Addition of Plasmapheresis Decreases the Incidence of Acute Antibody-Mediated Rejection in Sensitized Patients with Strong Donor-Specific Antibodies

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Background and objectives: The objective of this study was to investigate the effects of desensitization protocols using intravenous Ig with or without plasmapheresis in patients with donor-specific anti-HLA antibodies on prevention of antibody-mediated rejection and downregulation of donor-specific antibodies.

Design, setting, participants, & measurements: Thirty-five complement-dependent cytotoxicity T cell cross-match–negative but complement-dependent cytotoxicity B cell and/or flow cytometry cross-match–positive kidney transplant recipients were treated with high-dosage intravenous Ig plus Thymoglobulin induction treatment. Donor-specific antibody strength was stratified as strong, medium, or weak by Luminex flow beads. Group 1 patients had weak/moderate and group 2 strong donor-specific antibodies.

Results: Whereas no group 1 patients had acute rejection, 66% of group 2 had acute rejection (44% antibody-mediated rejection, 22% cellular rejection). The protocol was then changed to the addition of peritransplantation plasmapheresis to patients with strong donor-specific antibodies (group 3). This change resulted in a dramatic decrease in the acute rejection rate to 7%. During a median 18 mo of follow-up, patient survival was 100, 100, and 93% and graft survival was 100, 78, and 86% in groups 1, 2, and 3, respectively. During follow-up, 17 (52%) patients lost donor-specific antibodies completely, and 10 (30%) lost some of donor-specific antibodies and/or decreased the strength of existing donor-specific antibodies.

Conclusions: These results indicated that in patients with strong donor-specific antibodies, the addition of plasmapheresis to high-dosage intravenous Ig decreases the incidence of acute rejection. The majority of the patients, whether they received intravenous Ig alone or with plasmapheresis, lost their donor-specific antibodies during follow-up.


Donor-specific anti-HLA antibodies (DSA) in patients who are sensitized through pregnancy, previous blood transfusions, or organ transplantation is an important obstacle in kidney transplantation. Sensitized patients wait longer on the deceased-donor transplantation list, may not receive a transplant, and may have greater morbidity and mortality. Some sensitized patients may have living donor candidates, but transplantation cannot be performed because of cross-match positivity. Recent desensitization protocols using the combination of plasmapheresis (PP) or immunoadsorption to remove DSA and/or intravenous Ig (IVIG) and rituximab to downregulate antibody-mediated immune responses have made kidney transplantation feasible by abrogating complement-dependent cytotoxicity (CDC) T cell cross-match positivity. In previous studies, two protocols were examined: High-dosage IVIG (2.0 g/kg) (1–3) and PP with low-dosage IVIG (100 mg/kg after each PP session) (4–8); however, acute antibody-mediated rejection (AMR) continued to be an important barrier and was still observed in at least 30 to 40% of the recipients included in these desensitization protocols, even when rituximab was added to the protocol.

 Whereas CDC T cell cross-match positivity is an absolute contraindication to kidney transplantation, the clinical significance of CDC B cell or flow cytometry (FC) T and/or B cell cross-match positivity are less clear. Most studies have demonstrated that CDC T cell cross-match–negative but CDC B or FC T/B cell cross-match–positive patients with DSA are at higher risk for developing acute cellular, antibody-mediated, and chronic rejection and graft loss (9,10). The role of desensitization protocols for these patients has not been studied in a large cohort. We previously reported our initial experience using low-dosage IVIG (300 mg/kg) and Thymoglobulin induction treatment in 15 patients (11,12). Because of early AMR in three patients, the IVIG...
Kidney Transplantation in Sensitized Patients

Materials and Methods

Patients

Kidney transplant recipients with pretransplantation DSA were included in this study. All recipients and potential living-donor candidates were informed of the specific characteristics of kidney transplantation in sensitized patients and the desensitization protocols, in addition to standard educational programs provided to all recipients and donors. All patients had a negative CDC T cell cross-match and also did not have any other potential living-donor candidate with a negative DSA test. The study was approved by the institutional review board of Mount Sinai School of Medicine.

