Repeated cycles of high-dose intravenous immunoglobulin and plasmapheresis for treatment of late antibody-mediated rejection of renal transplants

Chih-Yuan Lee, Wei-Chou Lin, Ming-Shiou Wu, Ching-Yao Yang, Chi-Chuan Yeh, Meng-Kun Tsai

Background/purpose: Intravenous immunoglobulin (IVIG) plays a central role in the treatment of antibody-mediated rejection (AMR) of renal allografts, but the treatment outcomes for late AMR (>6 months after transplantation) are poor.

Methods: We performed a retrospective study to assess the response patterns of IVIG-based (2 g/kg) desensitization for late AMR. Patients who received desensitization after the pathological diagnosis of late AMR positive for complement component C4d were grouped as the Desensitized Group and compared to a historical Control Group with complement component C4d positivity in retrospective stainings.

Results: The 10-year graft survival of the Desensitized Group (73.9%, n = 35) was significantly better than that of the historical Control Group (35.0%, n = 40) without desensitization. In the Desensitized Group, a subgroup of patients (D2 Subgroup, n = 11), who responded to desensitization initially but deteriorated later, was identified to benefit from repeated cycles of desensitization at 31.1 ± 20.9 months. Patients receiving only one cycle of desensitization were further grouped into D1-good (n = 10) and D1-poor (n = 14) based on their long-term renal function. The D2 Subgroup patients did not exhibit significant improvements in renal function compared to the D1-poor patients, until 30 months after IVIG-based desensitization, suggesting desensitization therapy has a working window of approximately 24 months.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2016.07.007
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Introduction

Early antibody-mediated rejection (AMR) of renal transplantation has been successfully treated by desensitization therapy including plasmapheresis and administration of intravenous immunoglobulin (IVIG) or rituximab, an anti-CD20 antibody targeting B cells. Nonetheless, late AMR, diagnosed 6 months post-transplantation or later, remains a clinical problem causing graft dysfunction and eventually failure.1,2 Various therapeutic agents and combination regimens have been reported to treat AMR of renal transplants. The combination of plasmapheresis and IVIG was previously demonstrated to improve outcomes of early AMR, compared to plasmapheresis alone.3 In addition, IVIG in combination with rituximab stabilizes the progressive loss of transplant function in pediatric patients with chronic AMR.4 However, Gupta et al5 showed that late AMR cases responded poorly to plasmapheresis, IVIG, and rituximab therapy, even upon addition of bortezomib, a proteasome inhibitor used to deplete plasma cells. Rituximab and IVIG therapy for transplant glomerulopathy during chronic AMR do not change the natural course of chronic AMR and could be associated with serious cytopenia and infections.6 No randomized controlled studies have been conducted to study the treatment of late AMR do date; possibly because of heterogeneous patient populations and difficulty in research funding.6

IVIG plays a central role in desensitization therapy for AMR, thus, we have adopted a strategy of repeated desensitization using high-doses of IVIG (total dose: 2 g/kg) and double filtration plasmapheresis (DFPP) in our transplant center since 2007. In this paper, we present an analysis of treatment patterns and responses based on our single-center experience of late AMR treatment with high-dose IVIG and plasmapheresis.

Methods

Patient populations

A retrospective study was performed to assess the outcome of late AMR among 968 renal transplantation patients, treated at a single transplant center between January 1990 and December 2012. Renal biopsy results and medical records were reviewed from the date of transplantation to June 2015. Complement component C4d (C4d) staining was conducted in all renal transplant biopsies, including those obtained prior to the setup of the C4d staining method, if the paraffin-embedded specimens were available in our hospital. The results of C4d staining were incorporated into the original pathological reports of the patients as supplements, because positive staining of C4d in renal transplant biopsies is considered one of the predominant characteristics of AMR and suggestive of poor long-term graft survival. In the case of positive retrospective C4d staining, patients were asked to undergo an update biopsy, if the renal allografts were still functioning. Further treatment would be instituted according to the update biopsy. If patients were positive for C4d in the retrospective staining and desensitized according to the update biopsy, their results were not included. Approval of the research ethics committee was not mandatory for retrospective data analysis in this study.

