Desensitization Protocols and Their Outcome

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Summary
In the last decade, transplantation across previously incompatible barriers has increasingly become popular because of organ donor shortage, availability of better methods of detecting and characterizing anti-HLA antibodies, ease of diagnosis, better understanding of antibody-mediated rejection, and the availability of effective regimens. This review summarizes all manuscripts published since the first publication in 2000 on desensitized patients and discusses clinical outcomes including acute and chronic antibody-mediated rejection rate, the new agents available, kidney paired exchange programs, and the future directions in sensitized patients. There were 16 studies published between 2000 and 2010, involving 725 patients with donor-specific anti-HLA antibodies (DSAs) who underwent kidney transplantation with different desensitization protocols. All studies were single center and retrospective. The patient and graft survival were 95% and 86%, respectively, at a 2-year median follow-up. Despite acceptable short-term patient and graft survival, acute rejection rate was 36% and acute antibody-mediated rejection rate was 28%, which is significantly higher than in nonsensitized patients. Recent studies with longer follow-up of those patients raised concerns about long-term success of desensitization protocols. The studies utilizing protocol biopsies in desensitized patients also reported higher subclinical and chronic antibody-mediated rejection. An association between the strength of DSAs determined by median fluorescence intensity values of Luminex single-antigen beads and risk of rejection was observed. Two new agents, bortezomib, a proteasome inhibitor, and eculizumab, an anti-complement C5 antibody, were recently introduced to desensitization protocols. An alternative intervention is kidney paired exchange, which should be considered first for sensitized patients.


Introduction
Sensitization to HLA antigens, which occurs mainly through blood transfusion, pregnancy, and previous organ transplantation, limits the access to and success of kidney transplantation. There are currently >90,000 patients on the waiting list for kidney transplantation in United States, but only 16,829 kidney transplants were performed in 2009. The significant shortage of organs directly prolongs the waiting time, which is >5 years in some regions, and in the highly sensitized patients the waiting time is even more profound and some may never receive a transplant. Although the mortality rates of dialysis patients have improved over the years, 15% to 20% of dialysis patients still die each year. Currently, 35% of the patients on the waiting list are sensitized with panel reactive antibody (PRA) levels >0%, and 15% are highly sensitized with PRA levels >80%. Additionally, 17% of the patients on the waiting list were previous transplant recipients. Sensitized patients might have living-donor candidates but may not be able to receive a transplant because they are crossmatch incompatible with their living donors. Transplantation in patients with the presence of circulating donor-specific anti-HLA antibodies (DSAs) and positive cross-match is historically considered a contraindication. However, in the last decade, transplantation across previously incompatible barriers has become increasingly popular because of organ donor shortage, availability of better methods of detecting and characterizing anti-HLA antibodies, ease of diagnosis, better understanding of antibody-mediated rejection (AMR), and the availability of effective regimens to suppress antibody-mediated immune responses. Kidney transplantation is the preferred treatment modality for patients with ESRD because of improved patient survival and quality-of-life over dialysis (1–3). Since the late 1990s, there has been a quest for therapeutic strategies to allow for successful transplantation in highly sensitized patients. Most of the current protocols are a modification of high-dose intravenous Ig (IVIG) initiated at Cedars Sinai Medical Center or plasmapheresis (PP) with low-dose IVIG initiated at Johns Hopkins Hospital (4). In this review, we aim to summarize all manuscripts regarding sensitized patients with documented DSAs who underwent kidney transplantation by receiving IVIG and/or PP published since the first publication of desensitized patients in 2000 and discuss clinical outcomes including acute and chronic AMR rate, the new agents available, kidney paired exchange programs, and the future directions in sensitized patients.

Treatment Options for Sensitized Patients (Table 1)
Removal of Antibodies by PP or Immunoadsorption
PP and immunoadsorption (IA) techniques have been used to remove alloantibodies. PP is not specific
for Ig removal and results in a lowering of all plasma proteins, including clotting factors, and requires replacement with fresh frozen plasma and albumin. IA includes a sepharose-bound staphylococcal protein A column with a high affinity for binding IgG and developed to remove IgG antibodies. The advantages of IA over PP include specificity, a greater amount of antibody removal, and the elimination of the need to replace large volumes of plasma. One 3- to 4-hour treatment course with IA results in a 15% to 20% reduction and three to six courses of treatment result in >90% reduction in plasma IgG levels. However, anti-HLA antibody titers rebound and return to baseline levels within a few weeks after the completion of PP or IA (5). Most columns available in Europe and Japan for IA are not approved by the U.S. Food and Drug Administration (FDA) for clinical use in the United States.

Inhibition of Antibody Production

**Rituximab (Anti-CD20).** Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20 on pre-B and mature B lymphocytes (6). It is FDA approved for treatment of refractory or relapsed B cell lymphomas and is also used for treatment of posttransplant lymphoproliferative disease (PTLD). The dose is 375 mg/m² as an intravenous infusion for four weekly doses in the treatment of PTLD. Rituximab has been used off label in desensitization protocols for incompatible kidney transplantation (ABO-incompatible or cross-match positive) or in the treatment of AMR as a single dose of 375 mg/m². Plasma cells and pro-B cells do not have surface CD20 expression, which decreases the effectiveness of rituximab treatment on inhibition of alloantibody production. Rituximab can be detected for months, and B cell recovery takes 6 to 12 months after the completion of the treatment.

**Bortezomib (Proteasomal Inhibitor).** Bortezomib, a tripeptide and proteasomal inhibitor approved by FDA for the treatment of multiple myeloma, has been shown to cause apoptosis of normal plasma cells, thereby having the potential to decrease alloantibody production in sensitized patients (7). Bortezomib was given at 1.3 mg/m² and repeated on days 4, 8, and 11 intravenously over 3 to 5 seconds. Patients needed to be premedicated with methylprednisolone before bortezomib infusion. Peak concentration is reached at 30 minutes. Bortezomib is rapidly cleared, and as such drug levels can no longer be measured after 1 hour.

