Antibody-mediated rejection
after kidney transplantation
an overview of current treatment options

Varsha V. Jharapa, Manah Ahmadia, Saskia A.M.E. van Diessena, Ajda T. Rowshanc
a Medical student, Erasmus MC University Medical Center, Rotterdam, the Netherlands
b Biomedical student, Leiden University Medical Center, the Netherlands
c Supervisor, Department of Nephrology and Transplantation, Erasmus MC University Medical Center, Rotterdam, the Netherlands
Correspondence: Varsha Jharap, e-mail: 329134vj@student.eur.nl

Abstract
Acute antibody-mediated rejection (AMR) after kidney transplantation is an uncommon but serious event, usually leading to graft loss. The current treatment modalities combine plasmapheresis and intravenous immunoglobulin (IVIg). Based on our study of the relevant literature, we compared the efficacy of drug regimens either to treat or to prevent AMR.

A PubMed search was performed using kidney transplantation, graft rejection, humoral rejection and antibody-mediated rejection as search terms.

Fourteen studies were identified. The various treatment regimens used drugs designed to combat antibody formation and/or immune modulation of the effects of the antibodies. The following treatments for AMR were used: plasmapheresis, IVIg, plasmapheresis combined with IVIg, plasmapheresis combined with IVIg and rituximab, rabbit antithymocyte globulin, bortezomib, or splenectomy. Complement inhibitor eculizumab was used in one study to prevent AMR in immunologically high risk transplant candidates.

Evidence based conclusions cannot be drawn from these studies due to the lack of sufficient data, small numbers of included patients, and the extensive co-medication used, which made it impossible to determine the efficacy of a specific drug. Therefore, we suggest to perform a multi-centre RCT with a transparent design comparing the current standard therapy consisting of plasmapheresis and IVIG with eculizumab in a large cohort of patients who develop AMR in immunologically high risk transplant candidates.

Introduction
Recently, several studies have shown that acute antibody-mediated rejection (AMR) is associated with poor prognosis following kidney transplantation.[1] Acute AMR is a rare but serious event. The risk of allograft failure among highly sensitized patients is particularly high in the first three months post transplant.

The 1-year graft survival has been reported to be only 15-50% despite intensive conventional immunosuppressive therapy.[2]

Acute AMR occurs because of antibody-mediated complement activation and eventual lysis of graft endothelium. As such, AMR is associated with C4d deposition in peritubular capillaries. C4d is the complement split product resulting from the cleavage of C4b. C4d can then covalently bind to the vascular endothelium of the kidney graft.[3]

To justify the diagnosis of AMR, in case of graft dysfunction, 3 major diagnostic criteria must be in accordance with the latest Banff classification [4][5]:
1) morphological evidence of acute tissue injury;
2) immunopathological evidence of antibody activity;
and 3) serological evidence of circulating DSA or antibodies against other donor endothelial antigens. The heterogeneous clinical manifestations of AMR, extending, for example from deterioration of graft function to just only unexplained proteinuria, have been always a barrier for the transplant nephrologists to investigate the outcomes in completely homogeneous comparable patient groups. Of note, C4d negative antibody mediated rejection has been recently reported, but still needs more detailed description and definition in the future.[6]

Although no strict evidence-based treatment modality for AMR is available at present, current strategies rely on a combination of drug regimen. For instance, plasmapheresis, intravenous immunoglobulin (IVIg) and immunoabsorption, targeting removal of antibodies. Another treatment relies on plasmapheresis in combination with monoclonal anti-CD20 antibodies (rituximab) or bortezomib, targeting B cells and plasma cells. Furthermore, polyclonal antilymphocyte antibodies including rabbit antithymocyte globulin (rATG), in addition to maintenance immunosuppressive medication (tacrolimus, cyclosporine A, mycophenolate mofetil, and prednisone), have been used to treat AMR (Table 1). The aim of this review was to compare the efficacy of the reported drug regimen for treatment or prevention of acute AMR in renal transplant recipients.
Method
We systematically searched Pubmed, using the search terms; kidney transplantation, graft rejection, and humoral rejection/antibody-mediated rejection. In addition, we included the references from the meeting report of the FDA Antibody-mediated rejection workshop in 2011.[6]
With these terms the following search stream was established: (“Kidney Transplantation”[Mesh]) AND (“Graft Rejection/therapy”[Mesh]) AND (“Immunity, Humoral”[Mesh]) OR “antibody-mediated rejection”[All]).

The following inclusion criteria were applied to select the studies: published in English, based on clinical trials, and a study population of more than 5 patients. Studies were excluded if the full text was not available for Erasmus MC or LUMC students, no review or if the study concerned ABO incompatibility rejection. We also screened the references of the included studies for useful articles.

