

## CHAPTER 6.2 Diagnosis and treatment of antibody-mediated transplant rejection

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### 1 Definitions

Active antibody-mediated rejection (AMR) is diagnosed based on specifically defined histopathologic and molecular lesions, primarily the presence of microvascular inflammation (MVI, defined by the lesions glomerulitis and peritubular capillaritis) or, alternatively, by biopsy-based transcript-analysis; secondly, on the presence of circulating donor-specific antibodies (DSAs); and thirdly, on the extend of C4d deposition. However, a diagnosis of AMR can be made without DSAs or C4d. AMR is caused by the binding of circulating antibodies to donor alloantigens on endothelial cells in the graft, resulting in inflammation, cell damage and, ultimately, graft dysfunction. These antigens include human leukocyte antigens (HLA) class I and class II antigens, and in recipients of ABO-incompatible transplants, ABO blood group antigens. Other non-major histocompatibility complex (MHC) antigens on the endothelium may also be targeted [1–4]. Acute TCMR and AMR may coexist in the allograft at the same time (i.e., mixed acute rejection). Acute rejection may also coexist with chronic rejection. Of note, from a molecular (transcriptomic) perspective, chronic AMR appears to share more similarities with TCMR than with active AMR.

Clinically, chronic rejection is characterised by the gradual deterioration of allograft function, accompanied by varying degrees of proteinuria and hyperten-

sion. It is a significant factor in the loss of grafts in the long term. It typically develops after the first year post-transplant and may occur with or without active inflammation (see Chapter 6.3) [5].

## 2 Incidence and risk factors

A recently published analysis of 337 paediatric kidney transplant recipients from the CERTAIN registry revealed that the cumulative incidence of *de novo* donor-specific class I HLA antibodies (HLA-DSAs) post-transplant was 4.5% in year 1, 8.3% in year 3 and 13% in year 5. The corresponding results for *de novo* class II HLA-DSAs were 10%, 22.5% and 30.6% respectively [6]. Five years post-transplant, the cumulative incidence of active AMR was 10%, and of chronic active AMR, 5.9%. HLA-DR mismatch and *de novo* HLA-DSA, particularly double positivity for class I and class II HLA-DSA, were significant risk factors for AMR. Other established risk factors for AMR are: (i) delayed onset of graft function, (ii) a previous episode of rejection, (iii) receiving a second or subsequent transplant, and (iv) not adhering to medication.

## 3 Clinical and laboratory findings

As most patients with AMR are asymptomatic, the condition is usually identified through abnormal laboratory testing. The most common laboratory finding among patients with acute allograft rejection is an acute or slow rise in serum creatinine. However, a rising serum creatinine level is not specific to acute rejection. It is a relatively late development in the course of a rejection episode and usually indicates significant histological damage. New or increasing proteinuria of more than 500 mg/m<sup>2</sup> per day may indicate active or chronic (active) AMR. However, post-transplant proteinuria may also be caused by glomerulosclerosis or interstitial fibrosis and tubular atrophy (IFTA) from chronic rejection, recurrent glomerular disease, and *de novo* glomerulopathies.

The development of *de novo* antibodies directed against the donor's HLA antigens (HLA-DSAs) or an increase in DSA reactivity in a patient with pre-existing DSAs has been associated with AMR. A systematic review and meta-analysis of seven retrospective cohort studies found that the presence of HLA-DSAs, as detected by a solid-phase assay, was associated with a risk of AMR that was almost double as high as that observed in the absence of HLA-DSAs [7]. DSAs

to non-HLA antigens have also been observed in patients with AMR. These include the angiotensin II receptor [2, 3], MHC class I polypeptide-related sequence A (MICA) [4] and endothelial cell antigens [4]. However, a negative DSA test in serum does not rule out a diagnosis of AMR, as the DSAs could have been absorbed by the graft. Moreover, not all DSAs are equally pathogenic. A considerable number of studies have found that complement-binding antibodies (i.e., C1q-binding DSAs) are associated with a higher rate of AMR and poorer graft survival than non-complement-binding DSAs [8, 9]. However, testing for C1q-binding DSAs is not widely performed. In addition, it is likely that there are clinically relevant non-complement-binding DSAs that are not detected by this assay.

