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Alemtuzumab as Second-Line Treatment for Late Antibody-Mediated Rejection of Transplanted Kidneys

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ABSTRACT

Whether the anti-CD52 monoclonal antibody alemtuzumab can be an effective treatment option for late antibody-mediated rejection (ABMR) is not known. In a single-center pilot study, 12 patients with late ABMR were given 30 mg subcutaneous alemtuzumab. Median time from transplantation to biopsy was 22 months with 10 of 12 recipients fulfilling criteria for the histologic diagnosis chronic-active ABMR. The estimated glomerular filtration rate (eGFR) loss before diagnosis was 1.2 mL/min/mo with graft loss (eGFR <15 mL/min) expected to occur within 2 years in 11 of 12 cases. All recipients showed no or an inadequate response to initial treatment with steroids and intravenous immunoglobulin. eGFR at time of alemtuzumab administration was 35 mL/min/1.73 m² (IQR, 30-42) and stabilized or improved in 10 of 12 recipients within 12 months. Proteinuria was stable in the year after alemtuzumab. At 3-year follow-up, the death-censored graft survival was 68% (uncensored graft survival was 58%). Five cases of 10 cases that could be evaluated at 3-year follow-up had stable eGFR (on average 44 mL/min at 12 months and 42 mL/min at 36 months). Alemtuzumab was generally well tolerated and only 2 cases of opportunistic infections were noted. One case of symptomatic parvovirus B infection and 1 case of BK viral infection occurred, which both cleared at follow-up. In conclusion, alemtuzumab may be of value as a second-line treatment for late ABMR with rapid loss of eGFR.

LONG-TERM graft loss of the kidney allograft has changed little in the last decades and improving this outcome is considered an unmet need [1]. Late antibody-mediated rejection (ABMR; diagnosed ≥ 6 months after transplantation), often presents with a histologic (h) diagnosis of chronic-active ABMR (c-aABMRh) and is recognized as one of the major causes of graft loss in the long term in recipients of a donor kidney [2-4]. If left untreated, the prognosis is poor and progression to graft failure (GF) occurs in half of the cases within 3 years after diagnosis [5-7]. Treatment options vary among different transplantation centers but usually involve any combination of high-dose steroids, rituximab, intravenous immunoglobulin (IVIG), plasmapheresis or anti-interleukin 6 receptor (tocilizumab) [6,8-10]. Reported success rates vary and interpretation is limited by the serious shortage of randomized controlled trials. Currently, only 2 randomized trials have been performed that showed no benefit of rituximab or bortezomib in the treatment of c-aABMR [11,12]. The benefit of immune cell-depleting agents like antithymocyte globulins (ATG) and alemtuzumab is not clear. To date, only 1 small case series of late ABMR/c-aABMR in pediatric kidney transplant recipients has

been published, showing potential benefit for ATG as a rescue therapy [13].

Alemtuzumab is a humanized monoclonal antibody against the CD52 antigen and depletes T cells, B cells, and NK cells and to a lesser extent monocytes, dendritic cells, and granulocytes [14,15]. Prolonged depletion of T, B, and NK cells follows after alemtuzumab administration and restoration of normal numbers of circulating lymphocytes takes ≥ 1 year [16]. On theoretical grounds, depletion of T cells could be beneficial as circulating anti-donor antibodies arise as a result of continuous exposure of the recipient's immune system to foreign antigens. Most likely, the classical pathway of antigen presentation is followed, with involvement of helper T cells that direct differentiation of B cells to antibody-producing plasma cells [17]. Additionally, depletion of NK cells may be beneficial as

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antibody-mediated cytotoxicity of these cells is likely involved in the pathogenesis of c-aABMR [18–21,33].

However, despite the potential of simultaneous T, B, and NK cell depletion as a treatment for late ABMR, there is a paucity of data. In our center, patients with a biopsy-proven diagnosis of late ABMR/c-aABMR are treated with a combination of high-dose steroids and IVIG. In our experience, this leads to a favorable attenuation of estimated glomerular filtration rate (eGFR) loss and degree of proteinuria in about 60% of cases with prolongation of graft survival [5]. In nonresponding cases with a rapid loss of eGFR, alemtuzumab was given as a second-line salvage treatment.

Our results show that a favorable clinical response can lead to a significant number of rescued kidney transplants that would otherwise be lost within 2 years after diagnosis.