Results
Graft survival was the primary endpoint in all studies (Table 1). Only two studies [1,7] provided additional information on serum creatinine levels as the primary endpoint reflecting the actual graft function. Studies investigating prevention of AMR in a high risk population used the incidence of AMR as the primary endpoint. The majority of the population samples in the included studies consisted of Caucasians. Some studies also included minorities; i.e. black and Hispanic patients.

Studies on Treatment of AMR
Plasmapheresis/ IVIG/immunoadsorption targeting removal of antibodies or immunomodulation of the effects of antibodies Jordan et al. treated seven patients suffering from AMR with IVlg (2 g/kg) combined with maintenance immunosuppression consisting of cyclosporine, prednisone, and azathioprine. They reported on a 4 year follow-up in this case series. Graft survival of 100% was achieved. They concluded that treating acute AMR with IVlg and maintenance triple immunosuppression was effective in treating AMR.

| Table 1 - Published reports on treatment or prevention of acute AMR in kidney transplant recipients. |
|-------------------------------------------------|-----|---------------------------------|-----------------|-----------------|-----------------|
| Publication                                      | Treatment regimen                | N    | FUP              | Graft survival (%) | Patient survival (%) | Serum creatinine (mg/dL) |
| Jordan et al. (1998)6                           | 1x IVlg, CsA, Pred, and AZA       | 7    | 4 y              | 100               | –                | 1.2 – 1.7          |
| Pascual et al. (1998)4                          | 4-7x PPh followed by 1x IVlg, TAC, MMF, and Pred | 5    | 19.6 ± 5.6 m    | 100               | 100              | 1.2 ± 0.3          |
| Crespo et al. (2001)17                          | 5P Ph with TAC and MMF and IVlg | 19   | 29 m             | 80                | 100              | 1.5 ± 0.4          |
| Rocha et al. (2003)9                            | 4x PPh, 1-3x IVlg, Mpred pulses, CNI, MMF, and Pred1 | 16   | 457 ± 76 d      | 81                | –                | 1.6               |
| Shah et al. (2004)14                            | 6.8x PPh every other day, 6x rATG, TAC, MMF, and Pred | 7    | 1 y             | 85.7              | –                | 1.46 ± 0.33        |
| Becker et al. (2004)41                          | 1x RTX, Mpred, rATG with or without PPh, CsA or TAC, MMF, and Pred | 27   | 605 ± 335.3 d   | 85%              | 77.8             | 0.95 ± 0.29        |
| Böhmig et al. (2007)19                          | A: 9-14x IAf, TAC, and ALA or Pred | A: 5 | 2 y             | A: 80             | –                | A: 2.2             |
|                                                  | B: TAG and ALA or Pred2          | B: 5 | 20               | B: 20             | –                | B: 1.6             |
| Faguer et al. (2007)42                          | 3x Mpred, 4x RTX, 9x PPh, and TAC, MMF, and Pred | 8    | 10 m            | 75                | 100              | 153 µmol/L         |
| Everly et al. (2008)7                          | PPh, 4x BOR, TAC, MMF, and Pred3 | 6i   | 140 d           | 66.7              | –                | –                 |
| Lefaucheur et al. (2009)1                          | A: 4x IVlg, 3x Mpred pulses | A: 12 | 36 m          | A: 50             | –                | –                 |
|                                                  | B: 4x PPh and IVlg, and 2x RTX | B: 12 | 91.7           | –                | –                | –                 |
| Maintenance IS in both groups: TAC or CsA, MMF, and Pred |                     |      |                  |                  |                  |                   |
| Brown et al. (2009)9                            | 8.1x PPh, TAC or EVE, MMF, and Pred | 16   | 5 y             | 78                | 93               | 130 µmol/L         |
| Stegall et al. (2011)14                         | A: ECU, induction therapy with rATG, TAC | A: 26 | 11.9 m        | A: 100            | –                | –                 |
|                                                  | B: historical group: 4-14x PPh, induction therapy with rATG, TAC, MMF, and Pred | B: 51 | 48.8 m        | B: 96             | –                | –                 |
|                                                  | B: EVE, twice daily MS, and Pred | B: 61 | 98.4           | –                | –                | –                 |
| Tzvetanov et al. (2012)13                        | 7.2x PPh followed by IVlg, splenectomy as rescue therapy, Maintenance IS: TAC, MMF, and Pred | 11   | 25.8 ± 19 m    | 81.8              | 90.9             | 2.8 ± 1.5          |