**Complement Inhibitors**

Eculizumab is a humanized monoclonal antibody against complement protein C5 that binds to C5 protein with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing generation of the terminal complement complex C5b-9. This process halts complement-mediated cell destruction. The FDA has approved eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. It was used in the prevention and treatment of atypical hemolytic-uremic syndrome after transplantation (8,9).

**Intravenous Ig**

The mechanisms of IVIG are diverse, and numerous mechanisms have been proposed in which IVIG inhibits the immune response at multiple pathways (10). The immediate mechanism of IVIG is believed to be the neutralization of circulating anti-HLA antibodies through anti-idiotypic antibodies. However, a study involving 23 sensitized patients demonstrated that the predominant mechanism of IVIG is inhibition of complement activation but not anti-idiotypic activity (11). IVIG has been reported to bind C3b and C4b, to decrease their deposition on the cell membrane, and to neutralize C3a and C5a, thereby preventing the generation of the C5b-C9 membrane-attack complex (12). IVIG-derived Ig aggregates, monomers, and dimers compete for activating FcγRs, thereby blocking immune activation and enhancing the clearance of anti-HLA antibodies. IVIG was shown to induce the expression of FcγRIIB, which is a negative regulatory receptor on immune cells, inhibits the expression of CD19 on activated B cells, and induces apoptosis of B cells (13). IVIG also has inhibitory effects on cellular immune responses; nonspecific
inhibitory effects on the immune system by binding to Fcγ receptors on macrophages, neutrophils, platelets, mast cells, and natural killer cells; and inhibits cytokine, chemokine, adhesion molecule, and endothelial cell activity.

IVIG has been used in highly sensitized patients at the top of the waiting list to decrease PRA levels, in desensitization protocols of ABO-incompatible and cross-match-positive patients, and in the treatment of AMR. The dose of IVIG varies among protocols from 100 mg/kg to 2.0 g/kg and is usually given during a hemodialysis session or as a slow infusion in nondialysis patients.

Splenectomy
Splenectomy has been used in desensitization protocols of ABO-incompatible kidney transplant recipients. Splenectomy removes a major source of lymphocytes, including antibody-secreting B cells, B cell precursor cells, and plasma cells. It has also been used in the treatment of refractory AMR (14,15). However, the effect of splenectomy on the immune system is permanent, which may place the patients at risk for the development of life-threatening sepsis, especially from encapsulated bacteria.

Desensitization Protocols
We summarized the published studies of desensitization protocols applying PP/low-dose IVIG or high-dose IVIG in Table 2. The studies used different methods to identify DSAs, such as CDC (complement-dependent cytotoxicity), ELISA, FlowPRA, and Luminex single-antigen beads, which makes it difficult to compare the patient groups.

PP with Low-Dose IVIG
The PP and low-dose IVIG (CMVIg) protocol was first utilized in 1998 at Johns Hopkins Hospital in cross-match incompatible living-donor kidney transplant candidates (16). Patients received PP and CMVig at 100 mg/kg after each PP along with tacrolimus and mycophenolate mofetil treatment for desensitization starting 2 to 3 weeks before transplantation. The start of therapy depended on the DSA titers so that patients with low titers (<1:8) required two to three sessions of PP, whereas patients with higher titers (>1:128) had six to 10 sessions. Patients received transplantation if the cross-match became negative with the use of daclizumab induction therapy and continued for two to five sessions of PP after transplantation depending on the titers of DSA. Their initial experience in four patients resulted in AMR in all patients, but they responded to treatment and had 100% graft survival at 1 year. Using a similar protocol but with OKT3 induction instead of daclizumab, Schweitzer et al. desensitized 11 of 15 patients to allow for successful kidney transplantation. The acute rejection rate was high (36%), but patients had 100% 1-year graft survival (17).

The Mayo Clinic Medical Center modified the protocol by using anti-thymocyte globulin induction and added rituximab and splenectomy to the protocol in an attempt to decrease high acute rejection rate. Despite this modification, a 43% acute AMR rate was observed in 14 patients (18). Patient and graft survival were 86% and 78%, respectively, at 15 months. Brigham and Women's Hospital Transplant Center applied PP and low-dose IVIG with anti-thymocyte globulin (until 2004) or basiliximab (after 2004) and rituximab in 28 cross-match-positive patients. The acute rejection rate was very high (71%), and 39% had acute AMR (19). A similar desensitization protocol was used in 57 patients at the University of Illinois, where 6 patients failed to convert to negative cross-match with pretransplant immunomodulation (20). The acute rejection rate was 33% in 51 transplanted patients, who demonstrated 93% graft survival at 2 years.

The University of Maryland recently reported its long-term experience in 41 flow cytometry cross-match-positive patients using PP/low-dose IVIG with OKT3 or anti-thymocyte globulin induction treatment (21). Patients had lower acute AMR (12%) compared with the studies discussed above, but patient survival and graft survival at 4 years were only 78% and 66%, respectively.