MATERIAL AND METHODS

Study Population

Twelve recipients of a kidney transplant with a kidney biopsy-proven diagnosis of ABMR ≥ 6 months after transplantation received second-line rescue treatment with subcutaneous alemtuzumab 30 mg. First-line standard treatment had been IV methylprednisolone 1000 mg for 3 days in combination with a single infusion of IVIG 1 g/kg [5]. All kidney transplantations were ABO-blood group compatible with a negative complement-dependent cytotoxicity (CDC) assay before transplantation and no donor-specific antibodies against HLA. The clinical and demographic characteristics of the cases included are shown in Table 1. All recipients had a follow-up of ≥ 12 months after alemtuzumab with regular assessment of renal function and proteinuria. A formal flow chart cannot be given but in our center, about 180 kidney transplantations each year are performed and ABMR is relatively rare with an incidence of about 3% within the first year. The cases described here are the only cases of late ABMR that we have treated with alemtuzumab within the period 2014 to 2019. At our center, we do not give plasma exchange for late ABMR because of disappointing results in accordance with the experience by others with late ABMR [9].

The decision to treat with alemtuzumab as rescue therapy was essentially made on clinical grounds and was based on the rapid decline of eGFR over time, with an expected graft loss within 1 to 3 years and insufficient or no response after standard treatment. These aspects were balanced against the clinical condition and frailty of the patient and the remaining kidney function at that time (eGFR ≥ 20 mL/min). After alemtuzumab treatment, the immunosuppressive drugs were unchanged except for 1 recipient who was switched from everolimus to tacrolimus.

The HLA-typing of donor and recipient, CDC assays with calculation of panel-reactive antibodies (PRA; % of PRA, positive if $>4\%$) and assessment of donor-specific antibodies (DSA) were performed at the immunohematology laboratory Leiden as described previously [3].

At time of biopsy, the clinical and laboratory data, as shown in Table 1, were collected. Renal biopsies were scored according to the Banff 2017 criteria by an experienced renal pathologist [22]. Not all recipients had detectable donor-specific anti-HLA antibodies at time of diagnosis or positive C4d staining in the diagnostic kidney biopsy (Fig 1). Diagnosis of ABMR by using the criteria of either C4d or presence of DSA has unfortunately a major drawback as both are not always present. The 30% positivity of C4d in the biopsy is not an uncommon finding using immunohistochemistry in cases of (even DSA-positive) ABMR. This has tempered the initial enthusiasm for this marker as a criterion for ABMR. Similarly, DSA (meaning anti-donor HLA

Table 1. Clinical and Demographic Characteristics of Recipients With Late ABMR

| | |
|--|-------------|
| Men/Women | 6/6 |
| Age at transplantation in median years (range) | 55 (13-67) |
| Underlying disease | |
| Polycystic disease | 2 |
| Diabetes mellitus | 2 |
| Glomerulonephritis | 5 |
| Reflux/Amyloid/Unknown | 3 |
| Type of donor kidney: living/deceased | 9/3 |
| Recipients with re-transplantation, n (%) | 3 (25) |
| Median number of HLA-mismatches | |
| Class I | 3 |
| Class II | 1 |
| Class I and II | 4 |
| PRA $>4\%$ at time of transplantation, n (%) | 5 (42) |
| Time after kidney transplantation to diagnosis (mo)* | 22 (14-47) |
| Time of follow-up after diagnosis (mo) | 24 (19-51) |
| At time of diagnostic biopsy | |
| eGFR in mL/min/1.73 m ² | 43 (36-48) |
| Urine protein/Creatinine ratio (mg/mmol) | 97 (16-164) |
| At time of alemtuzumab administration | |
| eGFR in mL/min/1.73 m ² | 35 (30-42) |
| Urine protein/creatinine ratio (mg/mmol) | 70 (13-181) |
| Immune suppression at time of diagnosis | |
| Tacrolimus/MMF/Prednisone | 4 |
| Tacrolimus/MMF | 6 |
| Tacrolimus/Prednisone | 1 |
| Tacrolimus/Everolimus | 1 |
| Donor-specific antibodies detected | |
| Anti-HLA I only/anti-HLA II only | 0/4 |
| Anti-HLA I and II | 1 |
| ABMR/ABMRh [†] | 1/1 |
| c-aABMR/c-aABMRh | 7/3 |

