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EDITORIAL

Impact of donor-specific antibodies on the outcomes of kidney graft: Pathophysiology, clinical, therapy

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Abstract

Allo-antibodies, particularly when donor specific, are one of the most important factors that cause both early and late graft dysfunction. The authors review the current state of the art concerning this important issue in renal transplantation. Many antibodies have been recognized as mediators of renal injury. In particular donor-specific-Human Leukocyte Antigens antibodies appear to play a major role. New techniques, such as solid phase techniques and Luminex, have revealed these antibodies from patient sera. Other new techniques have uncovered alloantibodies and signs of complement activation in renal biopsy specimens. It has been acknowledged that the old concept of chronic renal injury caused by calcineurine inhibitors toxicity should be replaced in many cases by alloantibodies acting against the graft. In addition, the number of patients on waiting lists with preformed anti-human leukocyte antigens (HLA) antibodies is increasing, primarily from patients with a history of renal transplant failure already been sensitized. We should distinguish early and late acute antibody-mediated rejection from chronic antibody-mediated rejection. The latter often manifets late during the course of the post-transplant period and may be difficult to recognize if specific techniques are not applied. Different therapeutic strategies are used to control antibody-induced damage. These strategies may be applied prior to transplantation or, in the case of acute antibody-mediated rejection, after transplantation. Many new drugs are appearing at the horizon; however, these drugs are far from the clinic because they are in phase Ⅰ-Ⅱ of clinical trials. Thus the pipeline for the near future appears almost empty.

Key words: Donor-specific antibodies; Solid-phase techniques; Complement activation; Renal transplantation; Antibody-mediated rejection; Desensitization; New drugs for B-cells

Core tip: Clear evidence exists that shows that donor-specific-HLA antibodies (DSAs) are the primary players in the acute and chronic deterioration of graft. The emergence of sensitive techniques that detect DSAs, together with advances in the assessment of graft pathology, has enabled an improved understanding of antibody-mediated graft injury. Acute and chronic antibody-mediated rejection conditions have changed the nomenclature during recent Banff conferences and have enabled the dismissal of older terminologies, such as chronic allograft nephropathy. Therapies aimed at B cells and plasma cells and that control complement activation will be extremely important for improving long-term outcomes in kidney transplantations.

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INTRODUCTION

Despite improvements in renal transplantation outcomes,

kidney allograft loss remains substantial and is associated with increased morbidity, mortality and costs[1,2]. Clearly, the identification of the critical pathologic pathways underlying allograft loss and the development of therapeutic interventions that improve the duration and quality of allograft function are among the most important targets for transplant medicine. One of the most important advances of the past decade has been the realization that the insufficient control of the humoral arm of a recipient's immune system by current immunosuppressive regimens[3] is the factor primarily responsible for allograft dysfunction and loss[4-6].

ALLOGRAFT ANTIBODY EVOLUTION IN TRANSPLANTATION

The induction of allograft injury alloantibodies induced has now superseded the historical dogma that allograft losses were caused by the toxicity of calcineurin inhibitors (CNIs) and by chronic allograft nephropathy (CAN). Indeed, nephrotoxicity and CAN as causes of late graft failure are being challenged by the findings of the Long-Term Deterioration of Kidney Allograft Function (DeKAF)[6-8] and other studies[9,10].

In addition, recent therapeutic strategies that have permitted the human leukocyte antigens (HLA) to be crossed have created a new population at risk of antibody-mediated rejection (ABMR), which has enabled these patients to be studied over an extended time period.

The emergence of sensitive techniques that 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 ABMR.

The different technologies used by researchers and the significance of alloantibodies found by these technologies led recently to a consensus conference that elaborated upon consensus guidelines for testing and clinical management issues associated with HLA and non-HLA antibodies in transplant recipients[11].

As a consequence of this increase in knowledge, the term CAN was deleted in the Banff'05 meeting report[12]. In the Banff'07 and Banff'09 conferences[13,14], the concept of ABMR was further evaluated, and ABMR was definitively included in the Banff classifications.

The Banff'11 meeting report[15] and the recent Banff'13 conference (unpublished data) further elaborated upon new concepts in ABMR, which included the significance of C4d-negative and C1q-positive ABMR.

DETECTION OF ANTIBODIES AND THEIR SIGNIFICANCE

Preformed antibodies targeted against HLAs or antibodies formed *de novo* after transplantation predispose to either acute or chronic ABMR. These antibodies can be detected using several techniques.

A complement-dependent lymphocytotoxicity (CDC) cross-match is typically performed to detect cytotoxic DSAs. The main disadvantages of the CDC assay are that it is subjective and cumbersome and will only detect complement-fixing antibodies[16]. Indeed, ABMR has occurred in patients with a negative cross-match. This observation may indicate that the CDC lacks the sensitivity required to detect some clinically significant antibodies; moreover, acute ABMR can occur in recipients with immunological memory and undetectable levels of circulating HLA antibodies at the time of transplant[17]. Cross-match (XM) and antibody detection techniques have improved with time and show increased sensitivity and specificity[18,19].

Flow cytometry (FC) is another cell-based technique that was introduced more than 20 years ago to improve sensitivity. This test also lacks specificity, and with the introduction of solid-phase assays (SPA), the use of FC has been superseded. The introduction of SPA detection, while providing greater sensitivity than CDC assays, has resulted in a new paradigm with respect to the interpretation of DSAs. Although SPA using the Luminex instrument has permitted the detection of antibodies not detectable by CDC, the clinical significance of these antibodies is not fully understood. In addition, SPA testing raises technical issues that require resolution and careful consideration when interpreting antibody results. SPA, such as flow cytometry using antigen-coated micro particles, enzyme-linked immunosorbent assays (ELISAs) and Luminex, are now used to determine the specificity of anti-HLA antibodies and to better interpret positive CDC-XM results.

ELISA has an advantage over the CDC because is more sensitive and detects antibodies that not fix complement. However, non-specific binding to other immunoglobulins may occur in patients with autoimmune disorders. When detecting antibodies using flow panel-reactive antibody (PRA) beads, micro-particles are coated with purified HLA molecules[19]. The fluorescence is then measured using flow cytometry and the level of fluorescence is indicative of the level of antibody binding.

