REVIEW

Desensitization strategies: is it worth it?

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SUMMARY

Preformed donor-specific antibodies (DSAs) limit access to transplantation for thousands of renal transplant patients. While kidney paired donation offers the best strategy for patients with a living donor, for very highly sensitized patients and those without living donors, a strategy of desensitization offers the best hope of transplantation. Removal of DSAs with plasmapheresis, intravenous immunoglobulin and anti-CD20 antibodies can permit successful transplantation. While the clinical outcomes remain inferior to compatible transplant and the costs are significantly greater, when compared with long-term dialysis treatment, these strategies are offer improved survival and are cost-effective given nationally accepted benchmarks.

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Introduction

Renal transplantation is the preferred treatment of choice for patients with end-stage renal disease (ESRD) as it improves their survival, quality of life and costs lower after the first year compared to dialysis [1–5]. However, there is a paucity of kidney transplants performed annually compared to those in need of a kidney due to a limited number of organs available. For many of these patients, sensitization to human leucocyte antigens (HLA) from blood transfusions, pregnancy or a previous transplantation is an additional barrier to successful outcomes. A patient's extent of sensitization is reflected in the calculated panel reactive antibody (cPRA) score that can range from 0% indicating no anti-HLA antibody, to 100% that predicts incompatibility with 100% of the donor pool [6]. The presence of a cPRA greater than 80% creates difficulty in finding matched kidneys from compatible donors and low annual transplant rates [7]. Further, highly sensitized patients have higher rates of antibody-mediated rejection (AMR), early graft loss [8–10] and a higher chance of being removed from or dying on the waiting list [11]. Transplant candidates with a cPRA ≥98% are in a dire situation, as mortality rates on dialysis exceed those of most forms of cancer [3,12,13].

Four transplant possibilities are currently available for this disadvantaged group of dialysis patients. The first is to wait for a compatible deceased donor transplant, which may take years without a suitable donor ever being identified [14,15]. It is estimated that patients with a cPRA of 100% must be offered in excess of 300 000 donor organs before finding one that would lead to a negative crossmatch. [14]. Fortunate ones who have a living donor can undergo transplantation if the immunological barrier can be successfully crossed (option 2). Patients for whom a living donor transplantation is not possible due to unacceptable antibodies, have the option of enrolling in a kidney paired donation (KPD) programme (option 3) or undergoing a desensitization procedure (option 4). Desensitization therapies target removing and/or reducing donor-

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specific antibodies (DSA) prior to transplantation. Desensitization can increase access to both living and deceased donor transplants and can be used individually or in combination with KPD. This review discusses these two strategies to determine whether desensitization therapies are warranted as useful options for difficult to transplant highly sensitized ESRD patients.

Desensitization treatments

The goal of desensitization is to reduce/eliminate DSA, thereby preventing hyperacute rejection and allowing a successful transplantation. Desensitization protocols have typically combined an approach of removing circulating DSA with plasmapheresis (PP) [16], combined with agents that decrease antibody production, or ones that block their actions.

Plasmapheresis removes antibodies from the circulation. This technique is not specific for the removal of alloantibodies and therefore all plasma proteins are reduced including clotting factors. However, this removal is only short-lived with antibodies rebounding to pretreatment levels following re-equilibration between intravascular and interstitial compartments [16]. More importantly, PP does not affect ongoing antibody production by plasma cells and, hence, is a poor treatment choice for desensitization as sole therapy. Its side effects include coagulopathy, hypocalcemia, thrombocytopenia, hypotension and catheter-related infection and sepsis.

Intravenous immunoglobulin (IVIg) derived from the gamma globulin fraction of plasma from pooled donors has been shown to inhibit T- and B-cell proliferation, cytokine production, maturation of dendritic cells, induce B-cell apoptosis and inhibit complement activation [17,18]. It was first utilized in combination with PP in crossmatch incompatible living donor kidney transplant candidates [19]. IVIg-based desensitization can be divided into two general approaches: combined with alternate day PP at a low dose (100 mg/kg); or used at a high dose (1–2 g/kg) [20,21].