FUP = Follow-up; ACR = acute cellular rejection; AMR = antibody-mediated rejection; DSA = donor-specific antibodies; GFR = glomerular filtration rate; IV = intravenous; IV Ig = intravenous immunoglobulin; MMF = mycophenolate mofetil; PPh = plasmapheresis; PTC = peritubular capillaries; rATG = rabbit antithymocyte globulin; CsA = cyclosporine; Pred = prednisone; AZA = azathioprine; TAC = tacrolimus; CNI = calcineurin inhibitor; RTX= rituximab; IA = immunoabsorption; Mpred= methylprednisolone; ALA = anti-lymphocyte antibody; BOR = bortezomib; EVE = everolimus; ECU = eculizumab; MS = mycophenolate sodium

1 First 3 plasmapheresis once daily on consecutive days followed by sessions with intervals of 3 days for a period up to 6 weeks
2 Patients in group B had the option of immunoabsorption rescue after 3 weeks
3 Some patients also received rATG, rituximab, IVlg, or a combination of those treatments
4 Patients with mixed rejection; AMR & ACR
In the observational study of Brown et al., 18 patients were included. Plasmapheresis (up to 8 times), in combination with maintenance immunosuppression consisting of tacrolimus or everolimus, mycophenolate mofetil (MMF) and prednisone, was the therapy of choice. After a follow-up period of 5 years, the graft survival appeared to be 78%. The authors concluded that plasmapheresis was successful, with an excellent long-term graft and patient survival (93%).[8]

In another study performed in 1998, plasmapheresis (4-7 times) in combination with tacrolimus (0.14 g/kg/day) and MMF (2 g/day) was used to treat AMR. The authors concluded that this treatment is effective in preventing kidney graft loss due to AMR. The patients were followed for 19.6 ± 5.6 months. No graft was lost. They postulated that this mode of therapy is effective for patients who develop circulating DSA after transplantation."n= 1/5).[2]

A similar clinical trial published in 2001 reported on kidney transplant recipients who received five cycles of plasmapheresis together with tacrolimus (0.11 mg/kg/day) and IVIg (0.4/day). This study showed that acute AMR was reversible in 90% of patients. The authors concluded that the low dose of IVIg might have had an effect on the reversibility of AMR and on graft survival.[12] Rocha et al., on the other hand, used high dose IVIg (2 g/kg) in combination with plasmapheresis (4 cycles) to treat acute AMR. In their study the average one-year graft survival was 81%. AMR was strongly related to a higher occurrence of delayed graft function immediately after transplantation.[9]

In 2007, a RCT was performed to investigate the efficacy of immunoadsorption in treatment of acute AMR. In this study 10 patients were included and randomized as 1/1. The treatment arm (group A) underwent 9-14 immunoadsorption treatments next to standard treatment, whereas the control group (group B) was only treated with tacrolimus, prednisone and anti-lymphocyte antibodies. After inclusion of 5 patients in each arm, the investigators had to terminate the study because of the evidently superior clinical benefit of immunoadsorption therapy. Graft survival in group A was 80%, compared to 20 % in the control group. In immunoadsorption group all episodes of AMR were completely reversible compared to only 20% of rejection episodes in group B. The patients were then followed for two years. The authors concluded that immunoadsorption is capable of improving graft function within three weeks after starting the treatment and is superior to the treatment in control group in every aspect.[10]

Lefaucheur et al. investigated two treatment options; high dose IVIg (2g/kg) with plasmapheresis (4 times). The 24 patients were followed for 36 months. Patients treated with plasmapheresis showed a significantly better graft survival (p = 0.02 ). It was concluded that plasmapheresis is superior to high dose IVIg alone in treating acute AMR.[1]

Rituximab and bortezomib targeting B cells and plasma cells

Two studies evaluated the effect of rituximab on acute AMR. In the study of Becker et al., 27 patients were included. The patients received rituximab (375 mg/m2 ), intravenous methylprednisolon (500 mg/day), rATG (1.5 mg/kg/day) in combination with plasmapheresis. The follow-up time was 605 ± 335.3 days and the graft survival 85%.

In the study of Faguer et al, 8 patients were included. The patients received rituximab (375 mg/m2 ) in combination with methylprednisolone (10mg/kg/day) and plasmapheresis. Graft survival rate was 75%.

Altogether, both studies showed a similar graft survival. The first study concluded that rituximab might be effective in treating acute AMR, which is unresponsive to steroids [11], while the second study concluded that rituximab was effective in reversal of acute AMR.[12]

Everly et al., studied the effects of bortezomib on treating mixed rejection types after kidney transplantation. This study included patients, which received bortezomib (1.5 mg/m2 ) together with plasmapheresis as treatment regimen. The patients were followed for 140 days and the graft survival rate was 66.7%.The results led to the their conclusion was that bortezomib is effective in treating mixed rejection types with and that it has minimal toxicity.[7]

Other approaches; ATG, splenectomy and eculizumab

Another study on the effects of rATG in treatment of acute AMR showed no difference in survival between patients with or without AMR, indicating a good long-term survival.[15] Seven patients with AMR were included and received 6.8 times plasmapheresis and 6 times rATG (0.75mg/kg/day). The patients were followed for one year. Graft survival was 85.7%.