Cross-Match Methods and Detection of Anti-HLA Antibodies

The CDC assay was performed with the anti-human globulin method. The FC cross-match detected human IgG antibodies bound to the target T and B lymphocytes labeled with Becton-Dickinson (BD Biosciences, San Jose, CA) Mouse Anti-human antibodies (CD3-PercP and CD19-PE). The samples were run on a Becton-Dickinson FacsCalibur flow cytometer and quantified by median fluorescence intensity (MFI). The difference between these two samples determined the channel displacement (Chd). Cross-matches with a Chd of ≥40 for T lymphocytes and ≥150 for B lymphocytes were interpreted as positive.

Anti-HLA antibodies were studied by Luminex Flow Beads (LABScreen products; One Lambda, Canoga Park, CA) that use a panel of color-coded beads, which were coated with purified HLA antigens. Test serum was incubated with LABScreen beads, and HLA antibodies bound to the beads labeled with R-Phycoerythrin–conjugated goat anti-human IgG (One Lambda). Beads were analyzed with the Luminex 100 flow analyzer and IS V2.3 software. Antigen-specific analysis was performed, and the strength of the reaction was assigned (HLA Visual V2.0; One Lambda). The strength of the reactions was graded by two methods: Ratio (sample test bead/sample negative control bead)/(negative serum test bead/negative serum negative control bead) for the first five patients or baseline (sample test bead/negative serum test bead/negative serum negative control bead) for the remaining 30 patients. The following strengths were assigned to the reactions: Strong, median ratio ≥10 or median baseline ≥6000; moderate, median ratio ≥5 and <10 or median baseline ≥4000 to 5999; weak, median ratio ≥1.5 and <5 or median baseline ≥1500 to 3999.

Histopathology

Biopsies were performed for an increase in creatinine level and/or proteinuria. All biopsy specimens were examined by light microscopy and C4d staining. C4d staining was performed on paraffin sections using polyclonal rabbit anti-C4d antibody (Rabbit polyclonal; American Research Products, Inc., Belmont, MA). The histologic lesions and AMR were classified and scored according to the Banff classification (13,14). There are three types of acute AMR: Type 1, ATN-like, acute tubular injury with a few tubulointerstitial neutrophil infiltrates; type 2, mainly involves glomeruli with neutrophils and monocyte infiltration (glomerulitis) and fibrin microthrombi, resembling thrombotic microangiopathy; and type III, arterial inflammation with or without fibrinoid changes.

Immunosuppressive Treatment Protocol

All patients received Thymoglobulin (1.5 mg/kg per d for 5 d) induction treatment, along with tacrolimus, mycophenolate mofetil, and a steroid taper. Corticosteroids were initiated intraoperatively at 500 mg of methylprednisolone, followed by an oral prednisone taper to 10 mg/d by 2 to 3 mo and 5.0 mg/d by 4 to 6 mo after transplantation. All patients received mycophenolate mofetil at 1.0 g twice a day. Tacrolimus was started at 0.1 to 0.2 mg/kg twice a day, and the dosage was adjusted to keep trough levels 10 to 15 ng/ml for the first 3 mo, 8 to 12 ng/ml between 4 and 6 mo, and 5 to 8 ng/ml thereafter. All patients received valganciclovir 450 mg/d for 6 mo and trimethoprim/sulfamethoxazole for 3 mo.

All patients received high-dosage IVIG (1.0 g/kg during transplant surgery and 500 mg/kg on each of postoperative days 1 and 2). After early AMR was observed in four patients with strong class I DSA, all patients with strong class I DSA received PP. Living-donor kidney transplant candidates with strong class I DSA received four to eight sessions of pretransplantation PP over 2 to 3 wk and underwent transplantation after their DSA strength decreased to moderate or weak. Deceased-donor kidney transplant recipients with DSA received three sessions of PP every other day starting on postoperative day 1.