Low-dose IVIg and PP protocols have been used for ESRD patients with living donors and high levels of DSA. Depending on the titres of antibodies patients undergo varying numbers of PP sessions (higher titres, more sessions of PP) followed with the infusion of IVIg. Using low-dose IVIg with PP, AMR has been reported to be as high as 36% with 100% 1-year graft survival [22]. The low-dose IVIg with PP, protocol was modified to include anti-thymocyte globulin for induction along with the addition of rituximab and splenectomy in an attempt to decrease high acute rejection rates [23]. Despite the modification, acute AMR rate was 43% with a 78% graft survival at 15 months. A similar high incidence of acute AMR of 39% and graft survival of 89% was noted with a median follow-up of 22 months [24]. In another study of 57 patients subjected to low-dose IVIg and PP, six patients failed to convert to a negative crossmatch and in the remaining 51; acute rejection rate was 33% with 93% graft survival at 2 years [25]. The largest single centre analysis compared 8 year patient survival in 211 transplant recipients who were desensitized and underwent living donor kidney transplantation using this regimen [13] with two matched control groups of patients on a waiting list for kidney transplantation who continued to undergo dialysis (dialysis-only group) or who underwent either dialysis or HLA-compatible transplantation (dialysis-or-transplantation group). Patient survival was 90.6% at 1 year, 85.7% at 3 years, 80.6% at 5 years and 80.6% at 8 years, compared with rates of 91.1%, 67.2%, 51.5% and 30.5%, respectively, for patients in the dialysis-only group and rates of 93.1%, 77.0%, 65.6% and 49.1%, respectively, for patients in the dialysis-or-transplantation group. These data provided evidence that desensitization protocols could help overcome incompatibility barriers in live donor renal transplantation. However, being a single centre analysis in a centre with a very high volume of transplantations with kidneys from incompatible live donors, it was unclear whether these results were generalizable [26].

High-dose IVIg-based protocols [27,28] for desensitization have been reported in many single centre experiences with variable results [29–35]. In a randomized controlled trial of high-dose IVIg-based desensitization (2 g/kg) for patients on the deceased donor waiting list, 101 highly sensitized patients (cPRA > 50%) received either high-dose IVIg or placebo, IVIg induced a small decrease (approximately 10%) in PRA levels compared with placebo that persisted for approximately 6 weeks following the last IVIg dose. No difference in transplant rates was observed at one year; however, at two years, 35% of the IVIg group was transplanted compared to 17% of placebo-treated patients. A higher acute rejection rate was noted in the IVIg (53% vs. 10%) treated group [35]. In a study on its use in both living and deceased donors, IVIg (2 g/kg) was given to crossmatch-positive recipients following which patients underwent transplantation if cell-dependent cytotoxic (CDC) T-cell crossmatch became negative. AMR was seen in 13 patients (31%), and 3 (7%) lost the allograft secondary to rejection. Two-year patient and graft

survival rates were 98% and 89%, respectively [32]. Examination of AMR rates using different antibody induction regimens (Zenapax or Thymoglobulin) in patients with positive crossmatches desensitized with IVIG (2 g/kg) showed no difference between the two [36]. Rates of AMR were similar despite changing the induction agent to alemtuzumab [37].

As AMR rates remained high despite pretreatment intervention, the effect of adding rituximab to high-dose IVIg (2 g/kg) based regimen was then evaluated [18]. Fifty per cent of patients had acute rejection episodes with 30% of patients experiencing AMR. Most acute rejection episodes occurred within the first month post-transplantation and were reversed with treatment. Subsequently, a larger experience evaluated 76 patients who were transplanted after desensitization using a similar protocol [37]. AMR was noted in 29% of patients with patient and graft survival at 24 months was 95% and 84%, respectively. Other studies have questioned the ability of high-dose IVIg (2 g/kg) to lower the strength of HLA antibodies in highly sensitized patients [32–34]. Fifteen patients with a cPRA >40% received 2 g/kg IVIg per month for 4 months or until transplanted. Luminex single-antigen testing was performed before and after IVIg. Administration of IVIg was associated with a modest decrease in reactivity to both class I and II HLA antigens but did not significantly alter mean cPRA [32]. In a study of 27 patients whose median flow cytometric cPRA was 100% and mean wait-list time exceeded 4 years the effect of high-dose IVIg (2 g/kg) on HLA antibody profiles of sera obtained before and after treatment was examined. HLA antibody profiles, measured by cPRA, showed no significant change in response to IVIg treatment [33]. The effects of high-dose IVIG (2 g/kg) and Rituximab were examined in a prospective study on desensitizing transplant candidates with a cPRA >50% waiting for a deceased donor kidney for more than 5 years. It showed no significant reduction in patients' class I and II cPRA levels nor any change in the mean number of unacceptable antigens or their mean fluorescence intensity values [34]. These studies question the ability of IVIg alone to meaningfully decrease sensitization status. The higher transplant rates noted could be due to non-anti-HLA lowering or immunomodulatory effects of IVIg such as inhibition of complement.

