloantibodies are found in a substantial number of renal allograft recipients, and can induce chronic allograft injury, which is represented microscopically as transplant glomerulopathy and diffuse C4d deposition in peritubular capillaries (PTCs). Development of these injuries is significantly correlated with late allograft loss, and in this regard, it was included as a new disease entity named chronic antibody-mediated rejection (cAMR) in the updated Banff 05 classification. Usually, the prognosis of cAMR is poor and conventional immunosuppressants mainly targeting T cell-mediated immunity cannot prevent or reverse it. Therefore, some researchers have suggested that therapies directed at the humoral response may be required for the treatment of cAMR. Recently, some reports have suggested that the combined use of rituximab and intravenous immunoglobulin (IVIg) therapy may be useful for the treatment of cAMR. Our previous study also showed that rituximab and IVIg combination therapy effectively delayed the progression of cAMR. We administered rituximab and IVIg combination therapy to 18 biopsy-proven cAMR patients and found that it significantly slowed the decline of the estimated glomerular filtration rate. However, this effect was limited in patients with heavy proteinuria, and dissipated in all patients by 1 year post-treatment. Recently, new drugs targeting the humoral immune system, such as bortezomib and eculizumab, have been tested for the treatment of cAMR. However, the studies still lack definitive data in terms of successful treatment of cAMR. We speculate that those therapies will compensate for the limitation of previous anti-humoral therapies for cAMR.

**Key Words:** Kidney Transplantation; Chronic Rejection; Donor-Specific Antibodies; Pathology; Therapeutics

## INTRODUCTION

Chronic antibody-mediated rejection (cAMR), one of the main causes of late allograft loss, was suggested as a new disease entity for the first time in 2001 [1]. This study showed that a significant proportion of chronic rejection cases are mediated by alloantibodies, and C4d positivity can separate these cases from non-specific chronic allograft nephropathy [2]. Another study reported that complement activation in renal microvasculature may result in C4d deposition, characterized by typical features such as chronic transplant arteriopathy, glomerulopathy, and basement multilayering in peritubular capillaries (PTCs) [3]. Since then, several stud-

ies have suggested that alloantibody-induced chronic renal allograft injury should be distinguished from chronic T cell-mediated rejection [4-6]. Therefore, the updated Banff 2005 classification added cAMR as a category of antibody-mediated rejection (AMR) [4, 7,8]. Recently, this disease—initially identified as non-specific chronic rejection—has received increased attention as a major contributor of graft failure cases, and conventional immunosuppressants have been rendered unsuitable to prevent or reverse cAMR [2,9]. In this review, we introduce the clinical significance of cAMR and discuss the current issues in the treatment of this disease.

Correspondence to: Chul Woo Yang  
Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-040, Korea  
Tel: +82-2-2258-6037  
Fax: +82-2-536-0323  
E-mail: yangch@catholic.ac.kr

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## DIAGNOSIS AND HISTOLOGIC FINDINGS OF CHRONIC ANTIBODY MEDIATED REJECTION

The detailed mechanism for the development of cAMR has not been fully investigated; however, some studies suggest that antibody-mediated injury is the main pathogenic mechanism [10-12]. For example, biopsy-confirmed chronic rejection was preceded by the detection of *de novo* alloantibodies in the majority of cases [13]. In addition, circulating alloantibodies are found in a substantial number of renal allograft recipients with long-term follow up, and significantly correlated with the development of late graft loss [10, 14,15]. Histologically, chronic allograft injuries due to alloantibodies manifest as transplant glomerulopathy, peritubular capillary basement membrane multilayering on electron microscope, and antibody interaction with vascular endothelium was shown as diffuse C4d deposition in PTCs, or microvascular inflammation (g + ptc score) [5,9,16,17].

Based on the evidence provided above, and the updated Banff classification, the diagnosis of cAMR is based on the following findings: (1) transplant glomerulopathy and severe PTC basement membrane multilayering, interstitial fibrosis, and tubular atrophy with or without PTC loss, along with fibrous intimal thickening in arteries without internal elastica duplication; and (2) diffuse C4d deposition in PTCs or moderate microvascular inflammation (g + ptc  $\geq$  2) or increased expression of gene transcript indicative of endothelial injury; and (3) presence of anti-human leukocyte antigen donor-specific antibodies (HLA-DSA) [7,17,18].

