

Review

# ANTIBODY-MEDIATED REJECTION IN KIDNEY TRANSPLANT RECIPIENTS

Rafails Rozentāls and Ieva Ziediņa

Transplant Laboratory, Riga Stradiņš University, Dzirciema iela 16, Rīga, LV-1007, LATVIA;  
rafails.rozentals@stradini.lv

Contributed by Rafails Rozentāls

*This paper provides a review of the significant problem of humoral, or antibody-mediated rejection, in kidney transplantation. The main cause of antibody-mediated rejection is donor-specific anti-HLA antibodies. Patients with anti-HLA antibodies are called sensitised patients. The outcome of humoral rejection is unfavourable: graft dysfunction and failure have been frequent from the early post-transplant period and are continuing. International laboratories and clinics offer sensitive and accurate methods to determine antibodies before and after kidney transplantation, but the methods are not always successful in recognition of sensitised patients. For diagnostics of humoral rejection the important issue is detecting complement breakdown deposition (C4d) in peritubular capillaries during immunohistological examination. On the one hand, their presence is characteristic for humoral rejection, but on the other hand, they can occur without any clinical changes or can remain undetected during severe humoral rejection. Current methods of prevention, diagnostics and treatment of humoral rejection are discussed. Difficulties of evaluation of chronic antibody-mediated injury are particularly highlighted.*

**Key words:** kidney transplantation, donor-specific antibodies, antibody-mediated rejections, diagnostics, treatment.

## INTRODUCTION

Dysfunction and failure of grafts months or years after transplantation are a major problem in transplantation clinics. True chronic active T-cell-mediated or antibody-mediated rejection is the significant cause of this. The data discussed below mainly refers to kidney grafts, as their number worldwide is considerably higher than any other graft type and because various aspects of kidney transplantation have been better studied.

Rejection includes all processes involved when the host immune system recognises the donor alloantigens and leads to the graft failure. Principal risk factors of rejection are histoincompatibility, ischemia — reperfusion injury, and cellular and humoral response (Nankivell and Alexander, 2010; Hricik, 2011). Acute and chronic rejections are distinguished. Acute rejections develop mainly during the first three months after transplantation and chronic rejections in later periods.

There are two principal mechanisms of development of acute rejections: cellular and humoral. T-cell-mediated rejection is initiated when donor alloantigens are presented to the T lymphocytes of the recipient by antigen-presenting cells. Pathogenesis of the process includes: accumulation of

mononuclear cells, T- lymphocytes and macrophages in the interstitium of grafts leading to the inflammation of tubules and rarely to the inflammation of arteries. The treatment of cellular rejection begins with pulse doses of corticosteroids and, if there is no effect, polyclonal antibodies are added. This treatment is sufficient for the suppression of cell-mediated rejection. The rate of allograft failure, as a rule, is minimal (Danovitch, 2010; McDonald *et al.*, 2007).

Humoral or antibody-mediated rejection (AMR) is substantially more severe and more complicated to diagnose and treat. It is initiated by antibodies of different origin, especially donor-specific HLA antibodies (DSA) that are circulating in blood of a recipient. Patients with circulating antibodies are called sensitised patients. Sensitisation is determined by the rate of preformed antibodies to a panel of HLA typed blood donors. Patients with a level of antibodies less than 5% are called slightly sensitised patients, and those with a level more than 85% are considered highly sensitised patients. In the USA, 40% of candidates for kidney transplantation are sensitised or highly sensitised (Anonymous, A 2009). About 12–15% of patients are considered as such in the Eurotransplant countries (Anonymous, 2010).

Treatment of sensitised patients presents two main problems:

- it is almost impossible to find an appropriate kidney for them, because the complement-dependent cytotoxicity cross-match test is positive before surgery in the majority of cases (Fuggle and Martin, 2008).

- even if this test is negative, the risk of development of acute antibody-mediated rejection is high (Susal *et al.*, 2009). Retrospective observations demonstrate that patients having a kidney graft transplanted at a negative cross-match, but with DSA had significantly worse outcome (Lefaucheur *et al.*, 2009). It is very important to note that the increase of the antibody titre after transplantation is indicative of severe AMR and bad prognosis (Burns *et al.*, 2008).

AMR treatment is complex, expensive and not always successful. It often results in kidney graft failure at an early or late period (Mao *et al.*, 2007).