A report from the Mayo clinic details their single centre experience comparing their experience with both the low-dose IVIg with PP protocol and high-dose IVIg [38]. 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 post-transplant DSA monitoring (group III). Although only 5 of 13 (38%) high-dose IVIG-treated patients achieved a negative crossmatch, 84% and 88% of group II and III patients were able to do so. 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 crossmatch and lower acute rejection rates, but no regimen was completely effective in preventing AMR.

In a review of 21 studies published between 2000 and 2010, involving 725 patients with DSAs who underwent kidney transplantation (with different protocols) 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 rate was 28%, which is significantly higher than in nonsensitized patients (<10%) [21]. 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 [21]. A similar but different review that compared PP/low-dose IVIg regimen to high-dose IVIg regimen also concluded that high-dose IVIg alone has shown to be inferior in several reports [20].

Other agents used in desensitization include the following:

Bortezomib (BTZ) is a proteasome inhibitor (PI) that induces endoplasmic reticulum stress, NFκB inhibition and apoptosis in normal and transformed plasma cells [39,40]. This led to the hypothesis that treatment with the PI BTZ might deplete antibody-secreting long-lived plasma cells and have an impact on DSA production. A prospective iterative trial of PI-based therapy for reducing HLA antibody (Ab) levels was conducted in five phases differing in BTZ dosing density and PP timing. Forty-four patients received 52 desensitization courses. Only 19 out of 44 patients (43.2%) could be transplanted; however, they had a low acute rejection rate (18.8%). About 12.5% of subjects had *de novo* DSA formation [40]. In a study aimed to determine the safety and efficacy of 32 doses of BTZ in 10 highly sensitized kidney transplant candidates with alloantibodies against their intended living donor, no patient developed a negative crossmatch against their original intended donor, and the calculated panel reactive was unchanged in all patients [41].

Eculizumab is a humanized monoclonal antibody that blocks cleavage of the human complement component C5 and prevents terminal complement activation. It has been shown to be efficacious in the prevention AMR in renal transplant recipients who had a positive crossmatch against their living donor. Rates of AMR were compared between 26 highly sensitized recipients of living donor renal transplants who received eculizumab post-transplant and a historical control group of 51 sensitized patients treated with a similar plasma exchange-based protocol without eculizumab [42]. The incidence of AMR was 7.7% (2/26) in the eculizumab group compared to 41.2% (21/51) in the control group. This was the basis of a phase 2 randomized evaluate the safety and efficacy of eculizumab in preventing acute AMR in kidney transplant recipients who required desensitization [43]. One hundred and two patients underwent desensitization. Post-transplant, 51 patients received standard of care (SOC) and 51 received eculizumab. Treatment failure rates were 11.8% and 21.6% for the eculizumab and SOC suggesting a potential benefit for eculizumab compared with SOC in preventing acute AMR in recipients sensitized to their living-donor kidney transplants groups. It is unfortunately quite expensive with an average wholesale price of $21 000 per dose [44]. Another consideration is the risk of development of invasive infections with encapsulated organisms during eculizumab therapy due to which certain vaccinations are pre requisite [45].

