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REVIEW

Review of the Clinical and Economic Burden of Antibody-Mediated Rejection in Renal Transplant Recipients

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ABSTRACT

Antibody-mediated rejection (AbMR) is a leading cause of late graft loss in kidney transplant recipients, accounting for up to 60% of late graft failures. AbMR manifests as two distinct phenotypes: the first occurs in the immediate post-transplant period in sensitized patients; the second occurs in the late post-transplant period and has been associated with non-adherence to immunosuppression. The present review summarizes the current treatment options for AbMR, its clinical and economic burden, and approaches for reducing the risk of AbMR. While AbMR is typically refractory to treatment with corticosteroids, there are numerous other approaches focused on removal, inhibition or neutralization of donor-specific antibodies, or inhibition of complement-mediated allograft damage. AbMR treatment is generally expensive with one US study reporting costs of USD 49,000–155,000 per episode. However, leaving AbMR untreated puts patients at high risk of capillaritis, microangiopathy, necrosis and graft failure, which may ultimately result in much greater costs associated with a return to dialysis. Given the barriers to treatment, which include the high cost and the fact that pharmacologic treatments are currently used off-label, prevention of AbMR is important, with improvement in patient adherence to immunosuppression a key strategic approach that may be worthy of further evaluation.

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Keywords: Burden; Cost; Graft rejection; Nephrology; Renal transplant

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INTRODUCTION

Kidney transplantation is considered to be the optimal therapy for patients with end-stage renal

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disease (ESRD) and is associated with improved survival and quality of life as well as being cost-effective relative to dialysis [1–4]. However, not all renal transplants recipients will maintain a functioning renal graft and some experience graft failure resulting in a return to dialysis or retransplantation. In the UK, an estimated 15% of recipients of renal transplants following donor brain death will lose their graft within 5 years, whilst the corresponding figures for recipients of organs from donors following circulatory death and living donors are 14% and 9%, respectively [5]. If these rates are applied to the 2793 adult patients who received kidney-only transplants in the UK in 2014–2015 [5], an estimated 354 of these patients will lose their grafts within 5 years. The situation is similar in other settings with estimates from the US reporting that in 2008 alone over 5000 patients experienced graft loss [6], whilst in France in 2012 over 950 renal transplant recipients lost their grafts [7].

There are numerous events or complications that may ultimately lead to graft loss but the most common causes are glomerular disease and antibody-mediated rejection (AbMR) [8] with approximately 60% of late graft failures thought to be attributable to AbMR [6, 9, 10]. However, this figure may represent an underestimate of the role of AbMR in graft failure as, until recently, C4d staining was required for diagnosis of AbMR (it has since been recognized that AbMR may be present even in the absence of C4d staining).

AbMR may either be acute or chronic, may occur at any time post-transplantation and, although patients are at highest risk for acute AbMR in the immediate post-transplantation period, may also occur concurrently with T cell-mediated rejection processes. The 2011 Banff criteria defined two distinct phenotypes of acute AbMR: phenotype 1 occurs in the immediate post-transplant period in sensitized patients, that is, patients with existing donor-specific antibodies (DSA) due to prior exposure to foreign human leukocyte antigen (HLA) molecules from previous blood transfusion, parity or solid organ transplant; phenotype 2 occurs late post-transplantation due to the de novo formation of DSA raised against donor HLA or non-HLA antigens [11]. Phenotype 2 is thought to be related to non-adherence [12], which plays a key role in a substantial proportion of AbMR cases; indeed, non-adherence has been reported to be a contributing factor in 20–50% of AbMR cases [6, 8]. According to the 2013 Banff criteria, diagnosis of acute AbMR requires histologic evidence of acute tissue injury, evidence of ongoing or recent antibody-vascular endothelium interaction and evidence of DSA directed against HLA or non-HLA donor antigens [13]. In AbMR, endothelial tissue is a key target and damage to the graft is primarily attributable to antigen–antibody complex-mediated activation of the classical complement pathway, which triggers multiple downstream processes including the promotion of antigen presentation, recruitment of leukocytes and the promotion of inflammatory processes. Antibodies raised against donor HLA antigens may also induce damage to the graft via complement-independent processes such as the antibody-mediated activation of macrophages and natural killer cells. Chronic AbMR is characterized by the same DSA and C4d criteria as acute AbMR, but has a long subclinical phase and histologically manifests as transplant glomerulopathy, multilamination of the basement membranes of the peritubular capillaries, and transplant arteriopathy.