Study groups

Thirty-five patients who received timely desensitization therapy for late AMR (> 6 months after transplantation) were grouped as the Desensitized Group. We then identified a Control Group of 40 patients with C4d-positive (>50%) staining in their late-event-based biopsy who did not receive any desensitization therapy. Those who received rituximab, eculizumab, bortezomib, or any other antibody therapy were not included in this study. Demographics and clinical outcomes of the Desensitized and Control Groups were collected to test the hypothesis that desensitization of late AMR with IVIG and DFPP improves long-term graft survival. Furthermore, the Desensitized Group was subgrouped according to treatment and response to desensitization. Ten patients who responded well to one course of desensitization therapy and enjoyed long-term improved renal function were subgrouped as D1-good. Another 11 patients of the Desensitized Group receiving >2 cycles of desensitization therapy were subgrouped as D2. However, there were 14 patients, subgrouped as D1-poor, who did not receive repeated cycles of desensitization therapy even though their renal function deteriorated during follow-up.

Diagnosis of AMR

A renal biopsy was routinely suggested to renal transplant patients in our transplant center with a serum creatinine elevation > 30%, significant proteinuria, or persistent edema. The pathological findings were interpreted by an experienced renal pathologist. Patients included in this study were those with graft dysfunction combined with >50% C4d positivity in the peritubular capillaries and morphological evidence of tissue injury and microvascular inflammation.7 Those who had documented glomerulonephritis in the pathological reports, such as membranoproliferative or IgA glomerulonephritis, were not included in this study. Daily urine protein levels and flow...
Immunosuppressive therapy and desensitization

Immunosuppressive regimens for all patients were based on a calcineurin inhibitor (CNI), either cyclosporine (CsA) or tacrolimus (TAC), in combination with mycophenolate mofetil (MMF) (or mycophenolate sodium) or azathioprine. The initial target trough levels for TAC and CsA were 8–16 ng/mL and 200–400 ng/mL, respectively, and MMF was prescribed at an initial dose of 1–2 g/d. White blood cell counts were maintained at 4000–6000/mm³, unless intolerance occurred or the maximum dose was reached. The target blood levels at 12 months were 5–8 ng/mL for TAC and 100–200 ng/mL for CsA. Corticosteroids were routinely used after transplantation. The doses of oral immunosuppressive drugs including CNIs, MMF (or sodium) and steroid were basically not changed for the reason of AMR and desensitization.

The desensitization therapy for patients with late AMR included four sessions of DFPP and IVIG performed every other day. Patients with combined cellular rejection received a 3-day methylprednisolone (10 mg/kg/d) pulse therapy. DFPP was performed using a KM-8800 in a Kuraray plasmapheresis system incorporating a Plasmacure PS-06 and an Evaflux 4A as the plasma fractionator (Kuraray Medical, Tokyo, Japan), as previously described. The exchange volume was set at 50 mL/kg with 300–500 mL saline solution as the replacement fluid. IVIG was administered every other day at a dose of 0.5 g/kg immediately after each DFPP. Renal function, biochemistry, and coagulation profiles were regularly checked during the desensitization period. Coagulopathy was corrected by plasma transfusion.

Statistical analysis

Unpaired two-tailed t tests and Fisher’s exact tests were performed for normally distributed continuous variables and categorical variables, respectively. Renal transplant function was calculated by a four-variable Modification of Diet in Renal Disease (MDRD) equation. Transplant graft failure was defined as the return to renal replacement therapy for > 30 days. The serum creatinine levels after graft failure were estimated at 10 mg/dL, and patients who died with functional grafts were considered to have graft failure. The endpoints of this study were renal function and graft survival. Log-rank tests were performed to examine the prognostic significance of desensitization therapy, recipient gender, donor type, delayed function, initial CNI, previous cellular rejection, and combined cellular rejection. Cox regression analysis was performed to determine the prognostic significance of age at transplantation, age and HLA mismatch, AMR time, and MDRD-based estimated glomerular filtration rate (eGFR) for AMR. Additionally, for the Desensitized Group, pathological scoring, DSA levels, and 24-hour proteinuria at the time of AMR diagnosis were included in the statistical analyses to identify indicators of treatment responsiveness. Multivariate regression analysis was then applied step-by-step to factors with statistical significance in the univariate analysis to identify the independent factors for graft survival.