Interleukin (IL)-6 is a pleiotropic cytokine that has powerful stimulatory effects on B cells and plasma cells and is responsible, in conjunction with other cytokines, for normal antibody production. It has also been recognized as an important mediator of allograft rejection [46,47]. *Tocilizumab (TCZ)* a humanized monoclonal antibody directed at the IL-6 receptor has also been studied as a potential desensitization agent. A phase I/II pilot study was performed with TCZ and IVIg to reduce and eliminate anti-HLA antibodies as well as test its safety and efficacy in desensitization. Ten patients who were unresponsive to desensitization with IVIg and Rituximab were enrolled and treated with IVIg + TCZ. Two patients were removed from the study due to compliance issues. Of the remaining eight patients, five were able to undergo transplantation (mean time to transplant – 8.1 $\pm$ 5.4 months after TCZ) with an additional patient receiving frequent offers with negative crossmatches. No AMR was seen on protocol biopsies performed at 6 months, however, one patient developed mild AMR on 12 months for cause biopsy. Renal function in all transplanted patients was good (1.15 $\pm$ 0.5 mg/dl) at 12 months [48]. TCZ with IVIg appears to be an additional agent with potential in desensitization. Larger controlled studies are essential to better study its efficacy.

IgG-degrading enzyme derived from *Streptococcus pyogenes* (IdeS) that cleaves all four human subclasses of IgG has recently been used as an agent for desensitization [49]. Since the Fc region of IgG is critical for interaction with Fc receptors and complement binding, proteolytic activity on IgG molecules at this site prevents the occurrence of IgG-mediated antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity, two processes that are critical for AMR. Twenty-five highly HLA-sensitized patients at two international centres (Sweden and Unites States) were administered IdeS before the transplantation of a kidney from an HLA-incompatible donor. Out of the 25 patients, 22 had DSA present before transplantation. IdeS reduced or eliminated DSAs and permitted HLA-incompatible transplantation in 24 of 25 patients. AMR occurred in 10 patients at 2 weeks to 5 months after transplantation; all these patients had a response to treatment. The difference in immunosuppressive regimens used is noteworthy. Swedish cohort patients received induction with horse anti-thymocyte globulin, and those in the US cohort received alemtuzumab followed by IVIg. In the US study, all recipients received rituximab (either before or after transplant). Patients in both centres were maintained on standard triple-drug immunosuppressive regimens. Seven patients in the US study and three in the Swedish study developed AMR responsive to treatment. With such intense immunosuppressive regimens, the potential for long-term complications from infections and malignancy cannot be ignored. A different study on seven highly sensitized (cPRA 98–100%) kidney transplant candidates who had DSA resulting in positive crossmatches with their donors (five deceased, two living), examined the effect of IdeS given within 24 h prior to transplant [50]. All crossmatches became negative post-IdeS and the patients underwent successful transplantation. Three patients had DSA rebound and AMR, which responded to SOC therapies. At a median follow-up of 235 days, all patients had a functioning renal allograft.

Daratumumab is an IgG1κ human mAb that binds to CD 38 and inhibits the development of CD 38 expressing cells including plasma cells and plasmablasts. In this context, its potential to control the production of anti-HLA antibodies in a nonhuman primate was tested. Sensitized rhesus macaques were treated with daratumumab before undergoing a kidney transplant to

examine its effects on the development of DSAs [51]. Animals treated with daratumumab had significantly reduced DSA levels compared to untreated controls (57.9% vs. 13%). However, the reduction was not maintained and rapid rebound of antibodies developed with profound rejection. Though it raises the possibility of another potential therapeutic strategy, it shows that the removal of pathogenic HLA antibodies is still a considerable medical challenge.

Despite the availability of the above-described agents for desensitization, the quality of evidence comparing one to another is poor. There is no desensitization strategy that can universally allow transplantation in the presence of significant levels of anti-HLA antibody to the donor or a positive crossmatch. Despite combining the available therapies in different protocols abrogating the response of high levels of preformed DSA has posed a significant challenge with unacceptable rates of AMR after transplantation. This has led to a challenging question of whether sensitized patients are better of waiting on dialysis or undergoing desensitization. Two large multi-centre studies have attempted to answer this difficult dilemma.