Luminex technology also uses pools of HLA class Ⅰ or Ⅱ antigen-coated micro-particles. These beads are colored with a combination of two dyes. Serum reactivity is assessed based on the fluorescent signal of each HLA-coated micro particle[19]. The Luminex platform enables the determination of DSAs specificity by using single HLA-coated beads and provides a relative indication of the antibody strength and level in the circulation by returning results to the user in the form of mean fluorescence intensity (MFI)[20]. However, MFI is not standardized across labs, and there is some arbitrariness in determining the MFI thresholds. Molecules with equivalent soluble fluorochrome (MESF) and maximum fluorescence values, obtained using the Luminex machine, enable more standardized measures of antibody strength[21,22].

According to the consensus publication by the National Conference to Assess Antibody-Mediated Rejection in Solid Organ Transplantation[23], a current positive CDC or anti-human immunoglobulin-CDC (CDC-AHG)

Table 1 Technological advantages and limitations of luminex human leukocyte antigens single antigen bead

Technological advantages	Technological limitations
Qualitative: enables precise identification of all antibody specificities in complex sera (DSA)	Some positive results can be caused by antibodies to denatured HLA
Comprehensive: distinguishes antibodies to all common alleles for HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQA1, HLA-DQB1, HLA-DPA1, HLA-DPB1	Occasional high background binding requiring repeat testing and absorption protocols
Semiquantitative: enables determination of antibody levels (high, intermediate, and low)	Variable HLA protein density on beads. Blocking factors may cause false-negative or misleading low assessment of antibody levels (prozone?); IgM and C1 can block IgG binding
Sensitive: enables detection of weak antibody testing	
Rapid: enables real-time antibody monitoring for DSA. Pre-transplantation and post-transplantation antibody monitoring (assist diagnosis of ABMR). Virtual XM	Lot-to-lot variation requiring validation. Vendor-specific variation
Enables detection of non-HLA-specific antibodies (*e.g.*, MICA)	
Detection and differentiation between immunoglobulin class and isotype (*e.g.*, complement fixing and non-complement fixing C4d and C1q	Reagents not standardized

ABMR: Antibody mediated rejection; DSA: Donor specific HLA antibodies; HLA: Human leukocyte antigens; MICA: Major histocompatibility complex class I-related chain A; SAB: Single-antigen beads; XM: Cross-match.

cytotoxicity cross-match (CXM) predisposes to a high risk of ABMR or early graft loss. A current positive CDC or CDC-AHG CXM is a contraindication for transplantation unless DSAs can be reduced using desensitization protocols. A positive flow CXM or a remote (historic) positive CDC or CDC-AHG CXM poses an intermediate risk for early acute rejection and may require augmented immunosuppression.

The wide use of the Luminex technique with its increased specificity and sensitivity did uncover a new paradigm. Using the Luminex technique DSAs have been found in patients who show a negative classic CDC. Several studies have shown that these results represent a risk factor, but not a formal contraindication for transplantation[24-26].

These facts lead to workshops and Consensus Guidelines to further understand these technologies[11,27].

The recent consensus guidelines highlighted the technological advantages and limitations of Luminex as shown in Table 1.

In addition, the consensus guidelines[11] considered the following modifications to SPA for detecting new antibodies and assessing their functionality.

C4d assay

The C4d assay[28,29] shows superior specificity compared with the CDC. The C4d assay requires complement activation to occur and is influenced by complement regulatory factors. Clinical data obtained using various modifications of the C4d assay have shown that the presence of C4d+ antibodies correlates with graft survival in the kidney and hearts[28,29].

C1q assay

The C1q assay was designed to distinguish complement-fixing from non-complement-fixing antibodies and does not require complement activation other than the binding of C1q to the antibody[30]. It detects antibodies capable of binding complement and initiating the classical pathway.

The results of this technique still remain under debate. Although some authors[31] have reported no correlation with the clinical course in kidney transplant patients, others[32] have reported that both C1q and C4d Luminex assays show increased sensitivity and specificity and that they can be useful for both pre-transplant risk assessment and post-transplant monitoring.

Detection of antibodies targeted to non-HLA antigens

The endothelial cell is the principal target used to detect non-HLA antibodies involved in ABMR. Historically, different assay systems have been used to identify and characterize AECA including CDC[33], flow cytometry[34] and immunofluorescence[35].

The primary limitation is that the endothelial cells used for the detection and characterization of AECA have been derived from third-party donors, and that the cells used show different protein expressions and distinct phenotypes[36]. Surrogates of endothelial cells, such as MICA may be useful. However, MICA is not expressed constitutively on the endothelium; rather, its expression is induced under conditions of cellular stress.

Lymphocyte XM tests fail to detect AECA. The cross-match ONE assay is a Food and Drug Administration (FDA)-approved endothelial ECXM technique that uses endothelial cell precursor cells found in the peripheral blood at a frequency of 1%-2%[37]. An advantage of this test is that it detects DSAs and can be used to test for antibodies targeted to T lymphocytes, B lymphocytes and endothelial cells in the same assay[38].

Proteomics approaches using protein extracts from different sources, including cell lysates and protein microarrays are being used for antibody screening and identification of specificities[39,40].

A variety of non-HLA targets have been identified including MICA, vimentin, angiotensin Ⅱ type 1 receptor, tubulin, myosin and collagen Ⅴ. In general, single antigen bead (SAB) testing permits reassessment of the im-

munologic risk for kidney transplantation. Traditionally, high panel-reactive antibody, re-transplant and deceased donor grafts have been associated with increased risk. However, the risk factors for ABMR are DSAs, reduced HLA matching and evaluation of DSAs using different techniques[41].

PATHOPHYSIOLOGY

An increasing body of evidence suggests that patients with high titers of anti-HLA antibodies (particularly if they are donor-specific) that develop either pre-transplant or post-transplant, show a worse outcome. At any given time, approximately 25% of transplant recipients show antibodies against HLA antigens when evaluated using the newest, highly sensitive and specific techniques for DSAs monitoring[42,43]. Moreover, antibodies against non-HLA have also been implicated in ABMR[44]. Antibodies may mediate endothelial injury *via* complement-dependent or independent mechanisms by transducing signals that are pro-inflammatory and proliferative[45].

Preformed or *de novo* DSAs clearly cause acute and chronic ABMR; however the role and scope of non-HLA antibodies in mediating graft injury and loss remains less certain[46].

One hypothesis is that alloantigen sensitization occurs based on non-HLA polymorphic differences between the donor and the recipient [*e.g.*, major-histocompatibility-complex (MHC) class I -related chains A and B (MICA and MICB, respectively)]. Unfortunately progress in this area has been limited by a lack of validated clinical assays for non-HLA alloantibodies, the confounding presence of HLA-DSAs and, in the case of MICA antibodies, a lack of proof of specificity[47].