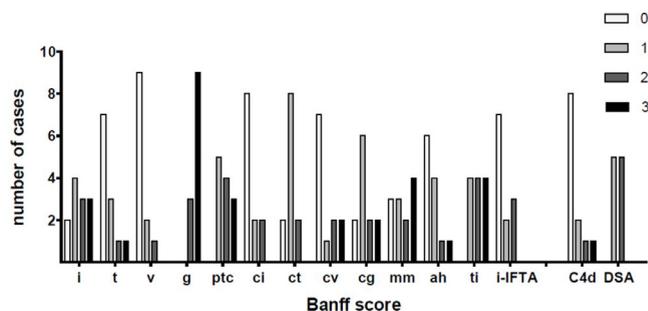
ABMR, antibody-mediated rejection; c-aABMR, chronic-active ABMR; c-aABMRh, chronic-active ABMR by histology; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; PRA, panel-reactive antibodies.

* All values given in medians with 25th-75th percentile between parenthesis.

[†] ABMR by Banff criteria, ABMRh by histology criteria, c-aABMR by Banff criteria, c-aABMRh by histology criteria.

antibodies) are usually detected in about 40% to 60% of cases with histologic findings in the renal biopsy that could fit the diagnosis of ABMR. In cases of c-aABMR the presence or absence of anti-HLA DSA is not related to the histology by Banff criteria and, more importantly, graft survival [32]. For this reason, the term *ABMRh* (h for histology) to define the cases of ABMR that do not fit in the most recent Banff criteria was introduced. The Banff criteria of 2015 allowed to call these cases suspicious ABMR but this category was dropped in Banff 2017, creating a category of cases with rejection that most clinicians interpret as humoral rejection (or at least not-T cell-mediated rejection) but without a Banff diagnosis. Therefore, if the first 2 Banff criteria were fulfilled a diagnosis of (chronic-active) ABMR histology (ABMRh) was made, in accordance with recent publications [5,22,23]. Chronic damage was assessed along the Banff criteria for glomerular endothelial basement membrane duplication, tubular atrophy, interstitial fibrosis, arteriolar hyalinosis, and vascular fibrous intimal thickening. A detailed description of the Banff classification is given in Fig 1, which shows microvascular inflammation with early signs of chronicity shown by glomerular membrane duplication in most cases. Detailed information on the number of cases with c-aABMRh and c-aABMR is given Table 1.

Fig 1. Banff scores, C4d positivity and the presence of donor-specific anti-HLA antibodies (DSA) are given for all cases of late ABMR (N = 12). Inflammation (i), tubulitis (t), v (arteritis/v-lesions), glomerulitis (g), peritubular capillaritis (ptc), interstitial fibrosis (ci), tubular atrophy (ct), glomerular endothelial cell basement membrane duplication (cg), arterial intimal thickening (cv), arteriolar hyalinosis (ah), mesangial thickening (mm), total inflammation (ti), inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA), C4d positive in ptc, donor-specific anti-bodies (DSA absent light grey bar, present dark grey bar).



Allograft failure was defined by the need for starting dialysis treatment or kidney retransplantation. The local medical ethical committee approved the study (MEC-2015-222) and humans involved in this study were treated in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Statistical analysis

Normally distributed data are expressed as mean \pm standard deviation, non-normally distributed data as median with the IQR (25th - 75th percentile). A $P < .05$ was considered statistically significant. Differences between groups of non-normally distributed data were analyzed by the Mann-Whitney test and the Wilcoxon signed-rank test for paired data.

Death-censored graft survival was assessed by Kaplan–Meier analysis. Statistical analysis was performed with software SPSS version 21 (IBM, Armonk, NY, United States).

RESULTS

Recipient Characteristics

The clinical and demographic characteristics of the cases included in this study are shown in Table 1. Age and kidney donor type (mostly living donor kidney) were representative for recipients in our transplantation center. The time from kidney transplantation to diagnosis of ABMR is relatively short, with a median of 22 months compared with the median of 6 years described in a recent case series of late ABMR patients from our center [5]. All recipients had stable trough levels of immunosuppressive drugs in the therapeutic range before the diagnosis of ABMR was made with no evidence for nonadherence to medication.

The average through level of tacrolimus at time of alemtuzumab administration was 6.8 $\mu\text{g/L}$ and did not change significantly during follow-up (7, 5.7, and 8 $\mu\text{g/L}$ at respectively 1-, 2-, and 3-year follow-up). Patients using prednisone continued with daily 7.5 mg and mycophenolate was continued and given in an average dose of 750 mg twice daily.