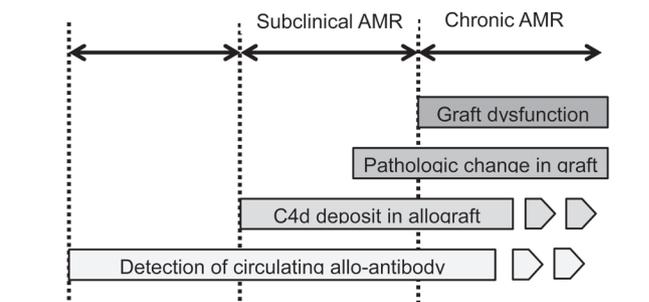
## RISK FACTORS AND CLINICAL COURSE OF CHRONIC ANTIBODY MEDIATED REJECTION

As mentioned above, development of cAMR is mediated by the activation of the humoral immune system; hence, the presence of HLA-DSA may be significantly associated with the development of cAMR. Indeed, the incidence of cAMR in patients with a positive crossmatch before kidney transplantation (KT) was 22% at 1-year posttransplantation. However, in ABO incompatible KT or conventional KT with low immunologic risk, the incidence was only 13% and 8%, respectively [19]. In another report, the rate of cAMR was nearly 50% in patients with a low titer of HLA-DSA who were not desensitized before KT. On the other hand, desensitization using rituximab and plasmapheresis effectively prevented the development of cAMR [20,21].

In different to acute antibody mediated rejection, which is characterized by abrupt deterioration of allograft function, cAMR showed indolent course characterized by gradual decline of allograft function over the years [22]. The typical clinical course of cAMR is presented in Fig. 1. The initial step is accommodation, in which circulating alloantibodies do not attack the allograft tissue. This is followed by subclinical AMR, in which allograft tissue injury progresses but its function is not compromised, and finally, overt cAMR with graft dysfunction [23]. Considering the clinical course, cAMR is usually detected 1 year after transplantation, and is characterized by a slow progressive loss of graft function, accompanied by proteinuria of various ranges [1,22,24]. Majority of studies suggest that the prognosis of cAMR is unfavorable [9,25]. For example, when transplant glomerulopathy, which is the hallmark of cAMR, is detected using protocol biopsies, nearly 50% of patients return to dialysis within 5 years. However, due to the heterogeneity of histologic findings in cAMR, no convincing data exist regarding the outcome of cAMR, with a diagnosis based on the Banff criteria. A well-designed prospective trial would be required to determine this issue.

## PROPOSED TREATMENT STRATEGY

As mentioned above, the mechanism of cAMR has not been fully elucidated; hence, an established treatment guideline does not exist [2,7,8]. The use of tacrolimus and mycophenolate mofetil rescue therapy in cAMR does not show significant improvement in allograft function, which means that a conventional immuno-



**Fig. 1.** Stages of chronic antibody mediated rejection. The first stage is accommodation, in which circulating alloantibodies do not attack allograft tissue. This is followed by subclinical AMR in which allograft tissue injury progresses but its function is not compromised. Finally, overt chronic antibody-mediated rejection with graft dysfunction develops and progresses to graft failure. AMR, antibody-mediated rejection.

suppressant regimen cannot prevent or reverse it [3]. Some researchers have proposed that therapies directed at the humoral immune response may be required to successfully treat cAMR, since antibody-mediated tissue injury, rather than T-cell mediated immunity, is associated with its development [21,22]. Thus far, several drugs have been introduced to suppress the various steps of humoral immune reactions, and several studies that apply these drugs for the treatment of cAMR are on-going (Fig. 2) [12,23,26].

## RITUXIMAB

Rituximab is a chimeric anti-CD20 monoclonal antibody that can induce antibody-dependent cell-mediated cytotoxicity, complement-dependent cell killing, and induction of apoptotic cell death, especially in B cells [27,28]. Initially, it was used in hematology for the treatment of malignant lymphoma or leukemia, but it was introduced in kidney transplantation because of its suppressive effect on humoral immunity [27]. Indeed, the use of rituximab in the introductory period effectively reduces the rate of cAMR after KT. For example, in ABO compatible KT, the rate of cAMR was 28.9% 2 years after KT, but it only 3.5% in patients undergoing KT from an ABO incompatible donor with a desensitization protocol that included rituximab [29]. In another study that suggests the therapeutic effect of rituximab on cAMR, the allograft survival rate after the diagnosis of cAMR was superior in the rituximab