High-Dose IVIG
Dr. Jordan at Cedars-Sinai pioneered studies using IVIG in kidney transplantation and showed that IVIG inhibits in vitro lymphocytotoxicity of sera from highly HLA-sensitized patients awaiting transplant and decreases anti-HLA antibodies in vivo (22,23). Later, high-dose IVIG (2 g/kg) treatment without PP was given to cross-match-positive recipients and the patients received kidney transplantation if CDC T cell cross-match became negative. The advantage of this approach was its applicability to deceased-donor kidney transplant candidates because the PP/low-dose IVIG protocol can be performed only in living-donor kidney transplantation. Jordan et al. reported their first experience in 42 patients, and the cross-match was completely abrogated in 35 patients and 7 remained CDC negative but flow cytometry cross-match positive (24). Patients received two doses of daclizumab induction treatment and another dose of IVIG (2 g/kg) 1 month after transplantation. AMR was seen in 13 patients (31%), and 3 (7%) lost the allograft because of rejection. Two-year patient and graft survival rates were 98% and 89%, respectively. Induction treatment was switched from daclizumab to anti-thymocyte globulin and the clinical outcomes of 39 anti-thymocyte-globulin-treated patients were retrospectively compared with 58 patients who had received daclizumab (25). The 2-year graft survival was 84% in the daclizumab group and 90% in the anti-thymocyte globulin group, whereas the acute rejection rate was 36% (22% AMR) and 31% (21% AMR), respectively. The graft survival was poor in 9 daclizumab- and 5 thymoglobulin-treated patients who received transplantation despite having positive CDC and flow cytometry cross-match (44% and 40%, respectively) but excellent in 28 daclizumab and 10 anti-thymocyte-globulin-treated groups in which the CDC/flow cytometry cross-match became negative (97% and 100%, respectively). Anti-thymocyte-globulin-treated patients (25) receiving transplantation with CDC negative but flow cytometry cross-match positive demonstrated higher graft survival (96% versus 81%) although the result was not statistically significant. The authors did not report the strength or the specificity of DSAs. These results indicated that neither agent was completely effective in reducing the incidence of acute AMR. Jordan et al. decided to use alemtuzumab induction treatment and added rituximab to their protocol to decrease
Table 2. Desensitization protocols and clinical outcomes

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Number of Patients</th>
<th>DSA Technique</th>
<th>Induction</th>
<th>Mean Follow-Up (months)</th>
<th>AR/AMR (%)</th>
<th>Patient Survival (%)</th>
<th>Graft Survival (%)</th>
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<tbody>
<tr>
<td>PP/low-dose IVIG</td>
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<td>OKT3</td>
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<td>Daclizumab</td>
<td>14</td>
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<td>23</td>
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<td>OKT3 or Thymo</td>
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<td>Thymo</td>
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<td>Thymo</td>
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<td>31/31</td>
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<td>Alemtuz/Ritux</td>
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<td>50/31</td>
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<td>Thymo</td>
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<td>Alemtuz/Ritux</td>
<td>24</td>
<td>37/29</td>
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<td>Luminex SAB</td>
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<td>MFI &gt; 6000 (n = 9)</td>
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AR, acute rejection; Thymo, anti-thymocyte globulin; Ritux, rituximab; Spl, splenectomy; Alemtuz, alemtuzumab; CXM, cross-match; HD IVIG, high-dose IVIG; LD IVIG, low-dose IVIG; NR, not reported; SAB, single-antigen beads; AMR, antibody mediated rejection; TX, transplantation; PRA, panel reactive antibody; CDC, complement-dependent cytotoxicity; MFI, median fluorescence intensity.
acute rejection rate and reported their experience in three consecutive manuscripts (26–28). Despite the patients having good graft survival at 1 year (94%) and 2 years (84%), acute rejection rate was still high (35% to 50%), as was the AMR rate (20% to 31%).

Glötz and colleagues in France used high-dose IVIG with anti-thymocyte globulin induction in cross-match-positive recipients (29). Acute AMR was observed in 41% of 32 recipients and the graft survival was 78% at 3 years (30).

Protocols have used high-dose IVIG and anti-thymocyte globulin induction without PP in CDC cross-match-negative but flow cytometry cross-match-positive patients with low-level DSAs, postulating that these patients might not be at high risk for AMR (31). Mai et al. transplanted 20 such patients, but acute rejection developed in 50% of the patients and acute AMR rate was 30% (32). Patients responded to rejection treatment and 3-year graft survival was 89%. Bächler et al. compared 67 CDC cross-match-negative patients with low-level DSAs who received kidney transplantation without anti-thymocyte globulin and IVIG (historical control) to 37 patients who received anti-thymocyte globulin and IVIG (2 g/kg) (33). Despite a significant decrease in the clinical acute AMR rate in anti-thymocyte-globulin- and IVIG-treated patients (11% versus 46%), subclinical AMR was seen in 27% of patients’ protocol biopsies.

Comparison of PP/IVIG to IVIG Alone

Stegall et al. at Mayo Clinic have used both methods in CDC T cell cross-match-positive recipients and reported their experiences retrospectively (34). Thirteen patients received high-dose IVIG (group I); 32 patients received PP, low-dose IVIG, and rituximab (group II); and 16 patients received PP, low-dose IVIG, rituximab, and pretransplant anti-thymocyte globulin combined with posttransplant DSA monitoring (group III). Although only 5 of 13 (38%) high-dose-IVIG-treated patients achieved a negative cross-match, 84% and 88% of group II and III patients achieved a negative cross-match. The acute AMR rate was 80% in group I and 37% and 29% in groups II and III, respectively. The authors concluded that PP/low-dose IVIG and rituximab demonstrated more success in abrogating positive cross-match and lower acute rejection rates, but no regimen was completely effective in preventing AMR.

At Mount Sinai Medical Center, CDC T cell cross-match-negative but CDC B cell and/or flow cytometry T and/or B cell cross-match-positive patients received a transplant with anti-thymocyte globulin and IVIG (300 mg/kg) (35,36). Acute AMR was observed in three patients, and the IVIG dose was increased to 2.0 g/kg. However, four early acute AMR episodes were observed among the following 12 patients despite the increased dose of IVIG. Investigators evaluated the strength of DSAs by median fluorescence intensity (MFI) values of the Luminex test. Interestingly, acute AMR was seen only in patients with pretransplant DSA MFI values >6000 (37). PP was added to the protocol for patients with high-level DSAs. Living-donor kidney transplant candidates received four to eight sessions of pretransplant PP over 2 to 3 weeks and underwent transplantation if their DSA MFI values decreased to <6000. Deceased-donor kidney transplant recipients with strong DSAs received three sessions of PP every other day starting on postoperative day 1. The acute rejection rate decreased to 7% from 44% in the following 14 patients receiving PP.