A second hypothesis is that auto antigen sensitization occurs due to exposure of cryptic epitopes after tissue injury or inflammation (including vimentin, K-α I tubulin, collagen V and agrin).

Although anti-HLA antibodies are responsible for the majority of antibody-mediated injuries, they do not underlie all ABMRs. In addition, as discussed above, the major histocompatibility antigens and a large number of minor antigens have been recognized as possible antibody targets[48-50].

Endothelial cells are targets for immune-mediated assaults *via* anti-endothelial cell antibodies (AECAs). The *de novo* development of circulating anti-endothelial cell antibodies, rather than pre-existing antibodies, is associated with post-transplant allograft rejection[51].

Apoptotic endothelial cells (ECs) release a bioactive C-terminal fragment of perlecan called laminin G-like 3 (LG3)[52]. LG3 behaves as a neo-antigen and induces the production of anti-LG-3 antibodies. Recently, these anti LG-3 antibodies have been documented to be novel accelerators of immune-mediated vascular injury and to obliterate remodeling[53].

Vimentin[54], collagen V[55] and K-α 1 tubulin[56] are involved in the ABMR of organ other than kidney as neo-antigens. The apoptosis of ECs and subsequent exposure of neo-antigens may induce an autoimmune response.

An autoantibody specific for angiotensin Ⅱ receptor type 1 has been associated with the development of hypertensive vasculopathy and acute renal allograft dysfunction[57]. Antibodies directed towards MHC class I polypeptide-related sequences A (MICA) and B (MICB), and not classical HLA molecules, have been implicated in transplant rejection in recipients who were otherwise well-matched for HLA due to the contribution of MICA antigens towards the activation of cellular and humoral immune responses[58].

The HLA complex encodes molecules crucial for the initiation and proliferation of the immune response. It is highly polymorphic and polygenic and its proteins are co-dominantly expressed. The *HLA* genes that are involved in the immune response belong to classes I and Ⅱ, which are structurally and functionally different. Recently, DSAs have been reported to activate endothelial cells, thereby increasing their potential to recruit and bind recipient leukocytes and increasing the potential for allograft inflammation[59,60].

Approximately 30% of patients on waiting list show detectable levels of HLA antibodies[61]. After transplantation, 25% of non-sensitized patients develop *de novo* HLA-DSAs.

In both groups of patients, the presence of these antibodies increases the risk of subsequent ABMR[9]. The development of a histological test to identify antibody-mediated complement activation on transplant biopsies (C4d staining) has provided a method for flagging potentially deleterious interactions between antibodies and the graft endothelium. In addition, molecular techniques, such as gene expression profiling, have enabled the identification of subclinical endothelial cell damage that can be present even in the absence of complement activation or detectable DSA[62]. Recent studies have documented the role of B cells and antibodies in transplantation. A study by Lynch *et al*[63] described a technique that may enable a more global assessment of B-cell reactivity to the allograft. Their results suggest that humoral responses to the allograft may be more common than previously appreciated. Antibodies reactive to donor human leukocyte antigen molecules, minor histocompatibility antigens, endothelial cells, red blood cells or auto antigens may trigger or contribute to rejection at both early and late time points after transplantation[64]. Often, the immune system shows an integrated response that results in allograft rejection involving parallel or simultaneous T cell mediated rejection (TCMR) and ABMR[65]. Antibody-mediated injury to the allograft is initiated by DSAs binding to HLA antigens or to other targets on the allograft endothelium. If DSAs are complement-activating, the classic complement pathway is rapidly activated *via* IgG binding and C1q activation[66]. This process typically results in the rapid loss of the allograft. Alternatively, DSAs can bind endothelial cell targets and stimulate cell proliferation or induce antibody-dependent cell-mediated cyto-toxicity with interferon γ release[45]. These processes appear to be more important for the development of the chronic

antibody-mediated injury that is more dependent on natural killer (NK) cells than the complement[67]. Antibodies may also bind HLA and other targets and incompletely activate the complement system without causing apparent injury. This process is referred to as accommodation[68].

ABMR is a continuous process, and its oscillation is characterized by fluctuations in DSAs, C4d deposition and dynamic and multidirectional glomerulitis and/or capillaritis scores[69]. The time to diagnosis of ABMR is highly dependent on the population studied. Early-onset ABMR (typically occurring within the first months after transplantation) is observed predominantly in patients with preformed DSAs, whereas late acute ABMR occurs primarily in patients who develop *de novo* DSAs after transplantation. Indeed, the pathologic and clinical manifestations may vary, including hyper-acute humoral rejection, acute humoral rejection, indolent or subclinical humoral rejection, "C4d"-negative humoral rejection and late acute humoral rejection.

ACUTE ABMR

Hyper-acute ABMR

The pathology of hyper-acute rejection overlaps completely with acute ABMR. It arises within minutes or a few hours after transplantation in pre-sensitized patients who have circulating HLA, AB0, or other alloantibodies to the donor endothelial surface antigens[70]. The outcome is always poor.

Acute ABMR

The diagnosis of acute ABMR relies upon the criteria shown: (1) morphologic evidence of acute tissue injury: acute tubular injury, neutrophils and/or mononuclear cells in PTC and/or glomeruli and/or capillary thrombosis, fibrinoid necrosis/intramural or trans-mural inflammation in arteries; (2) immuno-pathologic evidence for antibody action: C4d and/or (rarely) immunoglobulin in PTC; Ig and complement in arterial fibrinoid necrosis; and (3) serologic evidence of circulating antibodies to donor HLA or other anti-donor endothelial antigen. The endothelial injury has been recently reviewed completely by Drachenberg and colleagues[71]. Although acute ABMR generally occurs within the first year after transplantation in pre-sensitized patients[72], it may also develop years after transplantation and is often triggered by a decrease in immunosuppression (iatrogenic, non-compliance or malabsorption)[5,73-75].

Several patients with acute ABMR show a negative cross-match, which may be due to low level DSAs that are undetectable[76] or to *de novo* DSAs[77].

Recently, an increased risk of acute ABMR has been associated to elevated pre-transplantation soluble B-cell activating factor (BAFF)[78], whose neutralization may be an interesting therapeutic strategy.