AMR was treated with pulse methylprednisolone 250 mg for 3 d; PP four to eight sessions, with each session followed by IVIG 500 mg/kg; and a single dose of rituximab (375 mg/m²) after PP and IVIG treatment completed. Acute cellular rejection grade Ia and Ib was treated with pulse methylprednisolone 250 mg for 3 d, and rejection grade IIa or higher was treated with Thymoglobulin 1.5 mg/kg for 5 to 7 d.

Results

Patient Demographics

Thirty-five patients received IVIG and Thymoglobulin induction treatment for pretransplantation DSA. After four early acute rejection episodes observed in 12 patients, the strength of DSA by Luminex were retrospectively evaluated and stratified as strong, medium, and weak. Because the acute rejection episodes were observed only in patients with strong class I DSA, for the subsequent transplant recipients with strong class I DSA, peritransplantation PP was added, as explained in the Materials and Methods section. The demographics of all patients and each group (group 1, patients with weak- and/or moderate-strength DSA; group 2, patients who had strong DSA and received only high-dosage IVIG; and group 3, patients who had strong class I DSA and received PP and high-dosage IVIG) are summarized in Table 1. Overall, 26% of the patients were male and 43% were black; median age was 51 (range 24 to 75). Sixty percent of the patients received living-donor kidney transplantation.
The highest median panel reactive antibody (PRA) levels were 67% (14 to 100%), and 31% were retransplantations. All patients had negative CDC T cell cross-match result before transplantation. Thirty-one percent of the recipients were CDC B cell, 61% FC T cell, and 94% FC B cell cross-match positive. Four patients did not have pretransplantation FC cross-match measured because of previously documented DSA. Three patients were CDC B cell negative and FC T/B cell cross-match negative but had DSA. Thirty-one percent of the patients had only class I, 31% had only class II, and 38% had both class I and class II DSA. The mean number of class I plus II DSA was 2.3 ± 0.9.

The demographics of the groups differed such that 100% of group 1, 56% of group 2, and 29% of group 3 received living-donor kidney transplantation. Patients with strong DSA had a greater mean number of DSA compared with patients with weak/moderate DSA (2.3 ± 0.8 in group 2, 2.9 ± 1.1 in group 3, and 1.7 ± 0.8 in group 1) and more FC T cell cross-match positivity (92% in group 3 and 63% in group 2 versus 33% in group 1). Whereas 78% of group 2 patients were CDC B cell cross-match positive, 17 and 14% of groups 1 and 3 patients were CDC B cell cross-match positive. There were no differences among the three groups in terms of FC B cell Chd values (254 ± 83, 289 ± 63, and 290 ± 121 in groups 1, 2, and 3, respectively), but FC T cell Chd values were higher in patients with strong DSA (groups 2 and 3 85 ± 26 and 168 ± 117 versus group 1 60 ± 14).

Acute Rejection and Patient and Graft Survival
Whereas four (80%) of five patients who had strong class I DSA and were not receiving PP (group 2) had acute rejection within 10 d after transplantation (three AMR and one cellular rejection), none of the patients who had weak- and/or moderate-strength DSA and were not receiving PP (group 1) had an acute rejection episode (Table 2). After the addition of PP to the patients with strong class I DSA (group 3), none of the four living-donor recipients and only one of 10 patients who received a deceased-donor transplant developed acute AMR (7%). This patient had three strong class I and two class II DSA. Two of the four patients who had strong class II DSA and were receiving high-dosage IVIG without PP developed acute rejection. Overall, six (66%) of nine group 2 patients with strong DSA (class I and/or II) had acute rejection (44% AMR and 22% cellular rejection). After this experience, we decided to perform peritransplantation PP in all patients with strong DSA, whether class I or class II.