Desensitization of Patients on the Deceased-Donor Waiting List

Jordan et al. conducted a randomized, double-blind, placebo-controlled, and multicenter National Institute of Health–sponsored trial using IVIG in highly sensitized patients (PRA levels >50%) who had been on the deceased-donor kidney transplant waiting list for >5 years (38). A total of 101 patients were randomized to receive IVIG (2 g/kg monthly for 4 months) or an equivalent volume of placebo. IVIG significantly reduced the PRA levels, and although 17% of placebo-treated patients received transplantation during the study period, 35% of IVIG-treated patients were transplanted. Cedars Sinai has since modified the protocol to decrease the number of IVIG infusions (two doses of 2.0 g/kg) and added a single dose of rituximab (375 mg/m²). Results of this modified protocol were recently published with an 80% success rate of transplantation in 20 patients (27). However, the acute rejection rate was very high (50%).

Rituximab alone was given in three different doses (50, 150, and 375 mg/m²) in a few dialysis patients (three patients in each group) with high PRA levels (>50%) (39). Although two patients did not show any change in PRA levels, seven patients demonstrated some degree of decrease in PRA titers and one patient converted to a negative cross-match and received a living-donor transplant.

Immunoadsorption

Higgins et al. used IA immediately before deceased-donor kidney transplantation in 12 CDC or flow cytometry cross-match-positive patients (40). Nine patients had biopsies 20 minutes after removal of the vascular clamps and three showed glomerular thromboses but no other evidence of hyperacute rejection. There were 13 rejection episodes in those nine patients and only seven grafts were functioning at a median follow-up of 26 months. IA was used in 20 highly sensitized deceased-donor retransplant recipients immediately before transplantation and during the early posttransplantation period (median number of IA sessions 11, range 1 to 24) (41). Nineteen of those patients had a negative pretransplant cross-match, and in one patient a positive cross-match became negative by the pretransplant IA. Two grafts were lost because of vascular rejection, and retrospective analysis of 15 biopsies revealed 80% were C4d positive. The authors recently reported the outcome of 40 deceased-donor kidney transplant recipients, including 9 patients with positive cross-matches rendered negative by a single pretransplant IA. Three-year graft survival (78% versus 71%), acute rejection (11% versus 20%), and C4d-positive graft dysfunction (33% versus 32%) were similar in cross-match-positive and cross-match-negative recipients (42).

Current Problems in Desensitization Protocols

High Acute, Subclinical, and Chronic AMR Rate

Table 2 summarizes 21 studies published between 2000 and 2010, involving 725 patients with DSAs who under-
went kidney transplantation with different protocols. The patient and graft survival were 95% and 86%, respectively, at a 2-year median follow-up. Despite acceptable short-term patient and graft survivals, the acute rejection rate was 36% and acute AMR was 28%, which is significantly higher than in nonsensitized patients (<10%). The acute AMR rate was high regardless of which PP/low-dose IVIG or high-dose IVIG was applied or which types of induction agents were used (daclizumab, anti-thymocyte globulin, or alemtuzumab). The addition of rituximab or splenectomy did not appear to decrease the acute AMR rate. Recent studies regarding longer follow-up of those patients raised concerns about the long-term success of desensitization protocols (21,43). Lefaucheur et al. reported 61% 8-year graft survival in patients with pretransplant DSAs, which was significantly lower compared with sensitized patients without DSAs (93%) and nonsensitized patients (84%) (43). Haririan et al. also reported 69% graft survival at 5 years in desensitized patients, which was significantly lower than their center's control group (81%) (21).

The studies utilizing protocol biopsies in desensitized patients also reported higher subclinical AMR. The Johns Hopkins group obtained surveillance biopsies in cross-match-positive recipients at 1, 3, 6, and 12 months post-transplant (44,45). The frequency of subclinical cell-mediated rejection was 40% at 1 month and >20% at all other time points (44). The presence of diffuse C4d staining was observed in 20% to 30% of the biopsies at any time point. The mean increase in chronic allograft nephropathy score was significantly higher in patients with subclinical AMR, suggesting that subclinical AMR may contribute to development of chronic allograft injury (45). Loupy et al. reported 3-month surveillance biopsies of 54 kidney transplant recipients with DSA who received desensitization treatment with IVIG, PP, or rituximab (46). Subclinical AMR was 31%, and those patients had higher C4d and arteriosclerosis scores higher interstitial fibrosis/tubular atrophy (100% versus 33%), and higher transplant glomerulopathy (43% versus 0%) at 1 year compared with patients without subclinical AMR at 3 months.

Transplant glomerulopathy (TGP) is a distinctive glomerular lesion unique to renal allografts that is characterized on light microscopy by capillary wall widening and double contours. TGP, in the presence of circulating DSA and positive C4d staining, is classified as chronic active AMR (47). Although most studies demonstrated a strong association between TGP and DSA and C4d (48,49), TGP may develop in patients without DSAs or C4d positivity (50). Gloor et al. reported 22% TGP at 1-year protocol biopsies of cross-match-positive patients correlated with prior AMR (51). The authors reported recently that in 119 cross-match-positive patients, TGP rate increased to 44% at a mean of 18 months after transplantation (52). We recently reported clinical outcomes of 17 patients with acute AMR (53). Fifteen of 17 patients received desensitization treatment because of pretransplant DSAs. TGP developed in 30% of those patients during a median of 28 months of follow-up. Graft survival was only 35% in AMR patients, suggesting the importance of prevention of AMR to reach better long-term outcomes in sensitized patients. After patients develop AMR or TGP, the prognosis is poor (48,49,53–55).

Why is the AMR (acute or chronic) rate so high in desensitized patients, and how can we prevent the development of AMR?