Benefits of desensitization

A multi-centre analysis on the survival benefit of kidney transplants from HLA-incompatible live donors examined the results across 22 centres in the US with 1025 recipients [26]. Their outcomes were matched with controls who remained on the waiting list or received a transplant from a deceased donor (waiting list or transplant control group) and controls who remained on the waiting list but did not receive a transplant (waiting list only control group). Recipients of kidney transplants from incompatible live donors had a higher survival rate than either control group at 1 year (95.0% vs. 94.0% for the waiting list or transplant control group and 89.6% for the waiting list-only control group), 3 years (91.7% vs. 83.6% and 72.7%, respectively), 5 years (86.0% vs. 74.4% and 59.2%) and 8 years (76.5% vs. 62.9% and 43.9%) ($P < 0.001$ for all comparisons with the two control groups). These results contrast the analysis of the UK adult transplant waiting list that compared the patient survival of crossmatch-positive living donor HLA-incompatible kidney transplant with that of similarly sensitized patients awaiting a compatible organ [52]. Two hundred and thirteen patients who underwent HLA-incompatible transplant were matched in a 1:4 ratio with similarly sensitized patients listed for a transplant across the same time period. No difference in survival was noted between patients who underwent a HLA-incompatible transplant compared with the listed only group, or listed or transplant group.

Comparing these two studies is difficult as pointed out in the thoughtful analysis by Clayton and Coates [53]. The two studies have different definitions of sensitization, have different matching methods for patients awaiting a transplant, have studied different populations (the US study includes cases from select centres and controls from the entire waiting list whereas the UK study selected all patients from the entire waiting list), the waiting times are different in the two populations and the survival of dialysis patients is different (UK dialysis patients survive longer than those in the United States). In the US study, desensitized patients who were preemptively transplanted were matched to controls who received up to 3 months of dialysis potentially introducing lead-time bias and included only desensitized patients from 22 centres which could lead to a centre bias effect. Both studies also could not account for socio-economic factors that could have led to a bias in favour of patients receiving desensitization. It is also to be noted that the study periods are different in the two populations (1997–2011 in the US study and 2007–2013 in the UK population).

Long-term risks of desensitization

It is difficult to determine the impact desensitization therapies have on the long-term health since most published studies are short-termed. Desensitization therapies add to overall immunosuppression raising the obvious concerns of infection and other immunosuppression related complications including malignancies. A comparison of infectious complications between kidney transplant recipients desensitized with Rituximab and IVIg and nondesensitized patients showed no difference in bacterial, viral, fungal or serious infections over an 18-month follow-up period [54]. In 20 patients who underwent desensitization with IVIg and Rituximab, patients were questioned, after each infusion and at all follow-up visits, about the development of motor deficits, memory loss and other neurologic symptoms (to rule out reactivation of polyoma JC virus). Monitoring for adverse events and serious adverse events was continued after transplantation for a mean of 22.1 ± 6.0 months. No patients had neurologic symptoms suggestive of progressive multifocal leukoencephalopathy, nor were any viral infections [Cytomegalovirus (CMV), Epstein–Barr virus,

parvovirus B-19 and BK polyomavirus] detected [31]. The University of Illinois at Chicago experience with desensitizing 51 patients for transplantation with PP, IVIg and Rituximab reported 7% CMV disease and 4.9% BK nephropathy [25]. The reported prevalence is similar to that observed in standard transplant recipients. In the phase 2, randomized, study evaluating the safety and efficacy of eculizumab in preventing acute AMR in sensitized recipients of living donor kidney transplants requiring pretransplant desensitization, infections rates were 62.7% in the treatment group and 49% in the SOC group over the 28 month study period [43]. Interpreting long-term risks from the above-mentioned short-term studies is not possible. A nationwide cohort analysis of the Korean Transplantation registry investigated the impact of anti-A/B and donor-specific anti-HLA antibodies on clinical outcomes in kidney transplant recipients [55]. Patient survival rate was reduced in patients who underwent incompatible transplants (ABO, HLA, ABO+HLA) compared to standard transplants. The most common cause of death was infection-related. Multivariable risk factor analysis revealed that desensitization attempts rather than ABO or HLA incompatibility were more significant risk factors for infection-related mortality. Though this study has the limitations of a large registry analysis, it is important to recognize that infection-related mortality is a risk factor to desensitization. More studies are necessary to arrive at stronger conclusions.

Economic assessment of desensitization

In addition to increasing the medical complexity of renal transplant, desensitization therapies significantly increase the cost of the transplant procedure. Axelrod *et al.* [56] reported a national cohort study examining hospital reported cost and Medicare reimbursement in patients undergoing compatible and incompatible living donor kidney transplant. Incompatible living donor transplant was associated with a 42% increase in the cost of care ($151 024 vs. $106 636 $P < .001$). The incremental cost was highest in patients with positive cytotoxic crossmatch (58% increase) compared with patients who had only flow positive crossmatch (38% increase). Medicare reimbursement was also increased, with mean payment (excluding the cost of organ acquisition) of $92 150 for incompatible vs. $58 084 for compatible transplant.