Overall, it is estimated that 5–7% of renal transplant recipients will experience AbMR at some point [14]. The aim of the present review was to summarize the current treatment options

for AbMR in addition to data on its clinical and economic burden, and approaches for reducing the risk of AbMR. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

TREATMENT OF ANTIBODY-MEDIATED REJECTION

The prognosis associated with AbMR is worse than for cellular rejection, and AbMR is typically refractory to corticosteroid treatments that are directed primarily against T cell-mediated responses [15]. Several options are currently available for the treatment of AbMR, with the primary approaches focusing on the removal of DSA, inhibition or neutralization of B lymphocytes, or the inhibition of complement-mediated damage (Table 1) [16]. While many treatment options are currently in use, both the Kidney Disease: Improving Global Outcomes (KDIGO) and British Transplantation Society (BTS) guidelines note that recommendations for treatment of AbMR are based on low-grade evidence [17, 18].

Treatments to reduce circulating DSA concentration include both plasmapheresis and immunological techniques using intravenous immunoglobulin (IVIG) or rabbit antithymocyte globulin (rATG). Splenectomy is also available as a treatment of last resort in patients with treatment-refractory AbMR as this rapidly removes a large pool of antibody-producing plasma cells and memory B cells [16]. However, key limitations of splenectomy include surgical complications and the lifelong increased risk of infection and sepsis, particularly from encapsulated bacteria [19].

Treatments that target B lymphocytes include rituximab and bortezomib. Rituximab is a monoclonal antibody directed against the CD20 receptor, which is expressed on pre B cells, mature B cells and memory B cells. Rituximab thereby blocks B cell proliferation. A recent survey of 28 US transplant centers showed that six of the 28 used rituximab as first-line treatment, with a further two reserving the use of rituximab for treatment-refractory AbMR. Small-scale studies have shown that rituximab is an efficacious treatment for AbMR [20]; however [34], the first randomized, double-blind, placebo-controlled trial of rituximab in the treatment of AbMR was published in 2015 [21]. The trial compared plasmapheresis, IVIG and corticosteroids with and without rituximab in 38 renal transplant recipients with biopsy-confirmed AbMR. While the number of patients was small, the trial showed no significant benefit of rituximab over placebo in terms of the primary endpoint of graft loss or no improvement in renal function at 12 months. The authors noted a trend towards improved histological features and Banff scores at 1 and 6 months in the rituximab group, adding that controlled trials with larger enrollment and longer follow-up would be necessary to conclusively establish an effect [21].

Bortezomib is a proteasome inhibitor, which ultimately induces apoptosis in alloantibody producing plasma cells and has been used to effectively treat AbMR in small-scale studies and case series [22–24]. However, Flechner and colleagues noted that several patients (out of 20 case studies) receiving bortezomib experienced fatigue, gastrointestinal complaints, fluid retention, and thrombocytopenia, while only two patients (10%) had undetectable DSA after treatment

Table 1 Treatment modalities for antibody-mediated rejection

Modality	Class	Mechanism	Example and regimen
DSA removal	Polyvalent IgG antibody infusion	Not fully characterized; likely complement-dependent T cell lysis and T cell activation blockade	Intravenous immunoglobulin, five doses of 100 mg/kg given on alternate days after plasmapheresis at 0.6 ml/kg/h for first 30 min then 1.2 mL/kg/h for the remainder [32]
	T cell directed polyclonal antibody	T cell depletion through complement-dependent lysis, T cell apoptosis and induction of apoptosis in B cell lineages [57]	Antithymocyte globulin, 0.75–1.0 mg/kg/day for 5–10 days (alongside plasmapheresis) [58]
	Plasmapheresis	Extracorporeal DSA removal	Blood plasma replacement five sessions on alternate days [32]
	Surgical	Splenectomy	
Target B lymphocytes	Monoclonal IgG1 antibody	Anti-CD20 binding resulting in B cell depletion	Rituximab, average of 3.61 doses of 375 mg/m^2 BSA [59]
	N-protected dipeptide	Proteasome inhibition resulting in plasma cell apoptosis	Bortezomib, four doses of 1.3 mg/m^2 BSA [60]
Inhibition of complement-mediated damage	Monoclonal IgG2/4 antibody	High C5 affinity resulting in terminal complement cascade inhibition	Eculizumab, two doses of 600 mg [61]

BSA body surface area, *CD20* B lymphocyte antigen CD20, *DSA* donor-specific antibody, F_c constant fragment, *IgG* immunoglobulin G

and only 25% returned to baseline renal function prior to diagnosis of AbMR [25].