Results

Patient characteristics

Patient demographics of the Desensitized and Control Groups are summarized in Table 1. The gender distribution and mean age at transplantation were similar between the groups.

Table 1  Patient demographics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Desensitized group (n = 35)</th>
<th>Control group (n = 40)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplantation (y)</td>
<td>41.0 ± 12.1</td>
<td>39.8 ± 13.7</td>
<td>0.677</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>15:20</td>
<td>20:20</td>
<td>0.644</td>
</tr>
<tr>
<td>Donor type (deceased:living)</td>
<td>17:18</td>
<td>29:11</td>
<td>0.056</td>
</tr>
<tr>
<td>HLA mismatches</td>
<td>3.4 ± 1.4</td>
<td>3.3 ± 1.3</td>
<td>0.887</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>7/35 (20.0%)</td>
<td>11/40 (27.5%)</td>
<td>0.589</td>
</tr>
<tr>
<td>Calcineurin inhibitor (Tac:CsA)</td>
<td>21:14</td>
<td>22:18</td>
<td>0.815</td>
</tr>
<tr>
<td>AMR time (mo)</td>
<td>59.5 ± 34.5</td>
<td>50.4 ± 44.2</td>
<td>0.323</td>
</tr>
<tr>
<td>MDRD GFR on AMR (mL/min)</td>
<td>34.2 ± 13.9</td>
<td>30.4 ± 16.2</td>
<td>0.288</td>
</tr>
<tr>
<td>Previous cellular rejection</td>
<td>6/35 (17.1%)</td>
<td>17/40 (42.5%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Combined cellular rejection</td>
<td>15/35 (42.9%)</td>
<td>12/40 (30.0%)</td>
<td>0.336</td>
</tr>
<tr>
<td>Number of renal biopsies</td>
<td>2.7 ± 1.4</td>
<td>2.8 ± 1.5</td>
<td>0.477</td>
</tr>
<tr>
<td>5/10-y graft survival</td>
<td>94.0%/73.9%</td>
<td>60.0%/35.0%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>10-y patient survival</td>
<td>96.4%</td>
<td>94.4%</td>
<td>0.452</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>108.0 ± 38.1</td>
<td>86.6 ± 51.1</td>
<td>0.047</td>
</tr>
</tbody>
</table>

AMR = antibody-mediated rejection; CsA = cyclosporine; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; TAC = tacrolimus.
Desensitized and Control Groups. There were more live-donor renal transplants in the Desensitized Group (51.4%, 18/35) than in the Control Group (27.5%, 11/40; \( p = 0.056 \)); possibly because of a different attitude toward the cost and outcome of renal transplantation. The HLA mismatches, incidences of delayed function, and initial use of CNIs were similar between the two groups.

Treatment outcome of patients with late AMR

The Desensitized Group had late AMR at 59.5 ± 34.5 months after transplantation and the Control Group at 50.4 ± 44.2 months (\( p > 0.05 \)). The MDRD eGFRs at the time of late AMR were not significantly different between the Desensitized (34.2 ± 13.9 mL/min) and the Control (30.4 ± 16.2 mL/min) Groups. However, the Control Group had a significantly higher incidence of previous cellular rejection (42.9%, 15/35) than the Desensitized Group had (17.1%, 6/35) (\( p = 0.024 \)). At the time of late AMR, 42.9% (15/35) and 30.0% (12/40) of the Desensitized and the Control Groups, respectively, had combined cellular rejection. Importantly, the Desensitized Group had good graft survival of 73.9% at 10 years, which was significantly better (\( p < 0.001 \)) than that of the Control Group (35.0%; Figure 1). The patient survival rates between the two groups were equivalent, but the follow-up duration of the Desensitized Group (108.0 ± 38.1 months) was longer than that of the Control Group (86.6 ± 51.1 months; \( p = 0.047 \)); possibly because of better graft survival in the Desensitized Group.

