Using donor exchange paradigms with desensitization to enhance transplant rates among highly sensitized patients

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Purpose of review

Many sensitized patients have willing live donors but are unable to use them because of a human leukocyte antigen (HLA) incompatibility. The options for these patients include: remaining on the deceased-donor list, entering a kidney-paired donation scheme, or undergoing desensitization with high-dose IVIg or plasmapheresis and low-dose IVIg.

Recent findings

Mathematical simulations verified by actual data from several national kidney-paired donation (KPD) programs has shed light on which donor/recipient phenotypes are likely to benefit from each transplant modality. Pairs that are easy to match are likely to receive compatible kidneys in a KPD. Those who are hard to match may be better served by desensitization. The phenotype which is both hard to match and hard to desensitize due to board and strong HLA reactivity are most likely to be transplanted by a hybrid modality utilizing desensitization after identifying a more immunologically favorable donor in a KPD.

Summary

Recent outcomes from desensitization in which starting donor-specific antibody strength is low have been very good. For broadly sensitized patients with a high-strength cross-match, searching for a better donor in a KPD pool can facilitate a safer, less expensive, and more successful desensitization treatment course.

Keywords

desensitization, highly sensitized, kidney exchanges, kidney-paired donation, plasmapheresis

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Introduction

For eligible recipients, renal transplantation offers clear benefits in terms of quality of life, longevity, and cost to the healthcare system when compared with dialysis [1–3]. Live donation remains the most promising approach for the expansion of renal transplantation. Compared with deceased-donor kidneys, organs from live donors tend to have immediate function and better long-term patient and graft survival. Human leukocyte antigen (HLA) sensitization and ABO incompatibility remain the most significant barriers to further expansion of live donation. Approximately 30% of the patients waiting on the deceased-donor list in the USA are sensitized to HLA molecules. About 7500 are highly sensitized with panel-reactive antibody (PRA) in excess of 80%. There is a 35% chance that any two individuals will be ABO-incompatible (ABOi) with a potential live donor. Up to a third of potential live donors are lost due to ABO incompatibility.

There are two principle strategies to overcome HLA and ABO blood group incompatibilities. The incompatibility can either be avoided through kidney-paired donation (KPD) or confronted directly with desensitization protocols [4]. In KPD, a recipient who has a willing but incompatible live donor exchanges kidneys with another incompatible pair so that both recipients receive compatible organs from strangers. Successful desensitization protocols using high-dose intravenous immunoglobulin (IVIg) or plasmapheresis (or immunoadsorption) and low-dose IVIg have shown good early results for crossing both HLA and ABO barriers [5–7]. Many broadly sensitized patients with high donor reactivity will not benefit from either KPD or desensitization. These patients will require a hybrid strategy that involves using KPD to select a donor HLA genotype that would allow successful desensitization [8,9••].

Desensitization

There are two principal protocols for desensitization: high-dose IVIg and plasmapheresis and low-dose IVIg. Anti-CD20 has been used in both protocols to increase the efficacy of antibody depletion and immunomodulation. High-dose IVIg protocols involve monthly infusions of 2 gm/kg of IVIg until transplantation and not to exceed

a total of four doses. The multicenter prospective trial comparing IVIg to placebo demonstrated a significant reduction in PRA and a higher transplant rate (39 versus 17%) in the IVIg arm [10]. A study by Vo *et al.* [11] using monthly IVIg doses and anti-CD20 achieved an 80% transplant rate among 20 patients with good short-term outcomes.

Plasmapheresis is a reliable method of reducing HLA and ABO antibody strength [12]. The antibody reduction is not durable until the transplant is performed. For this reason current protocols have only been used to deplete antibody in preparation of live donor renal transplants when the date of the transplant is known. On the basis of the starting antibody strength, the number of treatments required to reduce the antibody to a well tolerated level for transplantation can be reliably estimated [13]. The end point for pretransplant plasmapheresis is usually to achieve an antibody strength that is at or below a positive flow cross-match. After each plasmapheresis treatment, 100 mg/kg of IVIg is administered. When the risk of antibody rebound is high (e.g. high starting titers or repeat mismatches with previous transplants) a single dose of anti-CD20 (375 mg/m^2) is given the night before transplantation. A study comparing one pretransplant dose of 2 gm/kg of IVIg and plasmapheresis/low-dose IVIg found that plasmapheresis was more effective in abrogating a positive cross-match especially when the strength of the cross-match was higher [14]. In general, the success of the transplant has been shown to be inversely proportional to the original strength of the donor-specific antibody. For this reason, we rarely attempt desensitization unless the strength is 8 or less on an anti-human globulin (AHG) complement-dependent lymphocytotoxic (CDC) cytotoxic cross-match. This criterion is rarely required now because of the high likelihood of locating a more compatible donor [lower-strength donor-specific antibody (DSA)] through KPD and combining KPD with desensitization.