In 6 of 12 patients, DSA were detectable and in 4 of 12, C4d staining was positive in the peritubular capillaries. This enabled a diagnosis of ABMR according to recent Banff criteria in 8 cases, and the remaining 4 cases were classified as ABMRh (Table 1).

Kidney Biopsy Characteristics

Glomerular basement membrane duplication was observed, albeit with a low chronic glomerulopathy score, in 10 of 12

cases classifying these cases of late ABMR as c-aABMR. By fulfilling the criterion of presence of DSA and/or C4d positivity in the peritubular capillaries, 7 of the 10 cases were c-aABMR by recent Banff criteria and 3 cases c-aABMRh (Table 1). In accordance with the relatively short time between transplantation and diagnosis, the chronic damage scores, in particular scores relating to interstitial fibrosis and tubular atrophy, were low. Instead the degree of microvascular inflammation within the glomeruli and peritubular capillaries was high with most cases classified as grade 2 or higher on the Banff Lesion Scores *g* (glomerulitis) and *ptc* (peritubular capillaritis) (Fig 1).

Alemtuzumab Favorably Attenuates eGFR Loss and Proteinuria

In the year before kidney biopsy, all patients showed rapid loss of eGFR with a median of -1.2 mL/min/mo (IQR, 1-1.7 mL/min/mo) projecting a time to graft loss (defined as an eGFR < 15 mL/min) within 2 years in 11 of 12 cases (Fig. 2 and 3). At time of biopsy, the median eGFR was 43 mL/min/1.73 m² (IQR, 36-48).

The proteinuria varied considerably but increased significantly over time from 12 months before diagnosis until time of biopsy (from 18 to 78 mg protein/mmol creatinine, $P = .04$; Fig 3). All patients had received standard therapy with high-dose steroids and IVIG within 2 weeks after diagnosis but that did not significantly improve the downward trend of the eGFR in 10 patients, whereas stabilization or slight improvement of eGFR was observed in 2 patients.

Alemtuzumab was given at a median time of 59 days (IQR, 13-101) after therapy with high-dose steroids and IVIG, which was given only once in all recipients. The median eGFR was 35 mL/min/1.73 m² (IQR, 30-42) when alemtuzumab was administered; 8 mL/min/1.73 m² lower compared with the time of diagnosis. On average, treatment resulted in stabilization of eGFR and proteinuria within the year after alemtuzumab (Fig 3). Individual lines for eGFR showed that in virtually all patients, the downward slope of eGFR was favorably attenuated but responses varied greatly (Fig 2). In 9 patients, there was a clear tendency to improvement of eGFR in the year after alemtuzumab. At 3-year follow-up, 10 of 12 patients could be evaluated (1 lost to follow-up at our center but with functional graft at 5 years and 1 with 3-year follow-up). One patient was retransplanted as the eGFR remained 16 mL/min, 1 patient was started on dialysis after 1 year, 3 patients showed progressive

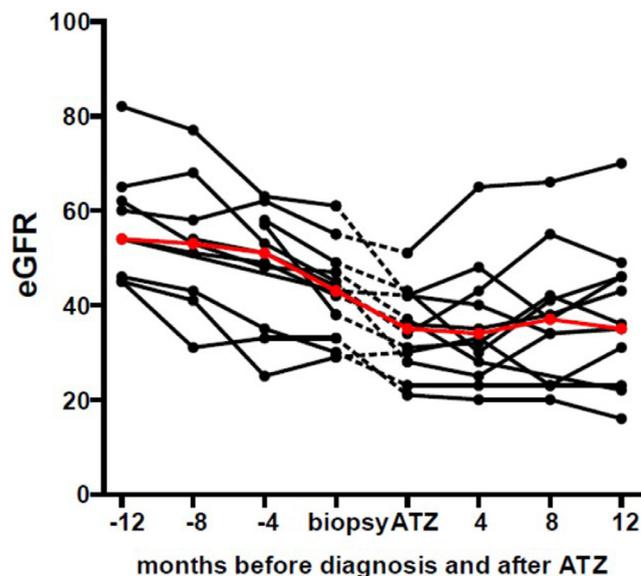


Fig 2. Estimated glomerular filtration rate (eGFR) in the months before diagnostic biopsy, at time of alemtuzumab (ATZ), and in the months thereafter are shown for individual cases of late antibody-mediated rejection (ABMR) (N = 12). Red line represents the median eGFR at all given points in time. Dotted lines connect the individual lines between time of diagnosis and time of ATZ administration.

loss of eGFR (1 died of malignancy and 1 of heart failure before graft failure) and the remaining 5 cases had stable eGFR (on average 44 mL/min at 12 months and 42 mL/min at 36 months).