#### CLINICAL RELEVANCE OF HLA ANTIBODIES IN DEVELOPMENT OF HUMORAL REJECTION

Peripheral B cells are formed in the bone marrow and develop from pro-B cells to pre-B cells and then immature B cells, which are released into the periphery. Following antigen encounter, B cells obtain T-cell help and enter the germinal centre. Here they undergo class switch recombination and affinity maturation. Germinal centre B cells with higher affinity for antigen are positively selected and differentiate into either memory B cells or plasma cells. A small proportion of plasma cells arising from a germinal center become established as long-lived plasma cells in the bone marrow. They do not proliferate, but act as long-term antibody factories, producing IgG (Clatworthy, 2011).

Plasma cells produce antibodies consisting of four polypeptide chains. There are five different types of antibodies: IgM, IgG, IgA, IgD, IgE. The main causes of the occurrence of HLA antibodies are blood transfusion, multiple pregnancies and previous transplantations (Bruce and Suranyi, 1995).

An anamnestic response engendered by previous exposure to the relevant antigen rapidly generates high titres of complement-fixing HLA antibodies (Terasaki, 2003). HLA antibodies bind to antigens expressed on endothelial cells in the graft vessels. The subsequent complement activation and cell adhesion result in endothelial-cell injury and necrosis, followed by platelet deposition and coagulation. Microthrombi, with hemorrhage and arterial-wall necrosis and infarction occur in severe cases (Colvin, 2007).

Together with anti-HLA antibodies, those of other origin also negatively affect the graft. Humoral rejections caused by angiotensin II type I (AT1) receptor antibodies have been described (Dragun *et al.*, 2005). In 11.4% of 1910 recipients sera antibodies against MICA antigens were found, which are also responsible for rejections (Zou *et al.*, 2007). Antibodies against ABO antigens, C1q-binding antibodies,

anti-Vimentin and Collagen V antibodies may also play a certain role.

Two phenotypes of antibody-mediated rejection are distinguished based on the presence and time of occurrence of DSA: phenotype 1 – early/acute rejection, which develops if antibodies are present before transplantation and phenotype 2 – late/chronic rejection with the *de novo* formation of antibodies at a later period after transplantation and is already a sign of start of chronic rejection (Halloran *et al.*, 2010, Mengel *et al.*, 2012).

Methods used to identify HLA antibodies are complement-dependent cytotoxicity (CDC) assays, antihuman globulin enhanced CDC (AHG/CDC) assays, enzyme-linked immunosorbent assay (ELISA), and solid-phase assays performed on flow cytometric and Luminex platforms (Gebel *et al.*, 2000; Zeevi *et al.*, 2006). The most longstanding and widespread assay to determine the level of anti-HLA antibodies is a complement-dependent cytotoxicity (CDC) test. As a CDC assay is cell-based (lymphocytes) method, not only HLA molecules, but also other irrelevant cell membrane structures may be the target for antibody reactivity. More sensitive and specific methods for diagnostics of HLA antibodies and prediction of rejection are ELISA and solid-phase assays. The advantages of solid phase tests include high sensitivity, specificity and high throughput. Solid-phase HLA antibody tests return results measured in arbitrary units, such as mean fluorescent intensity (MFI) for Luminex. The Luminex platform can identify alloantibodies to HLA Class I and -II molecules (Lefaucheur *et al.*, 2009).

These modern and sensitive methods still are not sufficient to determine individual risk for each patient. For this purpose possibilities of Luminex single-antigen bead assays, which is a technology that allows to identify DSA to multiple alleles of HLA molecule antigens, has been studied in the last years (Schnaidt *et al.*, 2011). Concurrently up to 100 various proteins (biomarkers), in particular, antigens to HLA class I and II antibodies, can be identified on the surface of microspheres used in this assay.

A great number of comparative studies of recipients with a range of DSA content using different methods of diagnostics have been conducted in many clinics and laboratories. The incidence of rejections and transplantation outcomes have been evaluated and positive results have been obtained. The Luminex system was found to be rather effective in determining the significant HLA antibodies in patients waiting for repeated kidney transplantation (Marrari and Duquesnoy, 2010). However, issues of standardization of the method and interpretation of obtained results from the point of view of making a correct decision for treatment of patients are still being discussed (Billen *et al.*, 2009; Cecka, 2011).

## CLINICAL MANIFESTATIONS OF ANTIBODY-MEDIATED REJECTION

The most severe form of transplant injury mediated by antibodies is the so-called hyperacute rejection, which develops during the first minutes or hours after surgery and leads to the immediate graft failure. After graft revascularisation, antibodies immediately form complexes with antigens in the presence of the complement. Endothelial cells are damaged and the hypercoagulation syndrome, thrombosis of microcirculatory vessels and transplant necrosis develop. The graft becomes black, the blood flow and urine production stop within several minutes. There is no effective treatment for hyperacute rejection. A hyperacutely rejected kidney needs to be removed.