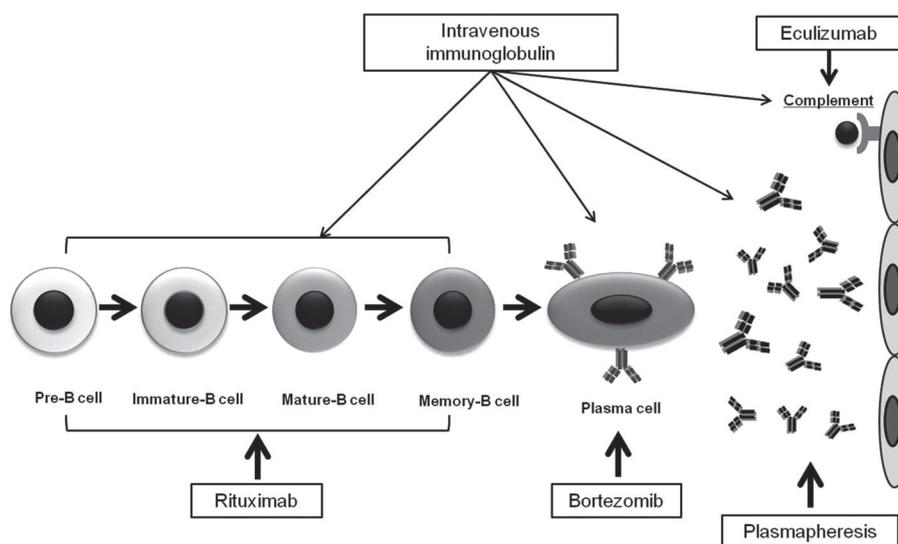
treatment group than in the control group [30]. All the above findings suggest that rituximab could be a relevant treatment option for cAMR.

## INTRAVENOUS IMMUNOGLOBULIN

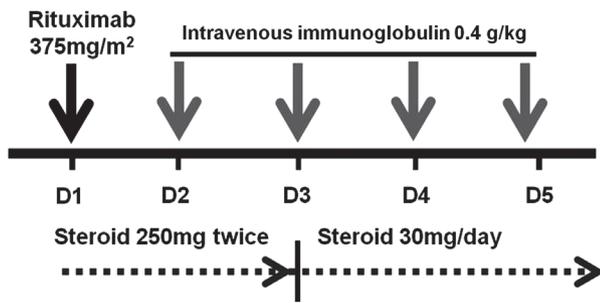
Intravenous immunoglobulin (IVIg) is known to have powerful and multiple immunomodulatory effects [31,32]. The exact mechanism of IVIg has not been elucidated, but it can suppress immunoglobulin synthesis, has anti-idiotypic activity against DSA with resultant neutralization of HLA-DSA, blocks the Fc receptor, inhibits complement activation, and has anti-cytokine activity [32]. In KT, a high dose of IVIg (2 g/kg) administered to highly sensitized patients significantly reduces the frequency of allosensitization and acute rejection episodes, resulting in improved long-term outcomes [33,34]. However, in spite of the proven efficacy of IVIg, its use is not completely effective in some patients, and the effect is not predictable in most cases. Hence, combination therapy with rituximab, rather than IVIg alone, has been evaluated for the treatment of cAMR as described below.

## RITUXIMAB/IVIg COMBINATION THERAPY CLINICAL TRIALS

In recent years, rituximab and IVIg combination therapy (RIT)



**Fig. 2.** Effect of drugs used for antibody-mediated rejection. Plasmapheresis removes circulating alloantibodies. Rituximab depletes B cells of all stages, and bortezomib directly suppresses antibody-producing plasma cells. Intravenous immunoglobulin can modulate various immune reactions through multiple mechanisms. Eculizumab inhibits the terminal complement pathway.



**Fig. 3.** Rituximab/intravenous immunoglobulin combination therapy protocol for chronic antibody-mediated rejection. On the first day, rituximab (375 mg/m<sup>2</sup>) was administered followed by intravenous immunoglobulin (0.4 g/kg) for 4 days. Concomitantly, 250 mg of methylprednisolone was administered twice a day, intravenously, for a period of 3 days, followed by oral prednisolone.

has been tested in patients with cAMR. Improved allograft function was observed after treatment, and hence, it is now accepted as the only treatment option with reported benefits [28,35,36]. At first, RIT was tested in 6 pediatric renal transplant recipients. They received 4 weekly doses of IVIg (1 g/[kg·dose]), followed by a single dose of rituximab (375 mg/m<sup>2</sup> body surface area) 1 week after the last IVIg infusion. Following treatment, allograft function improved or stabilized in 4 out of 6 recipients [28]. In a prospective study with a 2-year follow-up, this therapy significantly reduced or stabilized the progressive loss of transplant function in pediatric patients [35]. In adult patients with cAMR, RIT also showed similar effects in the improvement of allograft function in patients with cAMR [36].