There is no consensus on when to test for DSAs in the absence of allograft dysfunction. The frequency of DSA monitoring varies between transplant centres and depends on the patient's immunological risk. Some centres perform annual HLA-DSA testing in stable recipients. Monitoring for the development of HLA-DSAs post-transplant may permit the early detection of AMR and allograft dysfunction, particularly in high-risk patients (see Chapter 4.4 and Chapter 5.2). However, routine monitoring of DSAs in low-risk patients may have a more limited impact in detecting early AMR [10]. The presence of circulating HLA-DSAs alone does not indicate active rejection, but it does indicate that a patient is at a higher risk of AMR. Other clinical and laboratory parameters must be assessed alongside DSA testing. In cases of an increasing or new HLA-DSA, but with no other signs of acute rejection and a normal kidney allograft biopsy, most transplant centres would only increase maintenance immunosuppressive therapy.

## 4 Histopathology

There are no specific laboratory findings that can accurately diagnose acute rejection. Acute rejection is currently diagnosed histologically using a kidney allograft biopsy (see Chapter 6.3). Histopathology differentiates between T cell-mediated rejection (TCMR) and AMR, grades the severity of rejection accurately, and determines the extent of irreversible kidney damage (interstitial fibrosis/tubular atrophy [IF/TA]). A biopsy of the allograft can also reveal other causes of kidney inflammation and injury, including cytomegalovirus disease, BK polyomavirus-associated nephropathy, interstitial nephritis, pyelonephritis, *de novo* or recurrent glomerular disease, and post-transplant lymphoproliferative disease (PTLD) (see Chapter 6.3). The Banff classification has been developed

and revised by an expert panel of pathologists, immunologists, physicians, surgeons and immunogeneticists, with the aim of standardising the histological criteria for diagnosing and grading the severity of rejection [11]. Distinguishing between active AMR and severe acute TCMR can be difficult, and the two processes may coexist. In reality, AMR and TCMR diagnoses are part of a continuum representing different manifestations of the alloimmune response. In up to 25% of cases of allograft dysfunction attributed at least in part to AMR, the histological findings suggest only TCMR or acute tubular injury. It is important to identify AMR, if possible, since it is more resistant to treatment and often results in loss of the kidney allograft unless adequately treated [6].

DSA testing may produce a negative result among patients with AMR. Some of these patients may have antibodies against non-HLA antigens. If anti-HLA antibody testing is negative, but there is evidence of MVI (even below the threshold for AMR), testing for non-HLA antibodies may be advisable in selected scenarios [3, 4]. However, there are currently no universally established or validated clinical assays to detect these antibodies. Cases in which C4d staining is positive but DSA cannot be detected may result from DSA being below the level of detection due to immunoadsorption by the graft.

## 5 Chronic AMR

Chronic AMR refers to chronic microvascular injury that leads to remodelling of the glomerular or peritubular capillaries. Chronic AMR is further classified into chronic active and chronic inactive subtypes. *Chronic active AMR* generally develops more than six months after transplant and can occur in patients with or without a history of active AMR. The only difference in the diagnostic criteria between chronic active and active AMR is the presence or absence of chronic lesions (transplant glomerulopathy or severe multilayering of the peritubular capillary basement membrane [12]).

Chronic inactive AMR is characterised by chronic lesions in conjunction with MVI below the threshold for AMR, DSA positivity and C4d negativity. In patients with chronic inactive AMR, prior diagnosis of active or chronic active AMR and/or documented evidence of post-transplant DSA count as DSA positivity.

## 6 Prevention

Preventing AMR depends on detecting HLA-DSAs before (pre-existing) or after (*de novo*) transplantation. Patients with pre-existing HLA-DSAs prior to transplantation are at greater risk of AMR and graft failure than non-sensitised patients [7]. The complement-fixing capacity of the DSA is a key factor in this risk, with patients who test positive for complement-dependent cytotoxicity (CDC) having a higher risk of AMR and graft loss than those who test positive for flow crossmatch. In turn, these patients have a higher risk than those who test positive for virtual crossmatch (antibodies detected by single antigen bead technology) [7]. For patients with a potential living donor, the approach depends on the results of the most recent crossmatch. For patients with a positive CDC crossmatch or strongly positive flow crossmatch, many transplant centres opt for kidney paired donation (KPD) programmes over desensitisation due to the high risk of AMR and graft loss in these patients [13]. Such KPD programmes enable sensitised patients with immunologically incompatible living donors to receive transplants from other living donors in similar situations who are willing to exchange organs. KPD could help participating centres avoid complex desensitisation protocols while improving long-term outcomes. KPD programmes will soon be available also in Germany.