Pretransplant Immunologic Risk Assessment: Identification and Strength of the Antibody. Although CDC cross-match has been the standard test for >40 years and flow cytometry cross-match was introduced in 1983 as a more sensitive test, both tests lack specificity. Application of solid-phase antibody detection systems, ELISA, FlowPRA, and Luminex (single-antigen beads) have allowed for a more defined approach to determine the specificity of anti-HLA antibodies and interpretation of positive CDC and flow cytometry cross-match results. Not only the specificity but also the strength of the antibody can be determined in a Luminex test by MFI or molecules of equivalent soluble fluorochrome (MESF) values (Figure 1). The titers of the anti-HLA antibodies were correlated with MESF values (56). An increasing number of recent studies demonstrated an association between the strength of DSAs and risk of development of AMR, response to treatment of AMR, allograft survival, and success of desensitization protocols. As described above, a study from Mount Sinai Medical Center showed that CDC T cell cross-match-negative but CDC B cell or flow cytometry T and/or B cell cross-match-positive patients with low-level DSAs receiving kidney transplantation with anti-thymocyte globulin and IVIG treatment did not develop AMR (37). AMR was observed only in patients with strong pretransplant DSAs (MFI values >6000) and the addition of PP to decrease the strength of DSAs significantly decreased the AMR rate to 7% from 44%. A Mayo Clinic group stratified the cross-match-positive patients into three groups per strength of DSAs: group I, with a very high level of positive cross-match (CDC T cell cross-match positive); group II, with a high level of positive cross-match (mean flow cytometry cross-match channel shift [MCS] > 300 and MESF < 19,300 units); and group III, with a low level of positive cross-match (MCS shift < 300 and MESF < 19,300 units) (52,57). They showed strong association between development of AMR and graft failure and the strength of DSAs, although AMR was still observed in patients with low-tier DSAs. A Cedars Sinai group determined the strength of DSAs by standard fluorescence intensity (SFI) values of single-antigen Luminex beads and reported higher AMR in patients with DSA > 100,000 SFI and flow cytometry cross-matches > 200 MCS (26,58). Glotz and colleagues studied DSAs by ELISA to determine the strength of antibody and classified it into three groups by a score of 4, 6, and 8 in reactivity. Although AMR prevalence was 50% in desensitized patients with DSA scores of 6 to 8, it was only 5% in those with DSA scores of 4 (59). In a later study, the investigators studied the strength of DSAs by Luminex and showed that MFI values of peak DSAs > 6000 had more than 100-fold risk of developing AMR than patients with MFI < 465 (43). Higgins et al. transplanted 24 patients with DSAs (21 of which had pretransplant PP) and reported acute rejection in 62.5% of CDC cross-
match-positive patients, 33% of flow cytometry cross-match-positive patients, and 29% of CDC and flow cytometry-negative patients with DSAs identified by Luminex (60). The rejection rate was 73% in patients with MFI values $>2000$ and 12.5% in patients with MFI values $<2000$. Riethmüller et al. transplanted 20 CDC cross-match-negative patients without any desensitization treatment and retrospectively identified DSAs by Luminex after transplantation (61). AMR and cellular rejection rate were 35% and 40%, respectively, and the specificity of MFI values $>5200$ in prediction of AMR was 100%. Patel et al. reported 20% AMR in patients with pretransplant DSAs but negative CDC and flow cytometry cross-match receiving transplant without desensitization treatment (62). These studies emphasized the importance of not only identifying the DSAs by solid-phase assays before transplantation but also to determine the strength of the antibody for pretransplant immunologic risk assessment and decision-making for desensitization protocol or to cancel the transplant. Patients with strong DSAs should not receive a transplant unless the strength of the antibody decreases pretransplant or they will have a high risk for developing AMR and allograft loss. It is difficult to decide what is the acceptable cutoff value for the strength of DSA is to pursue the transplant because of the heterogeneity of desensitization protocols applied at transplant centers, different methods used for identification of DSAs, and various values used to determine the strength of the antibody (MFI, MESF, or SFI). Even if standard cutoff values for assessment of Luminex flow beads are established by transplant programs, these values will depend on the reagents used by the laboratory and may change slightly with each reagent lot number. Furthermore, because not all beads have the same amount of HLA antigen captured on the bead, cutoff indicators may vary slightly from one antigen bead to the next. In vitro determination of strength of the antibody may also not correlate with in vivo determinations because of differences in epitope affinities between antibodies. It is also not clear whether to decide the candidacy of a highly sensitized recipient for desensitization treatment not only with the strength of the DSA but also with the number of DSAs. What is the difference between patients with one very strong DSA to patients with three weak to moderate strength DSAs? There has not been any single prospective, randomized, and controlled study to compare different desensitization protocols, which makes it difficult to reach a scientific conclusion. All desensitization studies discussed in Table 2 are retrospective and single center. Locke et al. presented a randomized controlled trial in cross-match-positive kidney transplant recipients comparing anti-thymocyte globulin ($n = 21$) and daclizumab ($n = 20$) at the 2009 American Transplant Congress (63). Acute rejection rate (95% versus 67%, $P = 0.02$) was significantly higher in the daclizumab group, but there was no difference in patients and graft survival.

One of the shortcomings of using the Luminex test is the lack of information about whether antibodies identified by Luminex can activate complement and harm the allograft. A new method, [C4d]FlowPRA, which is based on flow-cytometric detection of alloantibody-triggered classical comple-
ment pathway and subsequent deposition of C4d to HLA antigen-coated microparticles, was introduced to overcome this problem. Wahrmann and colleagues showed that pre-transplant [C4d]FlowPKA-positive patients had worse graft survival than those with noncomplement fixing DSAs (64) and were strongly correlated with AMR (65). However, Honger et al. did not find any correlation in their patients with low-level DSAs pretransplant. Whereas AMR occurred in 55% of patients with C4d-fixing DSAs, it was 53% in patients without C4d-fixing DSAs (66). They argued against using this test pretransplant to define the clinical relevance of low-level DSAs.

A Cedars Sinai group developed an intracellular cytokine flow cytometry assay that detects intracellular IFN-γ production in CD3-negative non-T cell populations to assess sensitization from previous alloantigen exposure and showed that donor-specific reactivity better correlated with B cell cross-match results and development of AMR than DSA levels (67).