Graft Loss

The median follow-up was 24 months (IQR. 19-51). During follow-up, 2 patients died (1 died of cancer and the other of heart failure) and 3 patients lost their graft, resulting in a death-censored graft survival of 68% at 3 years after diagnosis (Fig 4). In all 3 recipients who lost their graft, the Banff scores for interstitial fibrosis (ci) at diagnosis were >0. This is significantly different from the remaining 9 patients where only 2 had scores >0 ($P = .04$). Additionally, the i-IFTA (inflammation in areas of fibrosis) scores were higher in the group with graft loss (3 of 3 >0) compared with the recipients without graft loss at follow-up (2 of 9 >0; $P = .04$). All other Banff scores, C4d positivity, and presence of DSA were not associated with graft survival.

Side Effects of Treatment

Alemtuzumab was generally well tolerated. Only 2 cases of opportunistic infections were noted. One case of symptomatic parvovirus B infection and one case of BK viral infection occurred; however, both cleared at follow-up. At follow-up, 2 urinary tract infections and 1 gastrointestinal infection occurred; neither required hospitalization.

DISCUSSION

Late ABMR is considered a prevalent cause of graft loss in the long-term but currently no effective treatment is generally accepted. In our center, patients with the diagnosis of late ABMR are mostly classified as c-aABMR. The average time to

diagnosis is 6 years after transplantation with a steady decrease in eGFR of about 10 mL/min/1.73 m² within 12 to 24 months before diagnosis by renal biopsy [10,22,24]. In most cases, this is accompanied by an increase in proteinuria although the degree of proteinuria is highly variable. According to protocol, all our patients with c-aABMR are given high-dose methylprednisolone and IVIG, which may favorably attenuate the downward trend in eGFR and stabilize proteinuria [5]. Most studies show that, if untreated, graft survival of patients with late ABMR or c-aABMR is only 50% at 3 years after diagnosis on average [25].

To date, there are no studies on alemtuzumab for late ABMR. Only 3 case reports described 5 patients with documented use of alemtuzumab for the treatment of ABMR with or without cellular rejection [26-28]. In these studies, alemtuzumab was used with plasmapheresis and IVIG, with or without rituximab. All these studies reported an initial response to therapy and a decrease in serum creatinine within 2 days to 2 weeks of therapy.

Only 1 case series has been published of 8 children who received ATG as a rescue therapy for late ABMR of their kidney transplant [13]. Although the authors conclude that ATG can lead to stabilization of eGFR, the follow-up was limited to only 9 months. Additionally, the time from transplantation to the diagnosis of ABMR was rather short (median 179 days) with a very steep decline in eGFR before treatment. These latter characteristics limit the generalizability of the results from this study.

In the present study, time between transplantation and c-aABMR diagnosis is also relatively short compared with the median of 6 years previously reported [5]. Also, patients had a relatively rapid loss of eGFR within the 6 months before diagnosis, a high microvascular inflammation score, and relatively low scores on chronicity lesions like glomerular basement membrane duplication, hyalinosis, and IFTA. These features