Many centres employ HLA desensitisation strategies in patients with a positive virtual crossmatch (antibodies detected by single antigen bead technology) or a mild to moderate positive flow crossmatch (i.e., median channel shift of < 200). These strategies include treatment with plasmapheresis, rabbit anti-thymocyte globulin (rATG), rituximab and imlifidase (see Chapter 5.2). We employ HLA desensitisation strategies in patients without a potential living donor. For all patients with a pre-existing DSA before transplant who undergo kidney transplantation, we use induction and maintenance immunosuppression therapies appropriate for patients at high risk of developing acute rejection [14].

For patients with pre-existing DSAs, routine monitoring of DSA levels is recommended at months 1, 3, 6 and 12 post-transplant, followed by annual monitoring [14, 16]. Highly sensitized patients should be monitored more frequently, for example on post-transplant days 5, 10, 14 and 21. Many centres perform a kidney allograft biopsy in patients with a significant rise in HLA-DSA or who develop a *de novo* HLA-DSA within the first three months. This practice largely aligns with the Consensus Guidelines on Testing and Managing Clinical Issues Associated with HLA and Non-HLA Antibodies in Transplantation [14].

Kidney transplant recipients who develop *de novo* HLA-DSAs after transplantation can experience late-onset antibody-mediated rejection (AMR). AMR in patients with *de novo* HLA-DSAs has been associated with poorer outcomes than AMR in patients with a pre-existing HLA-DNA. The two most common causes of AMR due to *de novo* DSAs are non-adherence to medication and inadequate immunosuppression. The latter is often attributed to minimisation strategies. Additionally, acute T cell-mediated rejection, malignancy and opportunistic infections, such as BK polyomavirus (BKPyV) and cytomegalovirus (CMV) infections, which require a reduction in immunosuppression, may also influence the development of late-onset AMR [15]. Preventing AMR requires addressing non-adherence and under-immunosuppression, while ensuring the long-term safety and efficacy of immunosuppression.