Lack of Efficacy of Current Protocols. Current desensitization protocols using a combination of high-dose or low-dose IVIG, PP, and rituximab have not been successful in decreasing the AMR rate, indicating the lack of efficacy with these agents, especially in patients with strong DSAs. Stegall and colleagues at Mayo Clinic investigated the lack of efficacy of current protocols. The investigators first studied the effect of these agents on splenic B cell populations in 25 spleens removed from desensitized recipients for ABO-incompatible or cross-match-positive transplantation. Although pretransplant multiple PP and low-dose IVIG did not have any effect on CD20- and CD79-positive naïve B cells, CD27-positive memory B cells, and CD138-positive plasma cells, the addition of rituximab reduced the number of naïve B cells but had no effect on memory B cells and plasma cells. Combination treatment with PP, IVIG, rituximab, and anti-thymocyte globulin showed a trend toward the reduction of memory B cells but had no effect on plasma cells (68). The authors later described two new assays used to determine the frequency and specificities of alloantibody-secreting cells (ASCs) in bone marrow taken during transplant surgery and peripheral blood using purified HLA as targets. The results demonstrated no effect of low-dose IVIG and PP or addition of anti-thymocyte globulin on ASC number or alloantibody production (69). They further tested four reagents to determine their ability to cause apoptosis on human bone-marrow-derived plasma cells and subsequently block alloantibody production in vitro (7). Although IVIG, rituximab, and anti-thymocyte globulin all failed to cause apoptosis and blocked antibody production, bortezomib treatment led to plasma cell apoptosis and thereby blocked alloantibody and anti-tetanus IgG secretion, indicating the importance of blocking plasma cell function to control alloantibody production.

Existence of DSAs after Transplantation

It has been well demonstrated that sensitized patients with pretransplant or de novo DSAs are at higher risk to develop acute or chronic rejection and have lower graft survival (43,70–73). Although Terasaki and colleagues believe that all chronic rejection is preceded by development of anti-HLA antibodies (72,74), a significant number of desensitized patients continued to have circulating DSAs and stable kidney function and normal transplant kidney biopsy (37,75–77), even long-term (78). A Johns Hopkins group followed up the DSAs of 49 kidney transplant recipients who underwent a desensitization protocol of PP/low-dose IVIG by ELISA and demonstrated that 63% lost DSAs at the end of the treatment and 89% did so by ≥2 months after the end of treatment (77). In a recent study, they studied the DSAs of 67 desensitized patients by Luminex instead of ELISA and reported that 53% of those patients eliminated their DSAs, which was less frequent than in the previous report (76). A DSA specific for DRw51, 52, and 53 was refractory to elimination (20%). However, the Mayo Clinic group showed that most desensitized patients studied (9 out of 11) continued to have low levels of DSAs at 4 months after transplantation (75). Of the 35 patients with DSAs receiving transplant at Mount Sinai, 52% of patients lost DSAs completely, and 30% lost some of their DSAs or had decreased DSA strength, indicating that the high-dose IVIG alone and PP/high-dose IVIG methods are effective in downregulating antibody production (37). However, it is not clear how to approach patients with DSAs, stable kidney function, and normal histopathology. Is it a state of “accommodation” that these patients do not need treatment or that these patients may develop chronic rejection in the future and need to be treated with IVIG, rituximab or bortezomib? Our current approach is not to treat those patients, to have close clinical follow-up with Luminex DSA strength, and to repeat biopsy if patients demonstrate worsening kidney function or increased MFI values of DSAs.

Interpretation of Allograft Biopsies: C4d-Positive Biopsy with Normal Histopathology. Prerogation or Accommodation? C4d-Negative AMR?

Introduction of routine C4d staining of transplant kidney biopsies is probably one of the most important biomarker discoveries in transplantation, which is now accepted as a footprint of antibody-mediated damage of allografts (79). According to the Banff classification, to reach the definitive diagnosis of acute or chronic active AMR, circulating DSAs, positive C4d staining, and histopathologic findings of allograft injury should be documented (47,80). The “widespread linear circumferential peritubular capillary staining in cortex or medulla, excluding scar or necrotic areas” is the criterion for positive C4d staining of paraffin sections (81). Focal staining is defined as <50% C4d positivity in peritubular capillaries (82), and the clinical importance of focal C4d positivity and glomerular C4d staining is not clear (83). The clinical significance of C4d-positive biopsies with circulating DSAs and normal histopathology is unknown and classified as a separate group in Banff (82). This finding is common in ABO-incompatible kidney transplantation, is seen in 70% to 80% of protocol biopsies (51,84–86), and suggests the possibility of “accommodation” in those patients. The existence of C4d with-
out tissue injury raises the possibility of potential inhibitory mechanisms involved at the distal end of the complement cascade after C4d cleavage, such as at the level of C3 or C5 activation. However, this finding is not common in ABO-compatible cross-match-positive kidney transplant recipients receiving desensitization protocols, so that most C4d positivity is associated with findings of tissue injury, suggesting acute AMR (51,85). There is currently no test to decide if C4d-positive biopsies with normal histopathology indicate a state of “accommodation” or “prerejection.”

Although >90% of allograft biopsies featuring acute AMR are C4d positive, C4d-negative AMR may develop through noncomplement activating alloantibodies. This is more problematic in interpretation of C4d-negative biopsies with TGP suggesting chronic active AMR, which is seen in almost half of the cases. This could be attributable to fluctuation of positive C4d staining over time, and Sis et al. showed increased endothelial gene expression in biopsies with histopathologic findings of AMR—circulating alloantibodies but negative C4d by microarray analysis (87).