Recently, Orandi *et al*[79] examined the long-term effect of early acute ABMR on kidney allograft and patient survival in 201 adult kidney transplant recipients who developed acute ABMR within the first year after transplantation. Each recipient was matched with 5 control patients. The majority of recipients were sensitized. Allograft survival rates at 1, 5 and 10 years in the group that developed acute ABMR were significantly lower than in the control group.

In another study[60] of a cohort of 355 adult kidney transplant recipients, all with a negative CDC-XM, C1q-fixing DSAs did not predict acute ABMR or allograft loss; however, the presence of class Ⅰ DSAs (versus class Ⅱ donor specific antigens) predicted acute ABMR and allograft loss.

Indolent or subclinical acute ABMR

Chronic rejection is often preceded by the occurrence of an acute ABMR due to the fact that modern therapeutic strategies fail to deplete antibody secreting plasma cells from the spleen and bone marrow of patients[80].

In addition, kidney transplant recipients who develop *de novo* DSAs are now recognized to often show pathologic features of indolent and slowly progressive microvascular abnormalities, which are referred referred to occasionally as subclinical acute ABMR[16,77,81]. The appearance of *de novo* DSAs likely results from inadequate immunosuppression and represents a dynamic process that begins early after transplantation and continues at varying levels thereafter.

C4d negative acute ABMR

Initial evidence for C4d-negative acute ABMR emerged in 2009 based on the work of the teams in Paris[69] and Edmonton[62]. The latter study demonstrated high endothelial-specific gene expression in kidney transplant biopsy samples with DSAs but without C4d. In this study, C4d-negative acute ABMR was characterized by the high intragraft endothelial gene expression of allo-antibodies, by histology typical of chronic or acute ABMR and by poor outcomes. Several hypotheses have been generated to explain the lack of complement deposition despite the evidence of micro-vascular inflammation and persistence of DSAs in the circulation. The low sensitivity of C4d[13,82] could be due to technical issues including the type of fixative used and the different methods used to detect C4d (immunofluorescence versus immunochemistry). Moreover, as documented by the Edmonton study, some DSAs, although showing poor complement-fixing ability, may nonetheless activate endothelial cells[62]. Another possibility is that the various prophylactic strategies used to prevent ABMR may decrease the burden of complement activation within capillaries[80].

Given the concerns over the lack of sensitivity of C4d for kidney transplantations, a working group was established at the 2011 Banff conference to refine the criteria used for diagnosis of ABMR in the kidney[15]. Although the 2013 Banff Conference, held in Fortaleza (Brazil) in August 2013, has ended, to the best of our knowledge, this work remains in progress.

Late acute ABMR

If the majority of early-acute ABMR depends upon pre-

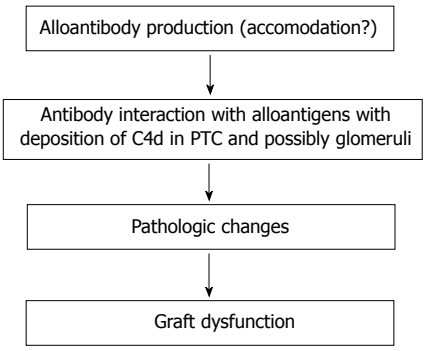

Figure 1 Stages of chronic antibody-mediated chronic rejection. PTC: Peritubular capillaries.

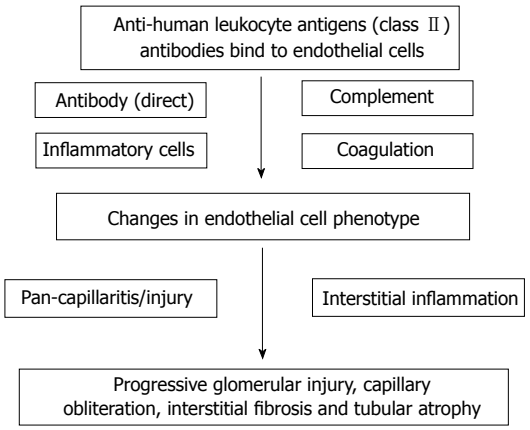

Figure 2 Proposed pathogenetic mechanisms for transplant glomerulopathy.

formed DSAs and primarily occurs in sensitized patients, late-acute ABMR often depends upon *de novo* DSAs.

De novo DSAs appear in 25% of non-sensitized patients[77]. *De novo* DSAs are often linked to late-acute ABMR and are characterized as occurring in patients who are young, with frequent non-adherence or suboptimal immunosuppression[74]. The observation that many cases of *de novo* DSAs are associated with prior therapy non-adherence or with a history of a clinical acute cellular rejection episode, suggests that immunosuppression is a potent inhibitor of the activation of mature, naïve B cells[83]. However, the observation that some cases of *de novo* DSAs formation appear in compliant patients suggests that either T cells capable of helping naïve B cells emerge despite immunosuppression or that some allo-reactive B cells may differentiate into antibody-secreting cells in the absence of T cell assistance. The antibody-producing cells may also originate from an existing population of memory B cells that do not require T-cell mediated activation[84].

CHRONIC ABMR

The clinical significance of chronic ABMR has been increasingly documented in recent years with some data suggesting that it may represent the leading cause of late allograft loss[4]. In contrast to acute ABMR, chronic ABMR is a long-term process that develops in sequential steps over a period of months to years[85]. Chronic ABMR has been proposed to arise over a series of stages or states[86]. The first common event is the production of alloantibodies followed by antibody interaction with alloantigens, resulting in the deposition of C4d in peritubular capillaries (PTC) and possibly glomeruli, followed by pathologic changes and graft dysfunction (Figure 1). Diagnostic features of chronic ABMR may include the presence of DSAs, transplant glomerulopathy (TG), peritubular capillary basement multilayering and the presence of C4d[27].

TG and PTC basement multilayering represent the histological hallmark of chronic ABMR. Transplant glomerulopathy is a morphological pattern of chronic kidney injury that lacks detectable immune-complex deposits and is associated with poor kidney transplant outcomes. It is primarily an endothelial pathology that affects kidney microcirculation endothelium, which is observed as a duplication (double contours) and/or multilamination of capillary basement membranes together with the substantial replacement of endothelial fenestrations with a continuous endothelial lining[87]. DSAs, particularly HLA antigen class Ⅱ antibodies may cause insidious graft injury and therefore constitute a central causative factor of transplant glomerulopathy (Figure 2). Although the international Banff consensus criteria classify transplant glomerulopathy as chronic ABMR if the pattern is accompanied by detectable DSAs and diffuse or focal linear C4d positivity in peritubular capillaries[4-6], Mauiyyedi *et al*[88] detected the deposition of C4d in peritubular capillaries in 61% of biopsies from patients showing chronic rejection with transplant glomerulopathy. In addition, a study by Regele *et al*[89] reported the presence of C4d in peritubular capillaries in 34% of patients with transplant glomerulopathy and this staining presaged the later development of transplant glomerulopathy.