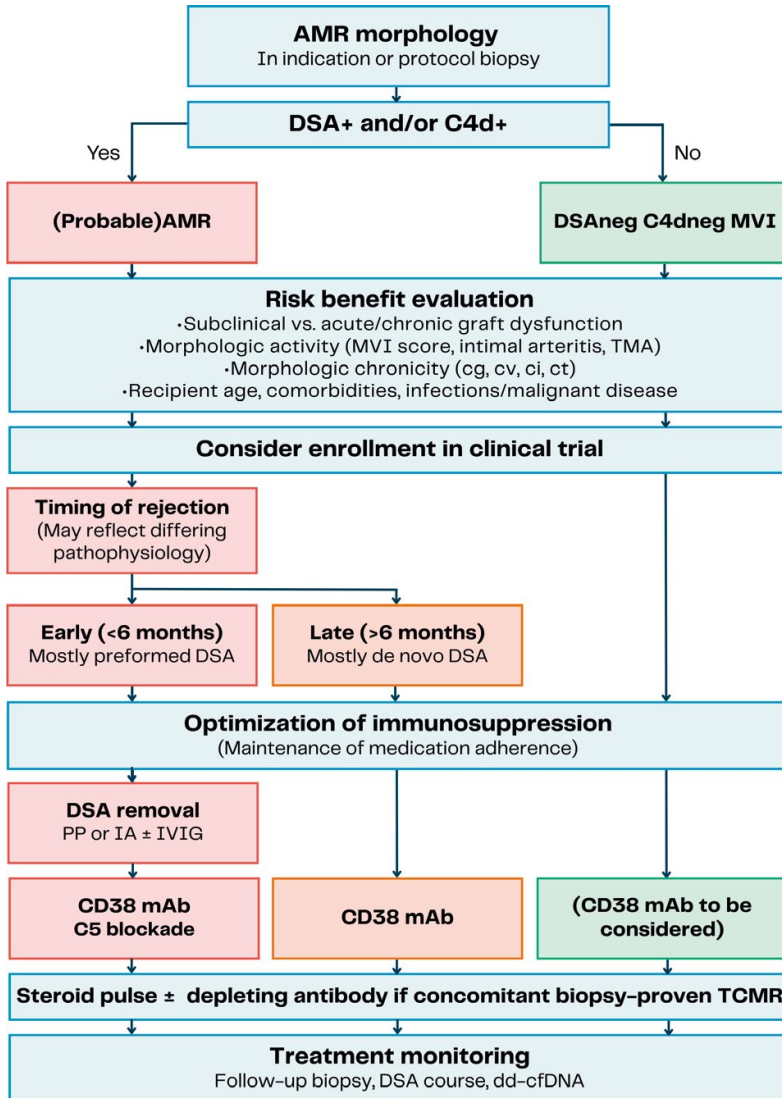
## 7 Treatment

### Active antibody-mediated rejection

The primary goal of treating AMR is to reduce the titres of existing pathogenic DSAs, eradicate the clonal population of B or plasma cells responsible for their production, prevent complement activation and reduce endothelial injury, and preserve graft function [16]. While previous trials primarily targeted the cause of AMR, recent data on the successful reversal of AMR activity by CD38 antibodies suggest that targeting the cellular inflammation with CD38-positive natural killer cells resulting from antibody binding to the endothelium could be an additional rational approach.

The following recommendations for treating AMR largely align with those set out in the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines and the 2019 Transplantation Society Working Group Expert Consensus [16, 17]. For patients diagnosed with active AMR within the first 6–12 months post-transplant (early onset), some authors recommend initial therapy comprising glucocorticoids (10 mg of methylprednisolone per kg of body weight daily for three to five days, followed by a rapid oral prednisone taper), whereas other experts recommend steroid pulse therapy only in patients with concomitant biopsy-proven TCMR (Figure 1) [18]. While DSA removal by plasmapheresis or immunoadsorption is supported by data from an RCT and recommended, the administration of IVIG is optional. Some experts also administer rituximab if the patient has better allograft function (e.g., eGFR of at least 20 ml/min/1.73 m<sup>2</sup> and lower chronicity scores on biopsy) and has

**Figure 1** Proposed therapeutic algorithm for the management of AMR and DSA- and C4d-negative MVI. cg, transplant glomerulopathy; ci, interstitial fibrosis; ct, tubular atrophy; cv, vascular fibrous intimal thickening; g, glomerulitis; IA, immunoadsorption; PP, plasmapheresis; ptc, peritubular capillaritis; TMA, thrombotic microangiopathy. Reproduced with permission from ref. [18].



evidence of severe disease (e.g., higher DSA MFI levels or DSA-load measured by cumulative MFI, diffuse C4d staining or more extensive microvascular inflammation, i.e., a glomerulitis score and a peritubular capillary sum score of at least 4) on biopsy. For all patients, we augment maintenance immunosuppression as needed. For example, we increase the tacrolimus maintenance dose to achieve a trough level 20–25% above that at the time of rejection and/or above 5 µg/L, while maximising the antiproliferative agent dose (e.g., mycophenolate) and initiating steroid maintenance therapy in those off steroids, as well as evaluation and management of non-adherence.

Plasmapheresis is performed daily or every other day for up to six sessions, or until the serum creatinine level is within 20–30% of the baseline level. The initial treatment typically involves a 1.5-fold volume exchange with albumin, while subsequent treatments involve a one-volume exchange with albumin. We prefer an every-other-day plasmapheresis schedule, since albumin alone can often be administered for replacement, with the prothrombin time, partial thromboplastin time and fibrinogen recovering to acceptable levels within the interval, without the need to administer fresh frozen plasma. This avoids the risk of antigen sensitisation. However, one to two units of fresh frozen plasma may be used for replacement at the end of plasmapheresis to reduce the risk of bleeding in an appropriate clinical setting, such as on the same day as a kidney allograft biopsy. We administer IVIG at a dose of 2 g/kg body weight at the end of the apheresis course [18]. Rituximab is administered as a single 375 mg/m<sup>2</sup> dose after plasmapheresis and IVIG have been completed. Immunoabsorption, proteasome inhibitors, interleukin (IL)-6 blockade, or complement inhibitors may be considered for patients who do not respond to the initial treatment.