Renal function after late AMR

While the eGFRs of the Desensitized and Control Groups were not significantly different at the time of late AMR, the eGFR changes of the two groups were markedly different during the first 6 months after AMR: the average eGFR improved from 34.19 ± 13.85 mL/min to 37.32 ± 13.19 mL/min in the Desensitized Group, but dropped from 30.44 ± 16.17 mL/min to 19.77 ± 15.18 mL/min in the Control Group. After 6 months of desensitization therapy, the average eGFRs of the Desensitized Group declined gradually during follow-up but were still significantly better than those of the Control Group. Six patients in the Desensitized Group and 28 in the Control Group had graft failure, and additionally, one patient in the Desensitized Group and two in the Control Group died within 48 months after AMR. The average eGFRs of the Desensitized and Control Groups were significantly different during follow-up (\( p < 0.001 \)). Details of the eGFRs of the Desensitized and Control Groups are shown in Figure 2.

Demographics of the three desensitized subgroups

The demographics of the three subgroups were not significantly different (Table 2). The D1-poor Subgroup included older patients, more male patients, and patients with more HLA mismatches. The D2 Subgroup (3.6 ± 1.6) underwent significantly more renal biopsies than the D1-poor Subgroup (2.2 ± 1.0; \( p = 0.017 \)). The D1-poor Subgroup had a longer average AMR time after transplantation, lower average eGFR on AMR, and more 24-hour urinary protein than the other two subgroups, although these differences were not statistically significant. All patients of the three subgroups were highly sensitized (PRA > 50%) to either class I or class II HLA (Table 2). The average highest DSA level of the D1-poor Subgroup (10365 ± 5919 MFI) was significantly (\( p = 0.015 \)) higher than that of the D2 Subgroup (3581 ± 2251 MFI). However, the difference in highest DSA levels between the D1-good Subgroup (2171 ± 2136 MFI) and D2 Subgroup was not significant (\( p = 0.079 \)). Every patient receiving desensitization therapy had a renal biopsy showing strong C4d staining (> 50%). The average percentages of the C4d staining among the three subgroups were comparable, and so were the criteria for interstitial
fibrosis (ci), criteria for tubular atrophy (ct), and peritubular capillaritis (ptc) scores, as defined by the Banff meeting reports.2,4 The cv and cg scores of the D1-poor Subgroup were higher than those of the other two subgroups, but the differences did not reach statistical significance; possibly because of the small number of patients included in this study. The duration of follow-up was not significantly different among the three subgroups. All the renal allografts of the patients in the D1-good and D2 Subgroups survived. In the D1-poor Subgroup, one patient died of a cerebrovascular accident, and eight had graft failure during follow-up.

Treatment response after desensitization

When eGFRs were compared, the D1-good Subgroup was not significantly better than the D2 Subgroup. The D2 Subgroup was also not better than the D1-poor Subgroup during the initial 18 months after desensitization (Figure 3). However, the D1-poor Subgroup had significantly better eGFRs than the Control Group during the first 24 months, suggesting that desensitization therapy was at least temporarily effective in treating late AMR. For the D1-poor Subgroup and the Control Group, the differences in eGFRs leveled out 24 months after IVIG and DFPP therapy. Interestingly, the eGFRs of the D2 Subgroup were not significantly lower than those of the D1-good Subgroup until 24 months after the first desensitization therapy. For the D2 Subgroup, based on follow-up biopsy and C4d staining, the second desensitization was performed 31.1 ± 20.9 months (median time: 24 months) after the first. One patient of the D2 Subgroup received a third desensitization therapy, 22 months after the second one. When compared with the D1-poor Subgroup with progressive deterioration of eGFRs, the D2 Subgroup had significantly better eGFRs 30 months after initial desensitization. Our regimen of desensitization including high-dose IVIG and DFPP seemed to have an average working window of about 24 months.