Pathologic patterns of chronic ABMR are observed in renal biopsies performed either for clinical indications or for protocol at a much later date after kidney transplantation[5-83]. In addition to reduced immunosuppression and non-adherence, early acute rejection appears to play a relevant role during late chronic ABMR. Indeed, several years ago, Cosio *et al*[90] documented that in 1-year surveillance biopsies, the degree of inflammation at 1-year post-transplant predicts the loss of graft function and graft failure independently of function and other variables (Figure 3).

Recently El Ters *et al*[91] reported that early acute rejection, even in the absence of pre-transplant DSAs, increases the risk of alloimmune allograft loss late after transplantation and that the phenotype of this late loss is chronic ABMR. The hypothesis of this study was that the formation of new DSAs, particularly class Ⅱ DSAs, may be a consequence of early acute rejection[92]. El Ters *et al*[91] noted that the presence of inflammation in 1-year protocol biopsies correlated with early acute rejection, presensitization, re-transplantation and HLA mismatch. He also observed that chronic ABMR was responsible for 43% of allograft loss.

Table 2 Anti-antibodies main drugs to date in use and mechanism of action

Steps	Cells or mechanisms involved	Drugs	Mechanism of action
Exposure to antigen	B Cells	Rituximab	Binds CD20 on B cells and mediates cell lysis
		ivig	Multiple B cell apoptosis, decrease in B-cell proliferation
Secretion of alloantibodies	Plasma cells; antibodies	Bortezomib	Decrease donor-specific alloantibody production
			Mechanical removal of alloantibodies
		Plasma- exchange	Multiple B cell apoptosis, decrease in B-cell proliferation
		ivig	
Binding of antibodies to the graft	Complement activation	Eculizumab	Blocks cleavage of terminal complement C5 and halts the process of complement-mediated cell destruction

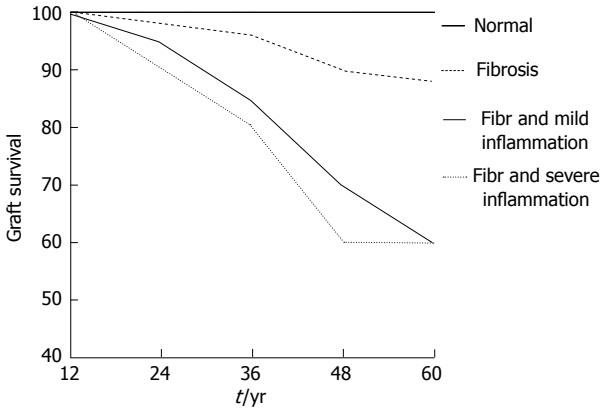

Figure 3 Five year post-transplant graft survival according 1-year post-transplant surveillance biopsy.

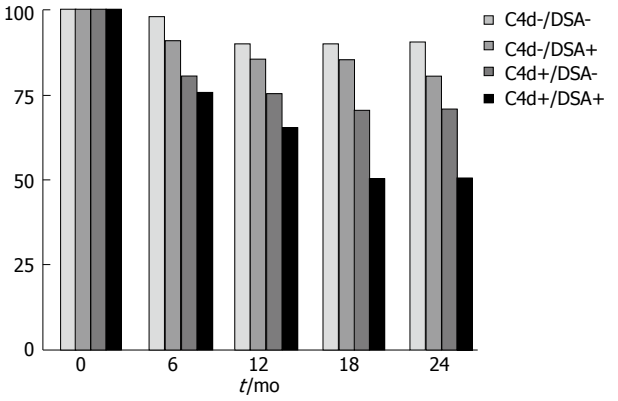

Figure 4 Deterioration of kidney allograft function study. Graft survival at 2-year according presence of donor-specific-HLA antibodies (DSAs) and/or C4d. HLA: Human leukocyte antigens.

In surveillance biopsies performed at 3 years after transplantation, Willicombe[93] reported that, despite excellent serum creatinine values, only one-third of biopsies were normal and that lesions appeared to correlate with the risks of immunological injury.

The 5-year follow-up data of the patient cohort from the DeKAF study[94,95] documented the role of antibodies in late graft dysfunction. Indeed, these studies showed a great number of patients with inflammation accompanying fibrosis or scarring, and their graft survival correlated with the presence of DSAs and/or C4d (Figure 4).

The therapeutic approach to these conditions is one of the major challenges to date in the treatment of transplanted patients.

Finally, recent studies[96,97] examining BAFF, a B-cell stimulating molecule, showed that the appearance of soluble BAFF levels early after transplantation correlated with the *de novo* development of DSAs and, ultimately, with the progression to chronic active ABMR in pediatric and adult first kidney transplant recipients who were highly desensitized prior to transplantation.

Hill *et al*[98] described a new insight into the pathogenesis of chronic ABMR. DSAs-positive patients showed a striking acceleration of arteriosclerosis. Pathologic examination revealed that the inner intima is hypercellular with actively proliferating myofibroblasts that lay down collagen that often overlies older, condensed collagen of pre-transplantation donor origin.

THERAPY

The primary drugs or systems used are shown in Table 2 and are divided based on their action on the different maturation steps of B cells. The primary therapeutic strategies used are the following: (1) removal of antibodies; (2) inhibition of antibody production; (3) complement inhibitors; (4) intravenous immunoglobulins; and (5) splenectomy.

Removal of antibodies by plasmapheresis or immunoabsorption

Plasmapheresis (PP) and immunoabsorption (IA) techniques have been used to remove alloantibodies. PP is not specific for immunoglobulins (Ig) removal and requires replacement with fresh frozen plasma and albumin. IA shows high affinity for binding Igs and has the advantage of specificity over PP.

However, due to the tendency of DSAs to rebound and return to baseline levels, several repeated treatments are required[99] or an additional inhibitor of antibody production is required.