For patients diagnosed with active AMR after the first 6–12 months post-transplant (i.e., late-onset AMR), we recommend initial therapy comprising intravenous immunoglobulin (IVIG) at a dose of 200 mg/kg every two weeks for three doses, with no plasmapheresis due to a lack of evidence supporting its safety and efficacy in late-onset AMR. Some experts administer rituximab if the patient has better allograft function, lower chronicity scores on biopsy and evidence of severe disease, e.g., higher DSA, diffuse C4d staining or more extensive microvascular inflammation (i.e., a glomerulitis score and a peritubular capillary score of at least 4 on biopsy). For all patients, we also increase maintenance immunosuppression as outlined above.

### Chronic active antibody-mediated rejection

Chronic AMR, the most common cause of graft failure, is more difficult to treat than active AMR since irreversible tissue damage to the kidney allograft has already occurred [19, 20]. While there is evidence to suggest that antibody-mediated injury requires a combination of strategies to inhibit B cell development, maturation and activity, it is unclear which combination of therapies is safe and effective for patients with chronic AMR. There is currently no high-quality evidence to inform optimal treatment for chronic active AMR, and the evidence supporting our treatment approach primarily comes from observational studies [21, 22]. The lack of strong evidence has resulted in substantial heterogeneity in clinical practice. A 2023 online survey in Europe [23] indicated that over half of adult patients with chronic active AMR receive no additional treatment beyond optimized immunosuppression. Common reasons highlighted in the survey to leave chronic active AMR untreated, despite the known association with impaired graft outcome, include appreciation of disease irreversibility, fear of costs and side effects, and the lack of robust trial data. When additional treatments are used, IVIG, steroid pulses, and apheresis are common, whereas rituximab or other biologics are used less frequently [23].

For paediatric patients with chronic active AMR, we recommend initial therapy involving IVIG and rituximab. In a prospective pilot study on antihumoral therapy consisting of high-dose IVIG (4 weekly doses of IVIG, 1 g/kg body weight per dose) and a single dose of rituximab (375 mg/m<sup>2</sup> body surface area 1 week after the last IVIG infusion) in 20 paediatric kidney transplant recipients, 14 patients (70%) responded: nine of nine patients (100%) without and five of 11 (45%) with transplant glomerulopathy [21]. C4d positivity in PTC decreased from 40 ± 18.5% in the index biopsy to 11.6 ± 12.2% in the follow-up biopsy. In four of nine biopsies (44%), C4d staining turned negative. During 2 years of follow-up, the median loss of eGFR in each of the four 6-month periods remained significantly lower compared with prior to therapy. Class I DSA declined in response to antihumoral therapy by 61%, class II DSA by 63% 12 months after intervention. IVIG and rituximab significantly reduced or stabilized the progressive loss of transplant function in paediatric patients with chronic AMR over an observation period of 2 years, apparently by lowering circulating DSA and reducing intrarenal complement activation [21]. All patients treated for active AMR should recommence antimicrobial and antiviral prophylaxis with a regimen identical to that administered in the immediate post-transplant period.

If the patient does not respond to initial therapy involving IVIG and rituximab, the anti-interleukin 6 receptor antibody tocilizumab could be considered, which is administered intravenously at a dose of 8 mg/kg once monthly. Limited data suggest that treatment with interleukin (IL)-6 blockade may benefit patients with chronic AMR [22]. Felzartamab, an investigational anti-CD38 monoclonal antibody that targets plasma cells and natural killer (NK) cells, was evaluated in a phase II pilot trial in which 22 adult kidney transplant recipients with AMR occurring after 180 days post-transplant (15 with chronic active AMR) were randomly assigned to receive nine infusions of felzartamab (16 mg/kg) or placebo [24]. At 24 weeks, mild to moderate adverse events (e.g., first-dose infusion-related reactions) occurred more frequently with felzartamab; however, the rate of serious adverse events was lower with felzartamab than with placebo (9% versus 36%). Patients receiving felzartamab had improved microvascular inflammation scores, lower molecular scores reflecting the probability of AMR and lower levels of donor-derived cell-free DNA (dd-cfDNA). A phase III trial with felzartamab is currently ongoing.

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