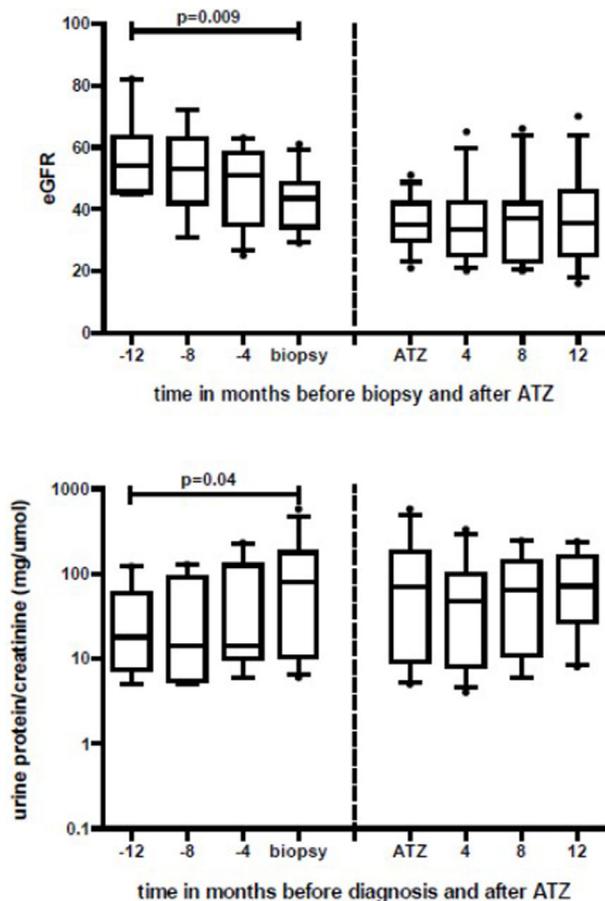


Fig 3. (A) Box plots for estimated glomerular filtration rate (eGFR) in the months before diagnostic biopsy, at time of alemtuzumab (ATZ), and in the months thereafter for all cases (N = 12). **(B)** Box plots for the urinary protein over creatinine ratio in the same time frames. Boxes represent the median (horizontal line in the box) with the 25th and 75th percentiles with whiskers showing the 10th and 90th percentiles. Data outside these latter percentiles are shown as individual dots.

are quite different from most of the c-aABMR cases that have high chronicity scores, probably due to a longer duration of microvascular inflammation with little eGFR loss in the beginning of the process [22,29]. Although generally the prognosis of c-aABMR is poor, few treating physicians are willing to treat chronic rejection with gradual loss of eGFR with a T cell-depleting agent because of its unknown efficacy for this condition.

The patients selected for the current report not only had a very poor projected graft survival based on eGFR downslope before diagnosis but also showed no or little response to standard treatment with methylprednisolone/IVIG. Despite that, alemtuzumab seemed to stabilize graft function, with few side effects, in most patients. Despite this initial response, graft loss did occur, leading to a 3-year graft survival of 68%; however, this is still significantly better than anticipated by their initial

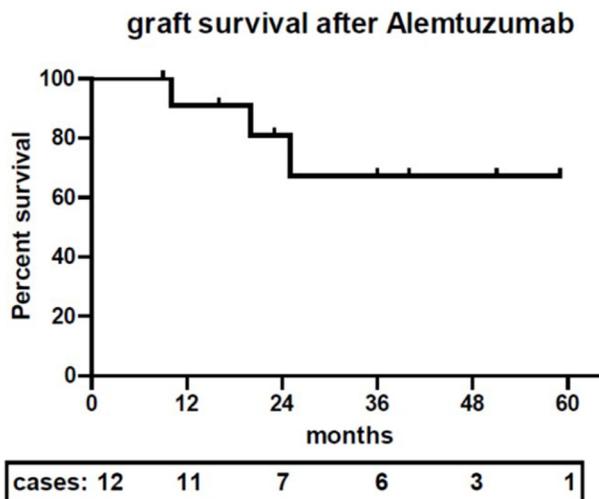


Fig 4. Death-censored graft survival of the kidney after alemtuzumab is given for late antibody-mediated rejection (ABMR) (N = 12).

eGFR loss. Proteinuria, which is another marker of effectiveness, stabilized after alemtuzumab administration in most patients. This latter result is similar to the published case series in children with late ABMR treated with ATG and in recipients responding to high-dose steroids and IVIG [5,13]. The results described in the present study are not definitive proof of a beneficial effect of alemtuzumab but are at least of interest. Publication of case reports and small case series are, in our opinion, important to generate new ideas and show early results of new treatments or rare cases.

Of note is that of all Banff scores, the presence of chronic interstitial fibrosis with inflammatory cells in the areas of fibrosis was related to graft failure at follow-up. This is essentially the same for c-aABMR diagnosed many years after transplantation where the presence of chronic damage in the tubulo-interstitial compartment predicts future graft failure [22,30]. This also, underlines that inflammatory cells within these regions of fibrosis (i-IFTA score) are important and may indicate a more severe pattern of damage by the ongoing underlying disease process [2,31].

This case series had obvious limitations, including the small number of cases, the selection of recipients, and the observational nature without rebiopsies of the kidney allograft. Additionally, a definitive diagnosis according to recent Banff criteria could not be made in all cases because either C4d staining was negative in the biopsy specimen or DSA could not be detected, as described extensively in the methods section.

CONCLUSION

To our knowledge, this is the first case series of late ABMR treated with alemtuzumab, indicating that there may be therapeutic potential in cases that show a rapid loss of graft function. Given the limitations of the present study, further research is

needed to prove efficacy of alemtuzumab for late ABMR beyond doubt.

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