Inhibition of antibody production

Rituximab (anti-CD20): Rituximab is a chimeric murine/human monoclonal antibody that binds CD20 on pre B and mature B lymphocytes[100,101]. Recently rituximab has been documented to also prevent an anamnestic

response in patients with cryptic sensitization to HLA[102].

BAFF blockade: BAFF, also known as B lymphocyte stimulator (Blys), is a member of the tumor necrosis factor cytokine family and is expressed primarily on T cells and dendritic cells for B-cell co-stimulation. BAFF binds to the receptor B-cell maturation antigen (BCMA), to the transmembrane activator (TACI) and to BAFF-receptor (BAFF-R) for B cell survival, proliferation and maturation[103].

BAFF blockade is a possible future therapy for renal transplantation. These drugs are highly promising because they selectively target B cells. Nevertheless no clinical trial is active in the field of transplantation although, these drugs have either been approved or are being examined for other diseases in large studies.

The best BAFF blockade drug is belimumab, which is a fully human recombinant IgG monoclonal antibody targeted against BAFF[104].

Bortezomib: Bortezomib is a proteasome inhibitor that is primarily used to treat acute ABMR or to decrease *de novo* DSA levels post-transplantation[105,106]. In further pilot studies, the authors used bortezomib in desensitization protocols with encouraging results[107,108].

Complement inhibitors

Eculizumab: Eculizumab is a humanized monoclonal antibody targeted against complement protein C5 that binds the C5 protein with high affinity and inhibits its cleavage to C5a and C5b, thereby preventing the generation of the terminal complement complex C5b-9. Eculizumab is used for the treatment of paroxysmal nocturnal hemoglobinuria and for atypical hemolytic uremic syndrome. Stegall *et al*[109] documented a decrease in post-transplant acute ABMR in sensitized renal transplant recipients, indicating its usefulness for desensitization protocols. Case reports have documented the effective rescue treatment of severe complement activation and reversal of acute ABMR by eculizumab in AB0-incompatible kidney-pancreas transplants and re-transplanted kidney recipients[110,111].

Intravenous immunoglobulins

Intravenous immunoglobulins show pleiotropic effects: They neutralize circulating anti-HLA antibodies *via* anti-idiotypic antibodies, inhibit complement activation by binding C3b and C4b and neutralizing C3a and C5a[112]. They also inhibit the expression of CD19 on activated B cells and induce the apoptosis of B cells[113]. Intravenous immunoglobulins (IVIGs) also show inhibitory effects on cellular immune responses with no specific inhibitory effects on the immune system by binding to Fcγ receptors on macrophages, neutrophils, platelets, mast cells and NK cells.

IVIGs are used to decrease PRA levels in highly sensitized patients, in desensitization protocols of AB0-incompatible and XM-positive patients and in the treatment of ABMR.

Splenectomy: Splenectomy has been used in desensitization protocols and in the treatment of refractory acute ABMR[114,115]. Splenectomy removes a major source of lymphocytes, but the effect on the immune system is permanent and places the patients at risk for the development of sepsis.

As discussed in the pathophysiology chapter, we should distinguish the following: (1) acute ABMR; and (2) chronic ABMR.

Acute ABMR

Early acute ABMR often occurs in patients with DSAs prior to transplantation with a CDC-XM-positive with the donor. Even after successful desensitization strategies and successful kidney transplantations acute ABMR occurs in up to 40% of recipients. A later occurrence of acute ABMR is typically noted in patients with *de novo* DSAs and often after the reduction of immunosuppression or non-adherence[116,117].

We should now distinguish between the prevention and the treatment of acute ABMR.

Prevention of acute ABMR: Patients waiting for a transplant may be highly immunized and many show detectable DSAs in their serum. Sensitized patients who are DSAs-negative with negative XM-CDC may be transplanted safely. They will likely require more immunosuppressive therapy and an induction therapy[118-120].

The different desensitization protocols apply primarily to DSA-positive patients who are XM-CDC positive. The majority of the current protocols are modified version of the high-dose IVIG initiated at the Cedars-Sinai Medical Center or of the PP with low-dose IVIG initiated at John Hopkins Hospital[121].

Jordan initially provided[122] high dose IVIGs (2 g/kg) to cross-match-positive recipients, and the patients received a kidney transplant when their CDC T cell XM became negative. Due to the high rate of acute ABMR, Jordan[123] decided to use alemtuzumab induction treatment and added rituximab to the protocol to decrease the acute rejection rate.

More recently, Vo *et al*[124]at the Cedars-Sinai reported on the 24-mo outcomes of the aforementioned desensitization protocol and showed a 2-years graft survival of 84% in 76 hyper immune XM-positive recipients.

The other approach to desensitization comprises 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[125]. Patients received PP and CMV Ig at 100 mg/kg after each PP, combined with tacrolimus and mycophenolate mofetil. In a recent study, Montgomery *et al*[126] successfully desensitized 211 DSA-positive recipients of living donor kidneys with PP and low-dose IVIG.

A differing approach is the use of peri-transplant

immunoabsorption rather than plasmapheresis. In 68 patients with deceased donors, Bartel and colleagues used peri-transplant IA followed by post-transplant IA and obtained excellent transplant outcomes[127].

Overall, over the last 13 years, almost 1000 patients with DSAs underwent kidney transplants and used varying desensitization protocols. The patient and graft survival rates are 95% and 86%, respectively, at the 2-year median follow-up. The primary issue is the high rates of acute rejection and of ABMR in particular (28%)[128]. New drugs are being developed to reduce this high rate of ABMR.

Stegall *et al*[109] added eculizumab during the pre-post-transplant period in DSAs-positive patients and obtained 7.7% post-transplant acute ABMR compared with 41.2% in the control group. However, at 2-years after transplantation the incidence of chronic ABMR was similar between the two groups. Chronic ABMR remains a major issue when transplanting hyper-immune patients.

A different option is to use the proteasome inhibitor bortezomib. In pilot studies, bortezomib has been used in desensitization protocols with encouraging results[107,108]. It is being used in a current ongoing a prospective iterative trial of proteasome inhibitor-based desensitization[129]. The trial has been approved by the International Review Board (IRB) and is being conducted under the auspices of FDA. Preliminary data suggest that bortezomib-based desensitization regimens comprising only two cycles (8 doses) may consistently reduce immunodominant HLA antibody levels and that multiple treatments with bortezomib (two-cycle regimen) may enable highly sensitized patients to undergo transplantation without IVIGs.

Treatment of acute ABMR: Acute ABMR in kidney recipients responds poorly to corticosteroids and antithymocyte agents alone, which are the standard treatment for acute cellular rejection.