**Prognostic factors for graft survival in patients with late AMR**

The underlying prognostic factors for the long-term outcome of renal transplantation with late AMR could be multifactorial; treatment, patient characteristics,
Desensitization therapy (eGFRs of the D2 subgroup were not significantly lower than regression analyses revealed that desensitization therapy and graft condition all play an important role. Stepwise the first 24 months (\( p < 0.05 \)) had significantly better eGFRs than the Control Group during randomized Group and in the Control Group. The D1-poor Subgroup (eGFR) of the patients in the three subgroups of the Desensitization Group 30 months after the initial desensitization. * Subgroup had significantly better eGFRs than the D1-poor Subgroup 30 months after the initial desensitization. ** \( p < 0.01 \). MDRD = Modification of Diet in Renal Disease.

and graft condition all play an important role. Stepwise regression analyses revealed that desensitization therapy (\( p < 0.001 \)), AMR time (\( p < 0.001 \)), and MDRD eGFR (\( p < 0.001 \)) were independent prognostic factors for patients with late AMR (Table 3). Desensitization therapy significantly reduced the risk of graft failure [risk ratio (RR) 0.2557]. The risk of graft failure was also reduced in function of the time of AMR (RR 0.9759/mo after transplantation). Importantly, the better the MDRD eGFRs of the patients were at the time of late AMR, the lower the risk of graft failure (RR 0.9411/unit of GFR). As for patients receiving desensitization therapy, 24-hour urinary protein was the only statistically significant prognostic factor (\( p = 0.025 \); Table 3). The RR for graft failure after desensitization was 1.0003/mg of urinary protein.

### Discussion

IVIG plays a central role in the treatment of AMR of renal transplants, and we demonstrated that high-dose IVIG and DFPP could rescue most of the patients with late AMR. However, we found that there was an average working window of \( \sim 24 \) months for our IVIG-based desensitization therapy. The patients in the D2 Subgroup in this study showed a temporary improvement in eGFRs up to 6 months after desensitization, but their renal function still deteriorated during later follow-up. Fortunately, repeated cycles of desensitization therapy at 31.1 ± 20.9 months after the first treatment stabilized the situation of the D2 Subgroup. Further prospective studies are needed to test for the working windows in different desensitization regimens. The D1-poor Subgroup was treated during the earlier stage of desensitization therapy evaluation, when repetition of desensitization was not included. When compared to the D2 Subgroup, the timing of AMR diagnosis in the D1-poor Subgroup could have been too late (70.9 ± 30.4 months vs. 50.8 ± 38.4 months after transplantation).

The duration of effect for IVIG has not been studied in patients with late AMR. As Kuitwaard et al. showed in patients with Guillain–Barré syndrome, serum IgG concentrations increased significantly for at least 4 weeks after a cumulative IVIG dose of 2 g/kg. A low ΔIgG after treatment was found to be independently associated with poor response rates, suggesting a second course of IVIG might be beneficial. Although the circulatory IgG levels could not possibly last as long as the average working window we observed, IVIG could exert its immunomodulatory effect via multiple mechanisms, including through the binding of Fc-\( \gamma \) receptors, foreign and self-antigens, as well as through inhibition of circulatory myeloid dendritic cells. Reduction of the IgG concentration to baseline levels or persistence of HLA antibodies was not necessarily associated with recurrent AMR episodes.

Strategies to treat AMR include antibody removal, depletion of B cells and/or plasma cells, complement inhibition, and pleiotropic immunomodulation by IVIG. Blockade of terminal complement by eculizumab, an anti-C5 antibody, was recently reported to be inadequate to control AMR. Combined therapy with rituximab and IVIG increased the graft survival rate of patients with chronic AMR, compared to IVIG alone. Although rituximab did not increase the risk of infection when used for

### Table 3

<table>
<thead>
<tr>
<th>Cox’s regression</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Risk ratio</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with late AMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Desensitization</td>
<td>-1.3637</td>
<td>0.3847</td>
<td>0.2557</td>
<td>-2.1177</td>
<td>-0.6097</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AMR time</td>
<td>-0.0243</td>
<td>0.0051</td>
<td>0.9759</td>
<td>-0.0344</td>
<td>-0.0142</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MDRD GFR on AMR</td>
<td>-0.0607</td>
<td>0.0145</td>
<td>0.9411</td>
<td>-0.0891</td>
<td>-0.0322</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Patients with desensitization therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h urinary protein</td>
<td>0.000347</td>
<td>0.000155</td>
<td>1.0003</td>
<td>0.000044</td>
<td>0.000650</td>
<td>0.025</td>
</tr>
</tbody>
</table>