**Side Effects of Agents Used in Desensitization Protocols**

Desensitized patients receive more immunosuppression treatment, including rituximab, PP, and anti-thymocyte globulin, compared with nonsensitized patients, which might increase the risk of infection (especially cytomegalovirus [CMV] and polyoma virus) and malignancy. A Cedars Sinai group monitored their desensitized patients by monthly CMV, Epstein-Barr virus, parvovirus B-19, and BK virus (BKV) testing. None of the 76 patients developed BKV nephropathy, 3 had BKV (4%), 2 had CMV (2.6%), and 1 had CMV/parvovirus viremia (26). One patient died because of donor-transmitted fungal infection at 1 month after transplantation. Of the 35 patients desensitized at Mount Sinai Medical Center, 1 patient developed BKV nephropathy (3%), 2 patients had CMV viremia (5.7%), and 1 had cryptococcal meningitis (37). Thielke et al. reported 7% CMV disease and 5% BKV nephropathy in 51 desensitized patients (20). BKV viremia was seen in 10% to 15%, BKV nephropathy in 3% to 8%, and CMV disease in 10% to 15% of transplant recipients. The prevalences reported in those three reports regarding desensitized patients are not higher than in average transplant recipients. There were no malignancies reported in these three studies. Kamar et al. reviewed the occurrence of infectious disease in 77 kidney transplant recipients who were treated with rituximab for treatment of AMR (n = 44), CDC B cell cross-match positivity (n = 4) or glomerular disease (n = 19), and PTLD (n = 6) (88). The median number of administered doses of rituximab was 4 (range, 2 to 8) at 375 mg/m². The incidence of bacterial and viral disease was not higher than in 902 control patients, but the rate of fungal infection was higher (17%), and 9 patients (9%) died as a result of infections, which were significantly higher than in the control group (1.6%). However, the dose of rituximab given in this report was 4 times higher than that used in desensitization protocols.

There are many IVIG products with specific side effects dependent on osmolarity, pH, sodium, and sugar components. Most adverse reactions to IVIG are mild and include headache, chills, nausea, myalgia, arthralgia, back pain, and increased BP, which may respond to slowing the infusion rate or premedication with antihistamines and non-steroidal anti-inflammatory drugs (89). Acute renal failure (ARF) secondary to osmotic injury to proximal tubular epithelia may occur because of sucrose or sorbitol components in some IVIG preparations. IVIG preparations that do not include sucrose or sorbitol (such as Gamimune-N, Gammagard, and Polygam) are preferred to avoid renal failure. As a serious side effect, thrombotic events such as acute myocardial infarction (AMI), deep venous thrombosis, and stroke have been reported with Gammagard and Polygam and linked to high sodium content and osmolarity. A Cedars Sinai group reviewed the side effects of IVIG in 279 desensitized patients (90). Although none of the patients receiving Gamimune-N had ARF or AMI, 4.7% of Polygam-treated patients experienced AMI and 8.2% in the Carimune group developed ARF. The investigators reported 18 patients with IVIG-induced hemolytic anemia in 16 non-O blood group patients (91). Rare side effects included acute aseptic meningitis, which occurred 48 to 72 hours after the administration of high-dose IVIG and resolved spontaneously (92). Very rarely, serious anaphylactoid reactions may occur in patients with IgA deficiency.

**Economic Effect of Desensitization Protocols**

These therapeutic strategies with PP, IVIG, and rituximab used in desensitization protocols are expensive. Considering the high-dose IVIG (2.0 g/kg twice) and rituximab (a single dose of 375 mg/m²) protocols, an additional cost of $21,000 is added to the transplantation cost. This is based on an average cost of $8700 for 120 g of IVIG (Gamunex) and $3900 for a 700-mg dose of rituximab at our center. When five sessions of PP are indicated, an additional $10,000 is added to the total cost of desensitization. If the patient develops AMR, which is seen in approximately 30% of desensitized patients, the IVIG, PP, and rituximab treatment will be repeated, doubling the cost, excluding hospital admission costs. The ultimate question is whether this strategy is cost-effective? To assess the cost-effectiveness of desensitization, one must relate this to the cost of maintaining ESRD patients on dialysis. Jordan et al. calculated a cost savings of approximately $300,000/patient transplanted versus those who remained on dialysis for the 5 years of the study (38,88). In a recent publication of the U.S. Renal Data System annual report, the cost of maintaining a patient on dialysis is $70,000/yr, and the cost of uncomplicated transplantation is $25,000 but could increase to $106,000/yr with any event. However, with a functioning graft, the annual cost per transplant patient is $17,000. When one considers the cost of dialysis as the only alternative therapy for highly sensitized patients, it is still cost-effective to use desensitization protocols with hopes of transplanting the highly sensitized patient with a successful outcome. The innovative agents such as bortezomib (cost of 2-mg dose for one cycle is $5500) and eculizumab ($8500 for a 600-mg dose) are also expensive, and we need further studies to assess their economic effect on the healthcare system.
New Agents

Two new agents were recently introduced to transplantation. Bortezomib, a proteasome inhibitor, was used successfully in treatment of AMR and abrogation of anti-HLA antibodies (93–96). Everly et al. treated six patients with AMR with bortezomib (93). Although all six patients had their AMR resolved with a decrease in DSA levels, three patients developed TGP. In a slightly different clinical setting, Sberro-Soussan et al. used bortezomib as the sole desensitization therapy in four renal transplant recipients who experienced subacute AMR with persisting DSA (94). Bortezomib treatment did not significantly decrease DSA MFI within the 150-day posttreatment period in any patient. A Mayo Clinic Group presented their experience with bortezomib for desensitization at the American Transplant Congress in 2010. Although one of nine patients treated with PP received a kidney transplant, three of six patients treated with bortezomib and PP received kidney transplantation (97).

Eculizumab, an anticomplement C5 antibody that inhibits the formation of the membrane attack complex, was used as a salvage treatment of severe AMR (98) or for prevention of AMR. Early results from a Mayo Clinic study showed that eculizumab treatment prevents development of acute AMR in cross-match-positive patients (99). Eculizumab was added to the desensitization protocol of 16 cross-match-positive patients at the time of transplant and weekly through week 4 (100). Although only one patient developed AMR (6%), six patients (37%) developed chronic AMR at 3.8 months after transplantation.