Acute antibody-mediated rejection was first described as a triad of allograft dysfunction, neutrophilic peritubular capillaritis i.e. microcirculation inflammation, and *de novo* anti donor class I HLA antibodies (Halloran *et al.*, 1990; Tripkov *et al.*, 1996). It typically occurs within the first few weeks after transplantation, when a sudden decrease in graft function is followed initially by good graft function. It is difficult to distinguish acute humoral rejection from acute cellular rejection clinically and by routine laboratory tests, Special methods of diagnostics and treatment are required, which are discussed further.

The most significant feature of acute antibody-mediated rejection is its obvious association to late kidney graft failure — the development of chronic rejection. Sellaras *et al.* (2012), in a follow-up study of patients for 32 years demonstrated that graft failures were either due to antibody-mediated rejections or due to non-identification of noncompliant patients.

Chronic antibody-mediated rejection is considered as a major cause of late kidney graft failure (Gaston *et al.*, 2010). In the case when microcirculation lesions and presence of HLA antibodies were used to define AMR (regardless of the C4d status), more than half of late kidney failures were attributed to antibody-mediated microcirculation injury, of which many were C4d-negative (Einecke *et al.*, 2009). The term “chronic” is less related to a certain time, but indicates morphological changes typical for antibody-mediated rejection, e.g. duplication of the glomerular basement membrane and/or multilayering of the peritubular capillary basement membrane (Roelen *et al.*, 2012). As the problem of late graft failure has not been solved and the ways to control chronic transplant injury are not always effective, the significance of antibody-mediated rejection in the late post-transplant period is in the focus of attention of many investigators.

## PREVENTION OF ANTIBODY-MEDIATED REJECTION

In organ transplantation clinics the first step to prevent the development of humoral rejection is restriction of blood

transfusions — one of main trigger factors of antibody production.

When a patient is included into the waiting list for transplantation, the presence or absence of preformed antibodies (presensitisation) should be clarified. The patient serum is typically added to a panel of blood donor antigens to identify the rate of preformed antibodies (panel reactive antibodies, PRA) by CDC method.

CDC cross-match between donor lymphocytes and recipient serum (containing potential HLA antibodies) is used to prevent hyperacute rejections before kidney transplantation. The test is considered negative when antibodies directed against donor HLA antigens expressed on lymphocytes are missing and that cell death will not happen. In such cases transplantation is possible and with high probability that no hyperacute rejection will occur (Chapman *et al.*, 1986).

The prevention of acute humoral rejection in sensitised patients, first of all, means the selection of an appropriate organ. Before transplantation of an organ from a deceased donor, a recipient most compatible by its antigens must be found (Lefaucheur *et al.*, 2010). Two methods are used at the same time to determine antibodies in sensitised recipients at the pre-transplantation period: CDC crossmatch and ELISA screening. The Luminex technology is added to the examination when transplantation from a living donor has been planned (Morath *et al.*, 2012).

Along with more precise diagnostics, there is a set of therapeutic and organisational measures that might improve transplantation results in sensitised patients.

The main therapeutic method is desensitisation — removing antibodies from the circulation of patient using plasmapheresis and/or immunoabsorption. Intravenous immunoglobulins (IVIg) due to their immunomodulatory effect are mandatorily used during treatment (once or twice) (Zachary *et al.*, 2003). Rituximab, a monoclonal anti-CD20 antibody with activity against B-cells, is usually administered before blood purification sessions. A similar method was applied for 61 patients before kidney transplantation from living donors and a negative cross-match was achieved in 85% of them and one-year graft survival was 82% (Stegall *et al.*, 2006). Transplantation needs to be performed at the time of the greatest drop in the level of antibodies under the impact of desensitisation and after a negative CDC cross-match is achieved. It has been observed in recent years that desensitisation immediately before transplantation is effective also in cases of kidney transplantation from deceased donors (Bartel *et al.*, 2010).

Continuous monitoring of the level of donor-specific HLA antibodies is recommended when preparing for desensitisation, during and after it. This provides additional information and possibilities to control the appearance of acute and chronic humoral rejection (Stegall *et al.*, 2009).