The histopathologic examination of the five AMR biopsies revealed that three were type 1 and two were type 2. All AMR biopsies were C4d+. Four of five patients who had acute AMR treatment responded to treatment with PP, IVIG, and one dose
of rituximab. One patient lost the allograft at 3 mo after partial response to AMR treatment.

During a median 16 mo of follow-up (range 8 to 35 mo) in group 1 and 22 mo (range 8 to 31 mo) in group 2, none of the patients died (100% patient survival; Table 3). In group 3, during a median 12 mo of follow-up (range 6 to 18 mo), one patient died as a result of gastrointestinal bleeding with stable kidney function (93% patient survival). Whereas all group 1 patients had functioning allografts (100% graft survival), one patient in group 2 lost the allograft as a result of acute AMR at 3 mo and the other as a result of sepsis and acute tubular necrosis 10 mo after transplantation (78% graft survival). In group 3, one deceased-donor kidney transplant recipient lost the allograft as a result of donor-related factors. This patient had four follow-up biopsies after transplantation, which showed progressive fibrosis, but all were

<table>
<thead>
<tr>
<th>Table 2. DSA before and after transplantation, and complications</th>
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<td><strong>Patient</strong></td>
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<td>Group 1</td>
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*aACR, acute cellular rejection; AMR, antibody-mediated rejection; CAN, chronic allograft nephropathy; CMV, cytomegalovirus disease; m, moderate, PNF, primary nonfunction; s, strong, TGP, transplant glomerulopathy; w, weak."
negative for acute rejection and C4d staining (86% graft survival).

**Chronic Rejection**

Twenty-three of 35 patients underwent 46 clinically indicated transplant kidney biopsies. Four patients in group 2 and one patient in group 3 showed chronic allograft nephropathy (CAN). None of the group 1 patients developed CAN. Two patients in group 2 and one patient in group 3 with AMR developed transplant glomerulopathy (TGP) at 2, 3, and 8 mo after transplantation, suggesting early development of TGP as result of endothelial damage from DSA.

**Donor-Specific Anti-HLA Antibodies**

DSA were studied after transplantation by Luminex Flow Beads in all groups 2 and 3 patients and 10 of 12 group 1 patients, and the results of DSA at the last clinic visit are shown in Table 2. Seven (70%) group 1 patients lost DSA completely, one patient lost all class I DSA, and only two patients continued to have weak DSA. In group 2, four (44%) patients lost DSA completely and three patients lost some of their DSA and/or decreased the strength of DSA. In group 3, six (43%) patients lost DSA completely, two patients all class I DSA, and four patients lost some DSA and/or decreased the strength of DSA. Overall, in 33 patients whose posttransplantation DSA were studied, 17 (52%) lost their DSA completely and 10 (30%) partially.

We analyzed the Luminex data for non-DSA. Our patients were highly sensitized with a median PRA level of 67 (range 14 to 100) and multiple anti-HLA antibodies, which makes difficult to interpret the outcome of each non-DSA specifically; however, the mean MFI of non-DSA decreased after transplantation in all three groups. The decrease in MFI of class I non-DSA was 34% in group 1 (from 2080 ± 2228 to 1383 ± 1402), 24% in group 2 (from 6040 ± 2887 to 4567 ± 3825), and 38% in group 3 (from 7707 ± 3792 to 4781 ± 3528). The decrease in MFI of class II non-DSA was 64% in group 1 (from 5625 ± 2213 to 1900 ± 1980), 31% in group 2 (from 8333 ± 3830 to 5714 ± 4645), and 24% in group 3 (from 9429 ± 3309 to 7128 ± 2650).

**Complications**

One patient each in groups 1 and 2 had non–tissue-invasive cytomegalovirus disease and responded to treatment, whereas none in group 3 had cytomegalovirus infection. One patient in the group 3 developed biopsy-proven polyoma nephropathy 14 mo after transplantation and has stable renal function with a creatinine level of 1.8. None in groups 1 and 2 developed polyoma nephropathy. One patient in group 1 developed cryptococcal meningitis 9 mo after transplantation and responded to treatment.