Treatments that inhibit complement-mediated damage include eculizumab, which is a humanized monoclonal antibody directed against the terminal C5 complement protein, thereby preventing the initiation of the terminal complement cascade normally started by the cleavage of C5 into C5a and C5b [26]. This cleavage inhibition blocks events that would ordinarily be triggered by the cleavage product C5a, including increased vascular permeability, leukocyte chemotaxis and induction of inflammatory mediators (e.g., reactive oxygen species and hydrolytic enzymes). Small-scale clinical trials and case studies have shown that eculizumab is efficacious in terms of preventing AbMR in highly sensitized patients and in the treatment of refractory AbMR [27, 28]. However, the use of eculizumab for the treatment of AbMR is currently off-label and a 2014 commissioning report from NHS England stated that eculizumab would not be funded for AbMR through routine commissioning [29].

Many of the therapies used in the treatment of AbMR including IVIG, ATG and the monoclonal antibodies rituximab and eculizumab are powerful modulators of the immune system and as such their use carries a

small risk of infusion reaction as well as an increased risk of opportunistic infections, some of which may be life-threatening. For example, rituximab carries a US Food and Drug Administration (FDA) black box warning for infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation and progressive multifocal leukoencephalopathy [30], whilst eculizumab carries a black box warning for life-threatening and fatal meningococcal infections [31]. Adverse events associated with IVIG include thrombosis, hemolytic anemia and renal failure.

The KDIGO guidelines on the treatment of AbMR list a number of options that can be used including plasmapheresis, IVIG, anti-CD20 antibodies or lymphocyte-depleting antibodies with or without corticosteroids [17]. However, no treatment algorithm is provided and decisions relating to first-line and second-line treatment for refractory AbMR therefore rely on the judgment of the treating physician. Guidelines from the BTS are similar to the KDIGO guidelines, stating that AbMR should be treated with steroids, plasmapheresis, IVIG, anti-CD20 antibody, or lymphocyte-depleting antibody either alone or in combination [18]. A protocol from the Edinburgh Renal Unit provides more specific recommendations, advocating a combination of methylprednisolone (500 mg IV daily for 3 days), plasmapheresis (5 alternate day exchanges) and IVIG (five doses of 100 mg/kg administered at the end of each plasmapheresis session) [32].

Both the KDIGO and BTS guidelines note that recommendations for treatment of AbMR are based on low-grade evidence. Reviews of the literature corroborate this assessment noting that, to date, clinical trials of interventions in AbMR have generally either been small and/or of low quality, and trials comparing the efficacy of newer therapies such as bortezomib and eculizumab are lacking [33]. Observational studies on the efficacy of AbMR treatments are also limited; evidence from a recent US-based study conducted in routine clinical practice has shown that the most commonly used treatment approaches are IVIG, followed by plasmapheresis, rituximab, bortezomib, rATG then eculizumab [34]. In part, the lack of high-quality data on AbMR therapies can be attributed to the fact that it is not recognized as a distinct indication by the FDA [35] and as such, all use of pharmacologic interventions is off-label.

COST OF ANTIBODY-MEDIATED REJECTION AND ITS TREATMENT

Although there are few studies on the clinical and economic burden of AbMR, the available data shows an association with substantial medical resource use and high direct costs (Table 2).

A recent study by Irish and colleagues reported hospital costs of USD 135,172 in patients with early AbMR versus USD 90,527 in patients with no AbMR, representing a 50% increase ($P < 0.0001$) [36]. Of those costs, USD 5476 were intensive care unit costs in the early AbMR cohort versus USD 2617, representing a 109% increase ($P < 0.0001$).

One US-based study estimated that the per-patient cost of AbMR was USD 25,000 (2011 USD), based on the costs of biopsy, 3-day hospital stay, pulse steroids, IVIG (2 g/kg) and rituximab (1 g) [37]. The same study also estimated a cost of USD 103,000 in the year of event for patients who experienced graft loss due to AbMR, the largest component of which was the cost associated with returning to dialysis. In 2011, Marfo and colleagues

Table 2 Studies reporting costs associated with the treatment of antibody-mediated rejection in renal transplant recipients