While desensitization treatments increase the cost of transplant, the overall economic impact needs to be considered in light of longer survival and a reduced need for haemodialysis. The cost-effectiveness of incompatible living donor transplant was assessed using a discrete event simulation model [57]. Over 10 years, incompatible living donor kidney transplant was associated with a greater mean cost of care ($440 234 vs. $292 117) and longer mean survival (5.47 years vs. 4.03). Thus, the incremental cost-effectiveness of desensitization was estimated to be $80 486 per quality-adjusted life year. In comparison, compatible living donor transplant was estimated to cost $39 939 per quality-adjusted life year.

Alternatives to desensitization: kidney paired donation

Over the last three decades, the practice of living KPDs has matured and become standard practice in many transplant centres [58]. In its simplest form, KPD is an exchange of donors between two incompatible pairs such that they are now compatible. It has grown to involve three or more pairs requiring sophisticated mathematical algorithms to best match patients for transplant. As reported to UNOS, national KPD numbers have increased from <10 in 2002 to 450 in 2010, to 587 in 2015 and to 642 in 2016. In the United States, there are many single and multi-centre registries in addition to a government funded KPD registry managed by UNOS. Traditionally pairs were entered into the registry due to ABO incompatibility but the use of KPD has extended and now commonly involves highly sensitized recipients. Overall match rates are approximately 50–60% in a large KPD registry with more than 1000 pairs [59].

Sensitized patients benefit from listing in KPD programmes and have transplant rates comparable to those less sensitized. Data from Australian and Canadian KPD registries show that those with cPRA between 50% and 96% had equivalent match rates as those less than 50% [60]. Patients with cPRA ≥95% though, are clearly disadvantaged because a lower proportion of them receive a transplant and spend long waiting times even on KPD registries [60]. In a US study, match rates have been reported to be as low as 15% for those who are highly sensitized and/or blood group O [59]. Their broad sensitization and high cPRA leads to only a limited number of compatible donors bearing rarer HLA genotypes [59,61].

A more recent report compared transplant rates of a KPD network (NKR – National Kidney Registry) with the Scientific Registry of Transplant Recipients database [62]. NKR transplants were performed on a significantly

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greater proportion of HLA hyperimmunized patients. Only 45.8% of the NKR recipients had a pretransplant cPRA of 0%, compared to 71.3% of all living kidney transplants, and 71% of living unrelated transplants in the UNOS. The NKR transplants representing the hard-to-match cPRA ranges of 80–97% were accomplished for 15.3% of the recipients compared to only 3% of all living kidney transplants, and 3.1% of living unrelated transplants in the United Network for Organ Sharing [62]. It is important to identify patients not transplanted after entering into KPD as well. In the NKR registry those unmatched based on cPRA were 23% for cPRA of 0%, 22% for a cPRA of 1% to 79%, 8% for a cPRA of 80% to 95%, 18% for a cPRA of 95% to 99% and 29% if they had a cPRA of 100% [62].

It is clear that KPD is beneficial to sensitized recipients and has the potential to maximize its efficiency with improved algorithms and increasing pool size though highly sensitized patients still suffer from low match rates.

Conclusion

The choice of desensitization or not remains difficult and should be approached individually rather than as a group. For patients with DSA's and high levels of HLA antibodies paired donor exchange programmes and transplant chains can provide access to organs where the immunological barrier can be avoided. KPD is associated with better outcomes and lower costs. However, for patients with rare HLA types, uncommon HLA antigens or very high sensitization levels, when no matches from kidney exchange programmes are forthcoming after a period of time, desensitization should be considered given the longer expected survival and improved quality of life. With newer medications being explored (including post-transplant treatment to modify antibody-mediated graft injury) there appears hope that the immunological barrier could be crossed effectively and safely. It remains to be seen if this can be done in a manner that is both clinically efficacious and economically feasible.

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Conflicts of interest

Dr. Axelrod reports have a consulting agreement with CareDx. Dr. Kuppachi reports no conflicts.

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