Using human recombinant C1-inhibitor, AMR was prevented in a sensitized baboon model (101). There are also new anti-B cell agents in the pipeline that were recently reviewed in detail (102). These include ocrelizumab and ofatumumab (humanized anti-CD20 mAb with decreased immunogenicity), epratuzumab (humanized anti-CD22 mAb), belimumab (humanized mAb to Blys, also known as BAFF [i.e., B cell activation factor]), and atacicept (fusion receptor protein that inhibits Blys and April). These agents are in early clinical trials for treatment of systemic lupus erythematosus and have the potential to be used in sensitized patients in the future.

Kidney Paired Exchange

Although desensitization protocols have proven beneficial to allow for successful transplantation in the highly sensitized patient, the burden of increased AMR rates and long-term poor outcomes calls for further options. An alternative intervention in addition to desensitization to allow for successful transplantation in the highly sensitized patient is kidney paired exchange. Kidney paired donation (KPD) arises when the donors in two donor/recipient pairs are blood-type or cross-match incompatible with their intended recipients. The exchange process allows each donor to donate a kidney and each recipient to receive a compatible transplant. This methodology was initially proposed by Rapaport in 1986 (103) but could not be applied because of ethical, administrative, and logistical constraints until the first paired exchange occurred in the United States in 2000 (104).

KPD programs gradually grew in the United States and mostly involved ABO-incompatible pairs. In 2006, Montgomerie et al. proposed domino paired donation (DPD), in which a series of simultaneous transplants is initiated with a nondirected donor and terminated in the deceased-donor pool (105). Nonsimultaneous, extended, altruistic donor programs are a variation of DPD in which the last donor initiates another chain at a later time instead of closing the chain with a deceased-donor pool (106). National registries were developed to attempt to increase the number of potential matches and facilitate transplant in highly sensitized patients. The National Kidney Registry is one of the biggest independent registries, currently involving 44 U.S. transplant centers. As more centers become involved in KPD, administrative and logistical challenges that have to be addressed include logistics of donor travel or shipping the kidney, simultaneous performance of the transplant operations, and the potential risk that one kidney may not be usable or a donor changes his or her mind.

Because the overall goal in transplanting the highly sensitized patient is to ensure optimal posttransplantation outcome, KPD may be more suitable in patient-specific scenarios because it is less expensive and requires less immunosuppression compared with desensitization and is expected to have a better graft outcome. Segev et al. developed a model that simulates pools of incompatible donor/recipient pairs (107). A national optimized matching algorithm would result in more transplants and better HLA concordance, and highly sensitized patients would benefit 6-fold from a national optimized scheme (2.3% versus 14.1%). In other patient-specific scenarios, the combination of desensitization and KPD could be considered in patients with low-level DSAs. Those candidates should have DSAs with low MFI values by Luminex single-antigen beads and low-flow cytometry channel shift values.

Approach to Sensitized Patients

Our review article demonstrates the importance of the strength of DSAs for development of AMR. Currently, we screen all transplant candidates for anti-HLA antibodies using Luminex single-antigen beads for the specificity and the strength of antibodies at our center (Einstein/Montefiore Transplant Center [Figure 2]). Anti-HLA antibodies with MFI values >5000 are reported to the United Network for Organ Sharing as unacceptable antigens. Patients with living-donor candidates but positive cross-match and/or DSAs are first considered for our internal KPD exchange program, and then the National Kidney Registry paired-exchange program. If KPD exchange is not feasible and patients are interested in a desensitization protocol, we then use the following algorithm:

1. CDC T cell cross-match-negative but CDC B cell cross-match and/or flow cytometry T and or B cell cross-match-positive patients with total T and B cell flow cytometry MCS values <300 and MFI DSA values <5000 receive transplant with thymoglobulin and high-dose IVIG (2.0 g/kg) without PP.

2. CDC T cell cross-match-negative but CDC B cell cross-match and/or flow cytometry T and or B cell cross-match-positive patients with total T and B cell flow cytometry MCS values >300 and or MFI DSA values >5000 receive pretransplant desensitization including PP, IVIG, and rituximab. Patients start immunosuppress-
sive treatment with tacrolimus, mycophenolate mofetil, and prednisone and one dose of rituximab (375 mg/m²). They receive four sessions of PP every other day starting 1 week after rituximab treatment. One dose of IVIG (2.0 g/kg) is given after the fourth dose of PP. Patients receive transplant if MFI and flow cytometry MCS values decrease to <5000 and <300, respectively.

3. CDC T and B cell cross-match-positive patients are considered for desensitization if they have less than three DSAs and only one DSA with MFI values >5000 with the same protocol described above.

Desensitized patients are followed closely with monthly DSAs and BKV PCR titers up to 6 months and at 9 and 12 months after transplantation. They undergo transplant kidney biopsy if there is an increase in creatinine levels or MFI values of DSAs or if they develop de novo DSAs.

Summary and Future Directions

The review of a decade of experience in highly sensitized patients shows that acute, subclinical, and chronic AMR rates are unacceptably high with current desensitization protocols despite acceptable short time graft survival. Recent reports raised the concerns about lower long term graft survival compared with nonsensitized patients. The strongest predictor for development of AMR is the pretransplant strength of DSAs and those patients should be evaluated by Luminex single-antigen beads MFI and flow cytometry MCS values. Patients with strong DSAs should not be considered for transplantation unless the levels are reduced pretransplant with desensitization protocols. There are no prospective and randomized trials comparing different desensitization protocols. There are presently no clear scientific data to recommend a certain protocol, but PP should be used in patients with strong DSAs to decrease the titers, and higher dose IVIG might have more immunomodulatory effect. All cross-match incompatible living-donor candidates should be considered first for paired exchange programs. Patients with low-level DSAs are probably safe to receive a transplant with IVIG and an induction treatment with anti-thymocyte globulin or alemtuzumab. The role that novel agents such as bortezomib and eculizumab will play is not clear and requires more clinical experience.

Disclosures

None.

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