Study	Country and year	Cost	Cost items included
Irish et al. [37]	US, 2006–2013	USD 135,172	Total hospital costs with AbMR (USD 90,527 without AbMR)
		USD 5476	Total ICU costs with AbMR (USD 2617 without AbMR)
Marfo et al. [40]	US, 2011	USD 21,000	Two high-dose IVIG infusions at 2 g/kg, single dose of rituximab at 375 mg/m^2
Muduma et al. [43]	UK, 2015	GBP 17,937	IV steroids, five PP sessions, 25 IVIG infusions at 0.1 g/kg
		GBP 19,897	IV steroids, five PP sessions, 25 IVIG infusions at 0.1 g/kg, four bortezomib doses at 1.3 mg/m^2
		GBP 22,027	IV steroids, five PP sessions, 25 IVIG infusions at 0.1 g/kg, 3.61 rituximab doses at 375 mg/m^2
		GBP 30,537	IV steroids, five PP sessions, 25 IVIG infusions at 0.1 g/kg, 2 eculizumab doses at 600 mg
Tanriover et al. [41]	US, 2005–2006	USD 49,000	Biopsy, 2-day hospital stay, IVIG infusion plus rituximab
		USD 155,000	Twenty-day hospital stay, 10 PP sessions, IVIG
Vo et al. [38]	US, 2011	USD 25,000	Biopsy, 3-day hospital stay, pulse steroids, IVIG infusion at 2 g/kg, and rituximab (1 g)

AbMR antibody-mediated rejection, *GBP* pounds sterling, *ICU* intensive care unit, *IV* intravenous, *IVIG* intravenous immunoglobulin, *PP* plasmapheresis, *USD* US dollars

considered a similar treatment protocol based on costs associated with desensitization protocols in the US [38]. The study assumed two high-dose IVIG infusions at 2 g/kg and a single dose of rituximab at 375 mg/m^2 at a total cost per transplantation of USD 21,000 [38]. This cost was assumed for every transplantation conducted in sensitized patients rather than as an AbMR treatment strategy, but the same procedure would be followed again in desensitized patients experiencing AbMR [40]. The authors noted that an additional USD 10,000 would be added to the total cost of desensitization in the case where plasmapheresis is indicated. A third US-based study estimated higher average costs of AbMR events, with estimates ranging between USD 49,000 (based on biopsy, 2-day hospital stay and treatment with IVIG plus rituximab) to USD 155,000 (based on 10 sessions of

plasmapheresis, IVIG and 20 days in hospital; 2005–2006 USD) [39].

To date there are no cost/cost-effectiveness studies relating to the use of bortezomib or eculizumab in the treatment of AbMR. Although the cost of one dose of bortezomib (USD 1200) is lower than that of rituximab 375 mg (USD 5200), a single dose of eculizumab 600 mg has a cost of USD 14,000 [40]. A UK-based study estimated the cost of a single AbMR event to be GBP 18,000; this is a conservative cost estimate based exclusively on the pharmacy costs of corticosteroids and IVIG as well as the cost of plasma exchange and does not include costs associated with diagnosis such as biopsy [41]. If rituximab, bortezomib or eculizumab were also used in addition to corticosteroids, plasmapheresis and IVIG, this increased the cost of a single AbMR event to GBP 22,000, GBP 20,000 and GBP 30,500, respectively [41]. UK data on the costs of immunoabsorption are lacking and the overall cost is dependent on the matrix used and the number of sessions required; however, two studies from Austria and Germany report that the cost per session is approximately EUR 1000 [42, 43].

There is limited information on the overall economic burden associated with AbMR. However, in the UK there were 3256 renal transplants in 2013–2014 [5]. If it is assumed that the rate of transplantation remains constant and that 5–7% of all incident renal transplant recipients experience AbMR at some point [14], the annual cost of treating AbMR in the UK is an estimated GBP 2.9–4.1 million (assuming a minimum cost of GBP 18,000 per event based on treatment with corticosteroids, plasmapheresis and IVIG alone; 2014 GBP). If 30% of cases are also treated with rituximab this figure increases to GBP 3.1–4.4 million. These are conservative estimates as they do not include costs associated with biopsy, second-line treatment for episodes refractory to initial treatment, any treatment-related adverse events, or costs associated with returning to dialysis for those patients who experience graft failure despite treatment. Reported graft failure rates for patients with AbMR range from approximately 30–50% [6, 39, 40, 44, 45]; if the most conservative of these estimates is applied to the UK setting, patients returning to hemodialysis following graft failure adds a further annual cost of GBP 1.1–1.5 million to the overall burden of AbMR (based on a cost of GBP 139 per hemodialysis session [41] and three sessions per week; 2014 GBP).

As stated, these cost estimates do not include the direct medical costs associated with any treatment-related adverse events, many of which may be associated with substantial medical resource utilization and high direct medical costs. Data on the indirect costs including lost productivity associated with AbMR are also lacking. However, these are likely to be substantial due to the fact that treatment involves several hospital days. In one US-based study of resource utilization with monoclonal antibodies used in oncology, a severe infusion reaction was associated with a mean length of hospital stay of 4 days [46]. Graft failure and subsequent return to dialysis is also likely to be associated with substantial societal costs arising from absenteeism, reduced workplace productivity and premature mortality.