Kidney-paired donation

Although KPD is the most rapidly growing segment of live donation in the USA, it has only realized a fraction of its promise. It has been estimated that a United States national KPD program utilizing two-way exchanges and an optimized algorithm could result in an additional 1500 live donor transplants each year [15]. Domino-paired donation (DPD) is another form of KPD in which a chain of compatible transplants is initiated by a nondirected donor [16]. All the transplants in the chain are performed simultaneously to prevent the chain from being broken. A DPD is terminated by a donation to the deceased-donor list. In this way, patients on the deceased-donor list benefit from the nondirected donor's gift. A variation on the DPD is the nonsimultaneous extended altruistic donation (NEAD) chain in which the last donor in the chain becomes a 'bridge donor' rather than donating to the deceased-donor list [17]. The chain is then extended further at a later time again involving incompatible pairs. The advantage of the NEAD is that it can unfold over a longer period of time and can involve only one transplant at a time. This approach enables multicenter participation and reduces logistic challenges when compared with DPD. NEAD chains do stall after a certain number of iterations as hard-to-match donor phenotypes are encountered. A comparison of the potential impact of DPD versus NEAD chains showed that each would be predicted to result in a similar number of transplants [18]. The use of compatible pairs would increase match rates beyond 50% [19].

Key points

- Only about 50% of the patients with incompatible live donors will match in a kidney-paired donation pool.
- For the remaining hard-to-match patients desensitization will be their best hope of receiving a successful transplant.
- A subpopulation of this group will have cross-matches with their donors that are too strong for successful desensitization.
- Patients who are both difficult to desensitize and difficult to match can be placed into a desensitization pool where a better donor for whom they have lower-strength antibody can be sought to facilitate desensitization.
- The future of incompatible transplantation will revolve around a better understanding of the donor/recipient phenotypes most likely to benefit from each transplant modality.

Much of what we know about the donor/recipient phenotypes that benefit from KPD has resulted from mathematical simulations validated by real-world early experience from Dutch and Korean national matching algorithms [20,21]. Match rates for individual phenotypes vary widely but over all about 50% of registrants in a large (>1000 pairs) KPD pool would be expected to match. What is clear from the data is that two large groups have low match rates (<15%); highly sensitized patients (PRA > 80%) and O recipients with A donors [3,15]. In contrast to HLA-incompatible transplants, there does not appear to be a measurable difference in outcome based on initial antibody strength for ABOi desensitization [22,23]. Thus, most O patients with A donors can undergo successful desensitization and transplantation if they do not rapidly find a match in a KPD. HLA-sensitized patients with a high strength of reactivity with their donor are hard to desensitize and have inferior outcomes and are both difficult to desensitize and difficult to match.

Why do so few highly sensitized patients match in kidney-paired donation

Under optimal conditions less than 15% of highly sensitized patients are predicted to find a compatible pair in a KPD match run. Why is this rate so low? First, KPD pools have an excess of O recipients because over 30% of the pool is made up of ABOi pairs in which the donor is a blood type A and the recipient is blood type O. These O recipients need O donors but for the same reasons KPD pools are deplete in O donors and have an excess of A donors. This blood type skewing significantly decreases the overall match rate [24]. Adding nondirected donors or compatible pairs to KPD pools brings normative blood types into the pool and relieves the blood type skewing [19]. This strategy can increase match rates from 50 to greater than 70%. Although the overall match rate increases, the impact is greatest on ABOi pairs and only modest for highly sensitized patients.

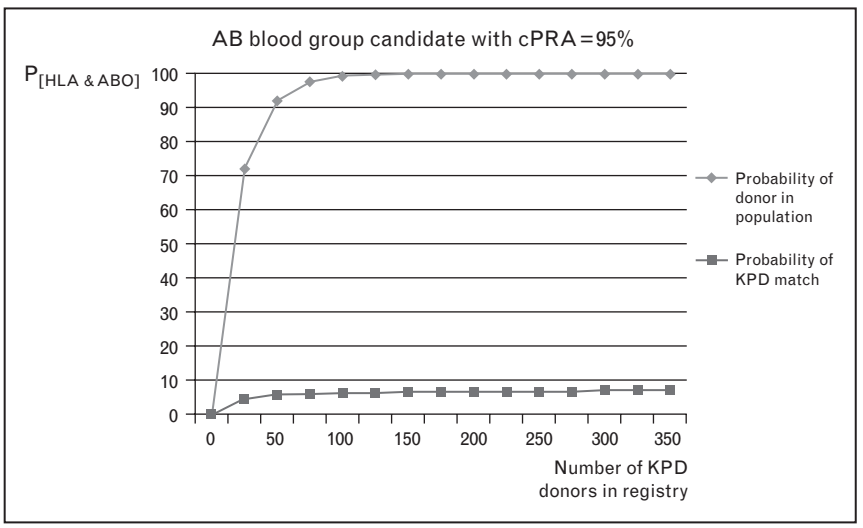
Figure 1 provides an explanation for why highly sensitized patients are the least likely group to benefit from KPD. If one searches the genotypes of the general population for a compatible donor for a patient with a cPRA of 95% the task can be accomplished by screening about 100 individuals. If the same recipient is enrolled in a KPD pool with 100 pairs there is about a 5% chance that a compatible donor will be found. High PRA patients are sensitized to common antigens. These HLA molecules have many shared epitopes with less common antigens. A highly sensitized recipient is searching for an unlikely, uncommon genotype. The low match rates result to a large extent from competition between recipients sensitized to the same common HLA molecules for the rare genotypes.