Besides desensitisation, there are also special organizational programmes for prevention of acute humoral rejection:

- Paired donation. For a recipient having an incompatible donor, another pair is selected that is also incompatible against each other. Then compatible donor-recipient pairs are formed from these two pairs and transplantations are performed. These are special national programmes in the USA and Netherlands that allow to reduce the waiting time and to ensure better transplantation outcomes (Montgomery, 2010).
- Eurotransplant acceptable mismatch programme. It includes hypersensitized patients (preformed antibodies above 85%). Antigens are defined towards which the patient has never formed antibodies. These antigens are defined as acceptable mismatches. If a donor with such antigens is found, transplantation becomes possible even without a direct cross-match (Claas *et al.*, 2009). In the USA this method is called virtual cross-match. The donor-recipient compatibility in these cases is defined by using the Luminex techniques (Vaidya *et al.*, 2006).

## CHALLENGES IN DIAGNOSTICS OF ANTIBODY-MEDIATED REJECTION

There are four criteria for diagnostics of AMR:

1. Graft dysfunction. This is characterised by increase in the serum creatinine level, reduction in glomerular filtration rate and development of oliguria or anuria. The occurrence of proteinuria at a later stage indicates a developing chronic rejection. The presence of graft dysfunction distinguishes clinical AMR from subclinical AMR (Archdeacon *et al.*, 2011).

2. Detection of donor specific antibodies. CDC, ELISA and flow cytometry methods are applied in clinics. Five-year observation of patients after kidney transplantation demonstrated a direct connection between formation of *de novo* DSA and reduction in transplant survival time (Mao *et al.*, 2007). Observation of 315 patients during ten years demonstrated 57% kidney graft survival in a group of patients with *de novo* DSA and 96% graft survival without *de novo* DSA (Wiebe *et al.*, 2012). The presence of DSA in blood is definitely a risk factor, but the degree of their development is not always correlated with the clinical picture and morphological changes in grafts. In some patients, even with a high DSA titre, no rejection occurs and long-term graft survival is ensured (Roelen, 2012). Thus, the statement that the presence of preformed antibodies is a contraindication to transplantation cannot be fully viewed as a dogma. An opportunity of more accurate diagnostics are offered by Luminex technology (Zachary *et al.*, 2009). However, at this stage of investigation, it also does not guarantee absolutely adequate data (Lefaucheur *et al.*, 2011). Much depends on the course of the pathological process, the phase and time when analysis occurs, applied treatment and some other individual factors of the body (Loupy *et al.*, 2009).

3. Morphological evaluation of the kidney graft. Acute tubular necrosis, peritubular capillaritis, glomerulitis, capil-

lary thrombosis, transmural arteritis and arterial fibronoid necrosis can be identified by light microscopy.

4. Immunohistological evaluation of the kidney graft. C4d depositions in peritubular capillaries, which are a breakdown product of activated complement, can be detected in capillary walls during AMR (Collins *et al.*, 1999). The presence of C4d deposition indicates a poor prognostic result. The presence of deposits can be observed in the majority of early dysfunctioning grafts (Feucht *et al.*, 1993). Irreversible dysfunction of kidney grafts was observed in 65% grafts with diffuse processes and in 33% grafts with focal distributions of C4d (Poduval *et al.*, 2005). Despite the practical meaning of this criterion, acute humoral rejection can occur with absolutely no C4d deposition. Due to the uncertainty in diagnostics, the classification of pathomorphological transplant injuries (Banff classification) was developed in 1991 by morphologists together with transplantation specialists in the Canadian city Banff. During the last meeting of professionals in 2011, the diagnostic significance of microcirculation inflammation of grafts (glomerulitis, capillaritis) was highlighted. This feature can be observed in early protocol biopsies at the 10th postoperative day (Mengel *et al.*, 2012).

For diagnostics of acute humoral rejection, three main features are taken into account: reduction in glomerular filtration rate, presence of circulating DSA and morphologically identifiable tissue injury: microcirculation inflammation and C4d deposition. There is no doubt in the diagnosis when all of them are present. Even the presence of two of these three criteria is sufficient to start treatment of an acute humoral rejection (Loupy *et al.*, 2011).

The practical use of these criteria for the diagnostics of chronic rejection is difficult, as the transplant glomerulopathy is already the final pathology of an antibody-mediated rejection (Gloor *et al.*, 2007). Microcirculation changes together with the presence of DSA in blood and a slowly developing transplant dysfunction are currently considered as a transition to the chronic rejection stage. In a study of 329 kidney transplant biopsies from 251 patients taken six days to 31 years post-transplant, during median follow-up time after biopsy of 26 months at total of 56 transplants had failed. The cause of graft failure in 64 % was antibody-mediated or mixed rejection (Sis *et al.*, 2012). Difficulties in the diagnostics of a chronic rejection have led to the use of new OMIC methods of diagnostics. Early development of interstitial fibrosis and tubular atrophy can be detected by gene expression and used as a morphological criterion of chronic rejection in kidney grafts (Muthukumar *et al.*, 2011).