PREVENTION OF ANTIBODY-MEDIATED REJECTION

The fact that AbMR is not a recognized indication, together with the high costs

associated with therapies that are off-label, represent practical barriers to treatment in many settings. NHS England commissioning reports for eculizumab and bortezomib state that these treatments will not be routinely commissioned for the treatment of AbMR [34, 47]. Similarly, in the US, the current lack of recognition of AbMR as a distinct pathological process at the regulatory level may mean that costly treatments, in particular, monoclonal antibodies and bortezomib may not be reimbursed by third-party payers. Additionally, cost-effectiveness analyses for AbMR are also lacking meaning that there are currently no data examining whether the high cost of AbMR treatments are mitigated in the long-term by improved outcomes. A key approach is, therefore, to improve prevention of AbMR.

AbMR is more common in sensitized patients than in those without prior exposure to foreign HLA class I and/or class II antibodies. In the US, sensitized patients represent approximately 30% of those on the waiting list for a renal transplant, corresponding to over 20,000 patients according to a 2012 study [11, 48]. Desensitization is aimed at removing existing anti-HLA antibodies prior to transplant, thereby improving long-term outcomes. Methods used in desensitization protocols are similar to the approaches used to treat AbMR, including plasmapheresis, immunoadsorption, rituximab, bortezomib, eculizumab and IVIG. The key distinction between AbMR prevention and treatment is pre-emptive rather than reactive administration of the same therapies, possibly with different administration schedules and dosing [38]. Whilst desensitization has improved short-term patient and graft survival rates, regimens consisting of plasmapheresis and IVIG alone have had limited impact in terms of AbMR, with rates remaining substantially higher in sensitized than non-sensitized patients [38]. However, a recent study of desensitization with eculizumab plus plasmapheresis showed this regimen to be effective in reducing the rate of acute AbMR compared with historical controls, although treatment had little impact on chronic AbMR in patients with persistently high DSA [49]. Whilst newer therapies have shown promising efficacy, high direct costs remain a barrier to their widespread use. This is compounded by the possibility of desensitization not resulting in transplant. For example, Vo et al. [37] reported that 29% of 207 sensitized patients were unresponsive to the desensitization regimen and were continued on dialysis, thereby incurring the high cost of desensitization in addition to the high ongoing costs of dialysis.

Improvements in HLA matching may have also reduced the incidence of AbMR. The introduction of solid-phase immunoassays (SPI) greatly improved many aspects of HLA characterization relative to complement-dependent lymphocytotoxicity (CDC) cross-matching assays. Solid-phase techniques have enabled the detection of low levels of HLA across all 11 HLA loci, allowed DSA levels to be "semiquantitatively" categorized into low, intermediate, and high, and enabled the identification of antibodies to HLA-Cw, HLA-DQA, HLA-DPA, and HLA-DPB, which was not previously possible in most diagnostic laboratories [50]. The importance of these HLA loci in renal graft rejection has only been characterized as result of SPI, and the interpretation of DSA would not have improved so drastically with older cell-based techniques; however, there is still some debate as to whether

antibodies that go undetected by CDC assays and are detectable exclusively by SPI bead assays directly influence outcomes such as AbMR [53].

One key factor that may help to reduce the incidence of AbMR is improving patient adherence to immunosuppression. Non-adherence has been implicated as a causative factor in a substantial proportion of AbMR events [6, 8]. In chronic conditions, adherence frequently worsens over time and is also influenced by pill burden with higher pill burden and dosing frequency being risk factors for non-adherence [51, 52]. The pill burden in renal transplant recipients is substantial. One study from the Spanish setting reported that renal transplant recipients take a mean (SD) of 7 (3) different medications and 11 (5) pills per day [53]. For twice-daily dosing, renal transplant recipients have significantly better adherence to morning dosing compared with evening dosing [54]. However, patients exhibit a preference for once-daily dosing (specifically morning dosing over evening dosing), leading to improved adherence [54–56]. Consequently, changes such as reduced pill burden or simpler dosing regimens, in combination with patient education on the importance of adherence, may have a positive impact; improved adherence may lower the rate of AbMR, which may translate into a reduced clinical and economic burden.

CONCLUSIONS

Overall, AbMR is associated with a substantial clinical and economic burden. Whilst there have been improvements in reducing the incidence of acute rejection, particularly T cell-mediated rejection in the immediate post-transplant period, AbMR remains a leading cause of late rejection and late graft loss. The lack of regulatory recognition combined with the high direct medical costs associated with therapies for AbMR may also represent a practical barrier to treatment in many settings. Prevention of AbMR is therefore important, with improvement in patient adherence to immunosuppression a key strategic approach.

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