**Discussion**

These results demonstrate that sensitized kidney transplant recipients with strong class I and II DSA by Luminex are at higher risk for developing early AMR despite receiving Thymoglobulin and high-dosage IVIG induction treatment. The addition of pretransplantation PP in living-donor recipients completely prevented the development of early AMR, and posttransplantation PP in deceased-donor recipients significantly decreased the incidence of AMR, despite being initiated on postoperative day 1. Seven percent acute AMR rate is the lowest reported in patients with DSA, who underwent desensitization protocol. These results demonstrate the importance of determining the strength of DSA before transplantation to decide the type of desensitization. The strength can be determined as titers by the CDC method; however, HLA antigen–coated

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<th>Outcome</th>
<th>IVIG Only</th>
<th>IVIG/PP</th>
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<tr>
<td></td>
<td>Group 1, Weak/Moderate DSA (n = 12)</td>
<td>Group 2, Strong DSA (n = 9)</td>
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<tr>
<td>Follow-up (mo; median [range])</td>
<td>16 (8 to 35)</td>
<td>22 (8 to 31)</td>
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<tr>
<td>Patient survival (%)</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Graft survival (%)</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>Acute rejection (%)</td>
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<td>0</td>
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<tr>
<td>AMR</td>
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<td>0</td>
</tr>
<tr>
<td>ACR</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Biopsy-proven CAN (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Median Cr (mg/dl; median [range])</td>
<td>1.1 (0.6 to 2.8)</td>
<td>1.2 (1.0 to 4.5)</td>
</tr>
<tr>
<td>Patients with Cr &lt;2.0 (%)</td>
<td>92</td>
<td>71</td>
</tr>
<tr>
<td>Patients with Cr &lt;1.4 (%)</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>CMV disease (%)</td>
<td>8</td>
<td>11</td>
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<tr>
<td>Polyoma nephropathy (%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Proteinuria (%)</td>
<td>0</td>
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aCr, serum creatinine level.
flow-bead assays are more sensitive and specific, but it is not feasible to determine titers by this method as a standard of the care in all patients because of significant costs. Mizutani et al. (15) demonstrated that titers of alloantibodies correlated to maximum fluorescence emission values obtained by Luminex. Our initial evaluation of DSA strength demonstrated a higher percentage of acute rejection in patients with strong class I DSA, which led to our protocol change by adding PP. Our subsequent experience with four patients with strong class II DSA revealed that two had acute rejection. These findings suggest that all patients with strong DSA, whether class I or II, may need PP to decrease the load of circulating alloantibodies and the incidence of acute AMR. Previous studies, summarized in a recent review article (16), showed that both class I and II DSA can be associated with acute and chronic rejection.

The acute rejection rate has been >30% in patients who receive desensitization protocols, and it is still not clear which protocol (high-dosage IVIG, PP/low-dosage IVIG), what type of induction treatment (Thymoglobulin, anti–IL-2R antibodies, alemtuzumab), or addition of rituximab is better for the prevention of early acute AMR. The Cedars-Sinai group using high-dosage IVIG reported the outcome of 97 kidney transplant recipients in terms of two types of induction treatment (3). Although 2-yr graft survival was 84% in daclizumab-treated and 90% in Thymoglobulin-treated patients, acute rejection rate was 36% (22% AMR) and 31% (21% AMR), respectively. These results indicated that neither agent was effective in reducing the incidence of acute AMR; however, the authors did not report DSA of the patients, and it is not clear whether patients with positive cross-match but negative DSA received transplantation. Thymoglobulin is a more potent induction agent compared with anti–IL-2R antibodies in terms of preventing acute rejection (17). Its efficacy may relate to effects on B cells, such as the ability to induce apoptosis of naïve and memory B cells in vitro (18) and treat acute AMR in vivo (19).