## TREATMENT OF HUMORAL REJECTIONS

The treatment of acute, including both cellular and humoral, rejections should be started only after obtaining transplant pathology data.



The first step needs to include pulse doses of corticosteroids.

The treatment of an antibody-mediated rejection usually starts with an attempt to deplete B-cells. Rituximab is used for this purpose. Its effectiveness is proven, although the possibility of development of severe infections must be accounted for in this case (Kamar *et al.*, 2010).

The removal of antibodies is done by plasma exchange or immunoadsorption. The number of sessions depends on the clinical condition of patients and the degree of DSA reduction. There are no studies directly comparing plasma exchange and immunoadsorption in terms of efficacy and safety for treatment of AMR, but both seem to be effective (Fehr and Gaspert, 2012). The use of large (1 g/kg/day) or average (500 mg/kg per day) doses of intravenous immunoglobulins (IVIG) is considered to be mandatory (Shehata *et al.*, 2010). In addition, the conversion to tacrolimus and mycophenolate mofetil in immunosuppression should be ensured. A timely started treatment has a rather good prognosis, when donor-recipient pairs are correctly selected; one-year patient survival can be 99%, and graft survival — 80% (Venetz and Pascual, 2007).

In recent years progress was achieved by using proteasome inhibitor — bortezomib. In a study, 26 patients with *de novo* DSA and who had received a kidney from living donors were preemptively treated with bortezomib. This allowed to achieve DSA reduction and to maintain remission in 69% patients at 25 months post-treatment (Everly *et al.*, 2012). The use of eculizumab — a complement inhibitor (anti C5) is also considered as perspective. Although there are effective protocols of its use for DSA induced AMR, further studies are required with a longer follow-up.

The treatment of chronic rejection followed by progressive reduction of glomerular filtration rate and proteinuria is very problematic. Firstly, the above mentioned drugs are not free from side effects that may worsen the condition of patients and transplants. Secondly, currently there are no therapeutic recommendations supported by controlled scientific studies (Fehr and Gaspert, 2012).

In summary, prevention, diagnostics and treatment of antibody-mediated rejection is not only an urgent problem, but also complicated and requires large financial expenses. In fact, the existing recommendations are just the beginning of a solution to this problem. Further progress depends on the conducting randomised controlled studies. When working in this direction, it must be kept in mind that saving of the function of renal graft always has an alternative — return to dialysis, which requires even larger financial expenses and significantly reduces the quality of life of patients.

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## ANTIVIELU VADĪTĀS ATGRŪŠANAS REAKCIJAS PACIENTIEM PĒC NIERES TRANSPLANTĀCIJAS

Šis pārskats ir veltīts svarīgai nieru transplantācijas problēmai — humorālai, jeb antivielu vadītai atgrūšanai (tremei). Galvenais iemesls antivielu vadītai tremei ir donorspecifiskās anti-HLA antivielas. Pacientus ar anti-HLA antivielām sauc par sensitizētiem pacientiem. Humorālai tremei ir nelabvēlīgi rezultāti: transplantāta disfunkcija un funkcijas zudums ir bieži novērojams kā agrīnajā, tā arī vēlīnajā pēctransplantācijas periodā. Starptautiskās laboratorijas un klīnikas piedāvā jūtīgas un precīzas metodes lai noteiktu antivielas pirms un pēc transplantācijas, tomēr tās ne vienmēr identificē sensitizētus pacientus. Viens no svarīgiem momentiem humorālas tremes diagnostikā ir komplementa sabrukuma depozītu (C4D) noteikšana peritubulāro kapilāru biopātū histoloģiskās izmeklēšanas laikā. No vienas puses, C4D depozīti ir raksturīgi humorālai tremei, bet, no otrās puses, tie var parādīties arī bez klīniskām izpausmēm, un otrādi, smagas humorālas tremes gadījumā tie ne vienmēr ir atrodami. Speciālistu vidū notiek plaša diskusija par humorālas tremes profilaksi, diagnostiku un ārstēšanu. Īpaši izceltas grūtības ar hroniskās antivielu vadītas tremes novērtēšanu.