AMR = antibody-mediated rejection; CL = confidence limit; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
desensitization of HLA or ABO-incompatible renal transplantation, Kumar et al\textsuperscript{19,20} showed that its use after kidney transplantation was associated with a high risk of infection and infection-related mortality. Late AMR patients were found to be less responsive to bortezomib therapy and to have a significant level of residual DSA afterwards.\textsuperscript{21} Repeated cycles of bortezomib were thus suggested to treat patients with refractory late AMR, which was consistent with our findings that repeated cycles of desensitization might be necessary and helpful.\textsuperscript{22} Further studies are required to establish the benefits and side effects of repeated bortezomib therapy in patients with late AMR.\textsuperscript{23,24}

Considering the effect of treatment repetition, repeated cycles of IVIG and plasmapheresis had an important impact on DSA clearance. Failure to reduce antibody levels, as Everly et al\textsuperscript{25} demonstrated, was significantly associated with renal allograft loss after AMR. Pascual et al\textsuperscript{26} showed that a rigorous protocol of plasma exchange would significantly reduce DSA and improve renal function, at least in the short term. However, DSA detection in the Luminex-based assay can indicate a significant risk of decreased graft survival, but does not predict the outcome in an individual patient.\textsuperscript{27} Patients with DSA do not always experience clinical AMR, and the renal allografts could absorb HLA antibody.\textsuperscript{28,29} The endpoints of our study were thus renal function and graft survival, instead of DSA levels. We could not evaluate the effect of our desensitization therapy in DSA reduction in this retrospective study because LabScreen Single Antigen PRA was not performed after desensitization therapy.

Many factors, including graft function, proteinuria, pathological scoring, and concurrent cellular rejection, were identified as indicators of responsiveness to desensitization therapy for AMR.\textsuperscript{30,31} Renal transplant patients have a better chance for graft survival when AMR occurs later and when its diagnosis and treatment start in the context of better renal function. With regard to treatment responsiveness, 24-hour urinary protein was identified as the only risk factor for graft failure at a risk ratio of 1.0003/ mg proteinuria. Actually, the ci score ($\text{p} = 0.0635$), cv score ($\text{p} = 0.0830$), and cg score ($\text{p} = 0.0686$) were of borderline significance in our study; statistical significance would probably be obtained with a larger patient sample size. Recognition of surrogate markers, including sensitization to HLA, proteinuria, and deterioration of renal function, is central to the early diagnosis of AMR and successful intervention.

Follow-up renal biopsy, in addition to renal function, is also an important indicator of treatment response and prognosis for patients with AMR.\textsuperscript{30,32} In this retrospective study, we did not regularly perform repeat renal biopsies in every patient after AMR; especially not in patients in the D1-good Subgroup with good recovery or patients in the D1-poor Subgroup with rapidly deteriorating renal function. It was difficult to persuade patients with stable renal function or with failing grafts to undergo renal biopsy. Patients in the D2 Subgroup underwent a significantly higher number of biopsies than the patients in the D1-poor Subgroup. We believe that there could be sustained AMR activity in the D2 Subgroup and even in the D1-good Subgroup. Further biopsy analysis and desensitization might be advisable in the long run of post-transplant follow-up.

In conclusion, for C4d-positive late AMR, repeated cycles of IVIG-based desensitization could be helpful to stabilize long-term renal function of patients with sustained AMR. There is a working window of $\sim 24$ months for IVIG-based desensitization therapy.

Acknowledgments

This work was supported in part by grants NSC 100-2314-B-002-150, NSC 101-2314-B-002-057, NSC 102-2314-B-002-092, and Dr. TY Lin’s Medical Research Foundation.

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