A clinical trial investigated the use of splenectomy as a rescue therapy for acute AMR. The 11 patients included in the study, who did not respond to the standard therapy consisting of plasmapheresis and IVIg (100mg/kg), received the rescue therapy. Patients were followed for 25.8 ± 19 months and the graft survival appeared to be 81.8%. The authors concluded that splenectomy can be used to treat patients who are unresponsive to the applied therapies. Unfortunately, this study was still not published in a peer reviewed journal.[13]

Studies on prevention of AMR

A recent case-control study concerned prevention of acute AMR using a historical control group. The authors examined the efficacy of complement inhibition with eculizumab, for the prevention AMR in immunologically high-risk recipients transplanted with a donor kidney after desensitization therapy. The incidence of biopsy-proven AMR in 26 highly sensitized recipients, who received eculizumab according to a special scheme starting at a pre-transplant time point, was compared to a historical control group of 51 sensitized patients treated with a similar plasma exchange-based protocol without eculizumab. The incidence of AMR was 7.7% (2/26) in the eculizumab group compared to 41.2% (21/51) in the control group (p = 0.0031). Stegall et al. concluded that eculizumab seems to be an effective therapy, because it prevented the development of AMR in highly sensitized patients compared to the controls; this result was statistically significant.[14]

Liefeldt et al. performed a post hoc analysis on the relationship between the use of everolimus vs. cyclosporine and the occurrence of donor-specific antibodies. In this study, 127 patients were included and the follow-up was 1273 days.
Group A received cyclosporine (100-150 ng/ml) and group B received everolimus (6-10 ng/ml). Patients treated with everolimus developed more acute AMR and new DSA than those treated with cyclosporine (p=0.048). The authors concluded that everolimus is associated with an increased risk for AMR development and suggested limiting the use of everolimus to patients with low immunological risk.[15]

Discussion
The treatment regimen published by Böhmig et al., a high quality RCT, seems to be a promising treatment for AMR. In this study the effect of immunoadsorption in combination with a standard immunosuppressive therapy was compared to the standard therapy alone. The function of immunoadsorption is to remove the DSA in the blood of the recipient. The results of this study showed that the reversibility of the rejection was significantly different between the two study groups. The study had to be terminated after inclusion of 5 patients in each arm because of superiority of treatment arm with immunoadsorption. All the patients treated with immunoadsorption showed reversal of the rejection and the graft survival was also better. Based on results of this well designed study, the proof of concept is delivered that removal of antibodies might be an essential step in the treatment of AMR.

The treatment regimen published by Stegall et al., seems to be an effective therapy to prevent the occurrence of AMR in high-risk patients. They used eculizumab in combination with induction and maintenance immunosuppressive therapy. The results showed a significant difference in the incidence of acute AMR, with less AMR occurring in the patients treated with eculizumab as compared to almost 40% AMR incidence in their historical control group. Therefore, eculizumab might be effective in preventing the occurrence of AMR.[14]

The treatment regimen published by Everly et al., could also be considered as a possible treatment option for AMR. Bortezomib has an effect on the plasma cells, the source cells for the production of the DSA. However, the side effects and high level of toxicity of bortezomib is a restriction. The agents inhibiting plasma cell activity with less severe side effects should preferably be investigated as soon as they become available.[7]

Limitations
Based on findings reported in the literature, evidence-based conclusions cannot be drawn from the aforementioned studies on treatment of AMR because of the lack of high-quality data, the small numbers of included patients and extensive co-medication used, which makes it very hard to determine the efficacy of a specific drug. Most of the studies were clinical series without a control group. Some included a historical control group. Lack of RCT design makes it difficult to assess and compare the efficacy of different treatment modalities. The results should therefore be interpreted with caution. Most of these clinical trials included only a small number of patients, i.e. the average number included was 7. In general the end points were well defined and relevant: kidney graft survival and function. Furthermore, the extensive and variable co-medication schemes limit the interpretation of the data obtained, which makes it impossible to draw any solid conclusions.

Concluding remarks
As it is clear, no evidence-based conclusions can be drawn about the superior therapy for treatment or prevention of AMR. More research is required to determine which treatment option is the most effective modality in treating AMR. However, it is our belief that eculizumab is effective in preventing the occurrence of AMR. Therefore, we suggest that a multi-centre RCT be performed with a transparent design comparing the current standard therapy consisting of plasmapheresis and IVIg, with eculizumab in a large cohort of patients who develop AMR. Graft survival and function should be investigated as primary endpoints with a longer follow-up period of 5-10 years. All patients should receive maintenance immunosuppressive medication in the same manner.

References