International guidelines do not define an evidence-based treatment for acute ABMR. 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[130].

Two studies have individually reviewed the current approach to the treatment of acute ABMR[46] and the randomized controlled trials treating acute ABMR[131].

Although the literature suggests that plasmapheresis with or without low-dose IVIG or high-dose IVIG alone shows evidence of efficacy against acute ABMR and that they may be considered for the standard of care (SOC), these treatment regimens have not been standardized or optimized.

Approaches vary based on the amount of replacement volume, type of replacement fluids, number of PP sessions and the dose, timing and formulation of IVIGs used.

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

Of these treatments, rituximab has been used most frequently, and two studies in particular have evaluated rituximab as part of a combination treatment approach[132,133]. The latter study included 54 patients and compared a historical group treated with plasma exchange and IVIGs with a later group receiving a single dose of 500 mg/m^2 rituximab in addition. The use of rituximab was associated with a 90% 2-year graft survival compared with 60% in the control group. Nevertheless, the benefit of adding rituximab remains in question when examining all published patient series.

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

The largest series of 20 patients treated with bortezomib was reported by Flechner[134]. Using this treatment regimen, a graft survival rate of 85% at 10 mo post-transplant was achieved. The mean decrease in the dominant DSA in 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 mo[135].

Taken together, these preliminary results on bortezomib in acute ABMR are promising; however carefully performed, controlled studies are required to prove its benefits.

In the setting of kidney transplantation, there is emerging but limited evidence that eculizumab is efficient in treating acute ABMR[136]. Thus far, only a few reports exist in the literature on the use of eculizumab in refractory acute ABMR[110,111]. Stegall *et al*[109] reported the largest study of eculizumab in renal transplantation in a desensitization strategy. In this study, eculizumab appeared to show no impact on DSAs production after transplantation. In addition, the incidence of chronic ABMR appeared unchanged either by the prevention of early ABMR or by the prolonged complement blockade.

Splenectomy: One last option to salvage a graft with acute therapy-resistant ABMR is rescue splenectomy and its use has been reported by at least three groups[137-139]. The majority of patients underwent this surgery prior to the advent of eculizumab, and in the future, splenectomy may be avoided by using eculizumab instead. Splenectomy is recommended only in resistant cases of acute ABMR where bortezomib or eculizumab have already failed.

In summary, the first step for managing acute ABMR includes steroid pulses and/or antibody removal with PP or IA and IVIGs. 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 rescue splenectomy.

Chronic ABMR: In contrast to acute ABMR, chronic ABMR is a long-term process that develops in sequential steps over months to years[84].

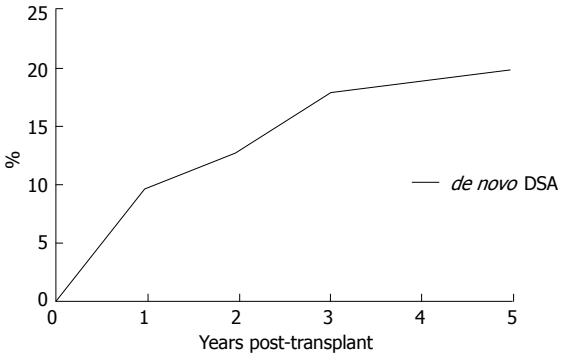

Figure 5 Actual 5-year post-transplantation cumulative incidence of de novo donor-specific-human leukocyte antigens antibodies (DSA). DSA: Donor-specific-human leukocyte antigens antibodies.

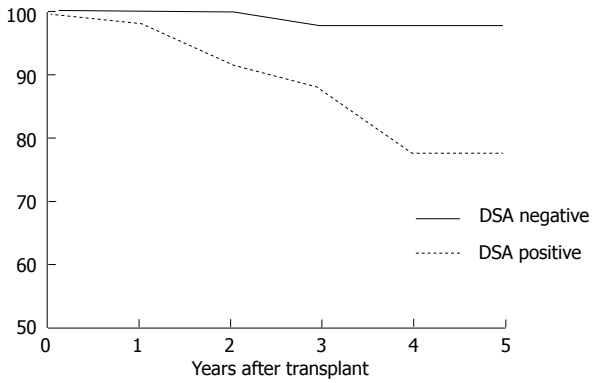

Figure 6 Probability of graft loss within 3 years after *de novo* donor-specific-human leukocyte antigens antibodies appearance. DSA:Donor-specific-human leukocyte antigens antibodies.

In theory, every option available to treat acute ABMR may also be applied to chronic ABMR. However, there are no controlled trials in the literature regarding the treatment of chronic ABMR. The only treatment option with some reported benefit is a combination of rituximab and IVIGs[140].

With respect to established chronic ABMR, there have only been three case series treated with this combination therapy[141-143]. DSAs decreased only in some patients, and the therapy showed limited effects in cases with massive proteinuria, more severe peritubular capillaritis and previous acute rejection.

Very few patients have received bortezomib as a rescue treatment for chronic ABMR and proteinuria, and they have shown mixed results[144,145].

An interim analysis of a very recent study[146] of eculizumab therapy in chronic ABMR documented an apparent stabilization of renal function.

Taken together, these results indicate that any treatment for chronic ABMR using drugs with potentially high toxicity should only be performed in the context of a randomized controlled trial.

A recent recognized context that should be distinguished from acute or chronic ABMR is the negative impact of *de novo* DSAs after transplantation on the transplant outcome.

Several authors have reviewed the incidence and impact of *de novo* donor DSAs, in both adult[77] and pediatric recipients[147].

The actual 5-year post-transplantation cumulative incidence of *de novo* DSAs in a low-risk population is 20% (Figure 5). Once DSAs appear, the probability of graft loss within the 3 years of the appearance of DSAs is 24% (Figure 6). In patients without DSAs, the relative risk of graft loss is 9-fold higher at 1 year after the appearance of DSAs. In a multivariate analysis[77], the primary causes of *de novo* DSAs were DQ locus mismatches, a younger age at transplantation and transplants from deceased donors. Others claim prior non-adherence or a history of a clinical acute cellular rejection as being causes of *de novo* DSAs[82].

If the appearance of DSAs is associated with the clinical signs of acute ABMR, the treatments used have already been discussed. The primary issue is how to treat when the appearance of DSAs is not associated with acute rejection.