A low-dosage IVIG with PP protocol has been used mainly in living-donor recipients. Schweitzer et al. (7) reported a 36% acute rejection rate by using this protocol. Stegall et al. (8) used several methods in CDC T cell cross-match–positive recipients, including rituximab, a chimeric murine/human mAb that binds to CD20 on pre-B and mature B lymphocytes. Thirteen patients received high-dosage IVIG (group 1); 32 patients received PP, low-dosage IVIG, and rituximab (group 2); and 16 patients received PP, low-dosage IVIG, rituximab, and pretransplantation Thymoglobulin (group 3). The acute rejection rate was 80% in group 1, 37% in group 2, and 29% in group 3. The authors concluded that no regimen was completely effective in preventing AMR. A significant decrease in AMR incidence in our patients with the addition of PP indicated that use of high-dosage IVIG is better than the low-dosage IVIG plus PP combination, probably because of increased immunomodulatory effects with high-dosage IVIG.

The clinical significance of positive CDC B cell or FC T cell or B cell cross-match results on graft outcome is controversial. Whereas some studies did not find any effect on graft outcome, most studies demonstrated increased acute and chronic rejection and decreased graft survival (9,10). The main reason for the controversial outcomes in the literature is the lack of studies to confirm DSA. Le Bas-Bernardet et al. (20) showed that only 23% of B cell cross-match–positive patients had DSA and demonstrated lower allograft survival, whereas cross-match–positive patients without DSA had similar graft survival to that of B cell cross-match–negative control subjects. Bray et al. (21) showed that whereas patients with pretransplantation-positive FC cross-match and 0% FlowPRA had 100% 1-yr graft survival, it was only 40% in patients with both FC cross-match positivity and DSA by FlowPRA. Our study demonstrates the importance of treating these DSA with an effective desensitization protocol despite the negative pretransplantation CDC T cell cross-match. Some patients may even have DSA without positive CDC and FC cross-match result. Patel et al. (22) reported that four of 20 patients with pretransplantation DSA but negative CDC and FC cross-match developed acute AMR. Three patients in our series also had DSA without any cross-match positivity.

One of the long-term problems in patients who receive desensitization protocol is TGP and chronic AMR. Two recent studies by Gloor et al. (23) and Anglicheau et al. (24) documented 22 and 28% TGP at 12-mo protocol biopsies of patients who received desensitization protocols, respectively. Three of our patients who had early AMR developed TGP 3 to 12 mo after transplantation. Because of lack of baseline as well as protocol biopsies, it is difficult to determine the true incidence of CAN and TGP in our patients.

Montgomery et al. (25) followed up DSA of 49 kidney transplant recipients who underwent a desensitization protocol of PP/low-dosage IVIG and demonstrated that 63% lost DSA at the end of the treatment and 89% ≥2 mo after the end of treatment; however, the Mayo Clinic group showed that the majority of their desensitized patients continued to have low levels of DSA (26). In our study, 52% of patients lost DSA completely, and 30% lost some of their DSA or decreased DSA strength, indicating that both methods, high-dosage IVIG alone and PP/high-dosage IVIG, are effective in downregulating antibody production. Not only DSA but also the mean MFI of non-DSA decreased in all three groups, suggesting a nonspecific decrease in overall antibody production.

Conclusions

Kidney transplant recipients with DSA are at higher risk for developing early acute AMR despite negative CDC T cell cross-match and require desensitization. All patients with a history of sensitization should be studied for DSA by sensitive methods, such as antigen-based flow beads. Not only should the presence of DSA be documented, but also the strength or titers of the alloantibodies should be determined to decide the type of the desensitization protocol. High-dosage IVIG alone dose not prevent AMR in patients with strong DSA, and the addition of peritransplantation PP significantly decreases the incidence of AMR. The effect of
addition of rituximab to the desensitization protocols or of PP to patients with strong class II DSA on allograft outcomes requires further prospective studies.

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Disclosures
None.

References