Our previous reports also demonstrated that RIT effectively delayed cAMR progression. We administered rituximab (375 mg/m<sup>2</sup>) followed by IVIg (0.4 g/kg) for 4 days (Fig. 3). In our preliminary study with 6 patients, allograft function improved or was stabilized in 3 patients who showed relatively early stage cAMR [24]. In a larger study group (n=18) with longer follow-up duration, the response rate to RIT was 66.7% (12/18), with a significant decrease in the decline rate of estimated glomerular filtration rate (eGFR) in the 6 months after RIT, compared to the rate observed 6 months before RIT. Clinical and histological features between the 12 responders and the 6 non-responders were not significantly different. However, non-responders had significantly higher proteinuria levels during RIT, which suggests that the proteinuria level may be an important prognostic factor for the response to RIT [37].

## LIMITATIONS OF THE RITUXIMAB/IVIG COMBINATION THERAPY

Despite the proven effect of RIT in delaying the progression of cAMR, it showed some limitations. First, RIT was not completely effective in all cases of cAMR, and its effect was limited in patients with advanced allograft tissue injury or high-grade proteinuria [28,37]. This suggests that RIT may reverse the progression of earlier stage cAMR, but it cannot reverse advanced stage cAMR, which is characterized by advanced fibrotic changes in the allograft tissue. Second, in the long-term follow-up, the therapeutic effect of RIT showed a decreasing trend with time, especially at 1 year after RIT initiation. In our previous study, 4 patients with a follow-up duration > 2 years were included, and a time-dependent decrease in eGFR was detected. Accordingly, repeated RIT therapy or other additional strategies for humoral immunity may be necessary to prolong the therapeutic effect [38-40]. Third, it is uncertain whether RIT promotes renal allograft survival, because the majority of previous studies were single-arm studies, which only investigate the change in clinical parameters that indicate allograft function before and after treatment. A randomized prospective trial may be required to prove its efficacy.

## BORTEZOMIB-BASED THERAPY

Bortezomib is a proteasome inhibitor that has a suppressive effect on antibody production by plasma cells, stimulates apoptosis of this cell type, and decreases the number of bone marrow-derived plasma cells [41]. Initially, it was approved for the treatment of multiple myeloma by the Food and Drug Administration and has now been introduced for use in KT and it is expected to show a stronger suppressive effect on humoral immunity than rituximab [42,43]. In an animal model, bortezomib effectively ameliorated glomerular, tubulointerstitial, and vascular changes of cAMR via the inhibition of antibody-producing cells [44]. In the clinical setting, very few patients have received bortezomib as a rescue treatment for cAMR, producing inconsistent results. Hence, the therapeutic effect of this drug has not yet been proven [45]. A randomized controlled trial to investigate the effects of bortezomib on cAMR (known as the BORJECT study) is now in progress, which can help determine the effectiveness of this drug (NCT01873157).

## UPCOMING TREATMENT STRATEGY- ECULIZUMAB

One promising agent for the treatment of cAMR is eculizumab. This agent inhibits the cleavage of C5 into C5a and C5b, thereby preventing the formation of the membrane attack complex [46]. Eculizumab has been approved for the treatment of paroxysmal nocturnal hemoglobinuria by the Food and Drug Administration; however, recent data also shows that eculizumab effectively suppresses humoral immune responses in KT. For example, post-transplant use of eculizumab significantly decreases the development of acute AMR as well as transplant glomerulopathy at 1 year following KT [12]. In regards to cAMR treatment, a prospective study is in progress and actively enrolling candidates [47].

## MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are of interest in transplantation owing to their potential immune-modulating effect [48]. This therapeutic potential is mediated by multiple mechanisms through the secretion of regulatory cytokines, activation of regulatory immune cells, and the capacity to increase cellular repair through the secretion of anti-apoptotic, anti-fibrotic, and pro-angiogenic factors [49]. The multiple functions of MSCs may lead to multifaceted strategies in various organs and diseases, including KT [50,51]. Indeed, in a trial that included 159 patients undergoing renal transplantation, the use of autologous MSCs, compared with anti-interleukin-2 receptor antibody induction therapy, resulted in lower incidence of acute rejection [52]. Additionally, a study involving KT recipients, evaluating the effect of MSCs in chronic allograft nephropathy, has been registered by the Uzhou Institute of China.

## CONCLUSION

Development of cAMR is a substantial obstacle to long-term allograft outcome. In the past decades, various therapeutic options such as RIT have been investigated, but has showed many limitations. Recently, several new therapeutic approaches, which can effectively suppress humoral immunity, such as bortezomib and eculizumab, have emerged. Extensive studies and longer follow-up may be needed to determine if these apparent advances will improve the outcome of cAMR.

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