To date, prophylactic treatments, such as rituximab and splenectomy[148] or eculizumab[109], do not appear to induce any effect on the appearance of DSAs.

Monitoring DSAs after transplantation appears to be essential because the appearance of DSAs is associated with a poor prognosis. Because procedures, such as antibody removal by PP or IA and the down regulation of antibody production by B cell- or plasma cell-targeting or complement cascade inhibition show very limited success when employed during the advanced phase of chronic ABMR[142,149,150], the prompt removal of *de novo* DSAs appears to be essential. However, no SOC exist for this issue. To date, only a multicenter antibody removal trial study in Italy is ongoing; it is using a randomized, prospective PP and low-dose CMV-IVIGs[151].

NEW AND FUTURE THERAPIES

Some of the drugs mentioned above that have been used to prevent or treat acute ABMR remain in pre-marketing clinical trials or have been approved for other diseases.

Drugs already known to control T cells also appear to be active in the long-term control of B cells.

Belatacept, a fusion receptor protein that blocks the co-stimulation pathway CD80/CD86-CD28, was recently approved for the prevention of acute rejection. Belatacept inhibited DSAs in phase 3 trials[152].

Another co-stimulation pathway is the CD40/CD40L pathway. Previous studies with antibodies directed against CD40L failed due to severe episodes of thrombosis. Indeed, CD40L is also expressed on the platelet surface, and its inhibition may induce thrombosis. More recently, the inhibition of the CD40/CD40L pathway by directly targeting CD40 has drawn interest from investigators particularly because CD40 is not expressed on the platelet surface. Humanized anti-CD40 antibodies prevented acute rejection and prolonged renal graft in non-human primates. In addition, these anti-CD40 antibodies appear safe and effective as maintenance immunosuppressive therapies[153-155]. To date, five monoclonal antibodies di-

rected against CD40 have been studied for different diseases including kidney transplantation (Clinical Trial.gov NCT01780844).

Newer drugs that target B cell have been described. The most exciting are likely those that target survival factors and are part of the tumor necrosis factor super family: BAFF, Blys and the proliferation-inducing ligand (APRIL)[103].

Belimumab has already been discussed: it is a fully human antibody that neutralizes BAFF and deprives B cells of this important survival factor. The FDA approved belimumab in March 2011 for systemic lupus erythematosus (SLE). A group from Pennsylvania has enrolled patients in a phase II clinical trial of desensitization in sensitized patients awaiting clinical transplantation (clinicaltrials.gov NCT01025193). In this context, the study was unable to demonstrate the efficacy of belimumab.

Atacicept is a fusion receptor protein that neutralizes both BAFF or Blys and APRIL. In allo-sensitized nonhuman primates, atacicept reduced T-cell and B-cell alloantibodies by 36% and 24%, respectively[156].

A further possibility is complement inhibition by C1 esterase inhibitors, a plasma-derived human C1 esterase inhibitor. Initially used in allotransplantation to protect against ischemia/reperfusion injury[157], it is now under investigation for solid organ transplantations and approved by the FDA for use in other disease states. A trial studying the safety and tolerability of C1 inhibitor therapy in the context of the prevention of acute rejection (clinicaltrial.gov NCT01134510) is now ongoing. However, thus far no patients have been recruited.

CONCLUSION

The relevant graft injury is now well recognized to be caused by alloantibodies. Both acute and chronic graft injury may be caused by alloantibodies, and the most recent Banff classifications have been modified to introduce acute and chronic ABMR. The latter appears to be the most relevant cause of long-term graft injury rather than CNIs nephrotoxicity and "chronic allograft nephropathy".

In addition to the major histocompatibility antigens, a large number of minor antigens have been recognized as possible antibody targets. The most important and the most widely studied antibodies responsible for graft injury are the HLA-DSAs.

The availability of new techniques for detecting circulating antibodies has enabled better understanding in recent years of the presence and role of antibodies in determining graft injury.

From a clinical point of view, we must distinguish between acute ABMR and chronic ABMR. In addition, we now recognize indolent ABMR and C4d-negative acute ABMR. Indolent ABMR develops sub-clinically. It often manifests in patients with *de novo* DSAs and causes slowly progressive microvascular abnormalities that lead to chronic ABMR. C4d-negative ABMR is cause for great discussion among scholars. It may be caused by an injury that is non-complement-mediated; however it may also be due to defective techniques. The Banff group is still working to improve understanding of this entity.

Recently, evidence has accumulated on the significant role of HLA-DSAs in the pathogenesis of slowly progressive graft injury and dysfunction. Several studies have shown that circulating DSAs (class Ⅰ or class Ⅱ) are found in a substantial fraction of renal allograft recipients and are associated with long-term graft loss.

The primary therapeutic approach comprises antibody removal, B-cells and plasma cells- targeting and inhibition of the complement pathway. The therapeutic approach used is based on the clinical conditions.

In patients waiting for transplantation who show positive XM-CDC, the removal of antibodies with or without B- or plasma cell-inhibition remains the best approach.

Patients with acute ABMR should be treated with a heavy regimen of T/B cell-targeting drugs (pulse corticosteroids and ATG), by removing antibodies, and using specific B- or plasma cell-inhibition or by complement inhibition.

No SOC exists for chronic ABMR, and only randomized controlled trials will indicate the best therapeutic option.

What may we hope for in the future? Unfortunately, the pipeline is almost empty.

Essentially, we may consider two types of drugs that are either already on the market or remain in premarket trials: (1) drugs targeting both T and B cells; Belatacept has already been approved by the FDA for the prevention of acute rejection. In a 3-year follow-up study[152], it proved to be effective on DSAs also in CNIs free protocols. The blockade of CD40-CD154 with humanized anti-CD 40 antibodies has prevented acute rejection[154]. In addition, these antibodies appear safe and effective in maintenance therapy; and (2) drugs targeting B cells or the complement pathway.

BAFF-blocking drugs: Represent new interesting drugs that target B lymphocyte stimulators. Belimumab, a fully human recombinant IgG monoclonal antibody to BAFF, was approved in 2011 for the treatment of SLE; however the above-mentioned phase Ⅱ trial for desensitization failed. Atacicept was evaluated in diseases including rheumatoid arthritis, SLE, multiple sclerosis and B-cell malignancies. It awaits evaluation in human transplant patients.

While waiting for the approval of eculizumab, the C1 esterase inhibitor is being studied. This drug has been FDA-approved for treating hereditary angioedema; however it appears to be far from approval for use in transplantation.

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