Selecting the best option for individual donor/recipient pairs

In the clinic transplant providers will be faced with many different immunologic and blood group phenotypes. Deciding which modality will give the recipient the best outcome with the least amount of therapy and expense becomes the challenge. The answers to the following two questions will help guide therapy: How difficult will they be to match in a KPD? How difficult will they be to desensitize? The answer to the first question is drawn from extensive simulation data about who matches in a KPD. The answer to the second question is emerging from the clinical experience of several transplant centers that have performed large numbers of desensitization procedures.

Not all donor/recipient phenotypes benefit from KPD. Examples of phenotypes that do benefit include non-O recipients, recipients with O donors, and those with a narrow breadth of sensitization. Unsensitized patients with A/B and B/A donor/recipient blood groups match at a 70% rate versus about 15% of O recipients with A donors. Sensitized patients with a PRA less than 80% and an O donor have a match rate around 50%. Phenotypes

Figure 1 Competition between highly sensitized kidney-paired donation candidates in established registries lowers the actual match rate with an HLA-compatible donor



Likelihoods for identifying an HLA-compatible kidney-paired donation (KPD) donor for an AB blood group candidate with a cPRA of 95% was determined in registries of different sizes using the formula $P_{(ABO\ \&\ HLA)} = 1 - (cPRA)^n$, where n equals the number of available KPD donors. The likelihood of the same candidate actually matching with an HLA-compatible KPD donor was determined using the formula $P_{(ABO\ \&\ HLA)}(1/N)$, where $N = 16$ and represents the number of KPD candidates predicted to have similar unacceptable antigens.

with poor match rates include recipients who have AB donors or broad sensitization (high PRAs).

Recipients who start with high strength of antibody reactivity with their donor are more difficult to desensitize and have inferior outcomes. We generally consider a patient with a titer of at least 8 on an AHG CDC cross-match to be a marginal candidate for desensitization. Thus there will be a substantial group of highly sensitized patients who are both difficult to desensitize and difficult to match in a traditional KPD.

Combining desensitization with kidney-paired donation

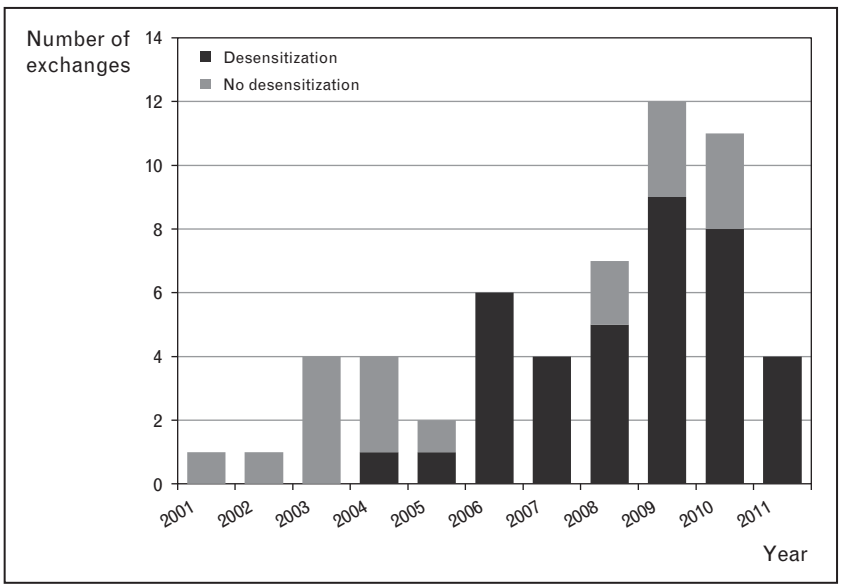
The most dramatic increase in match rates for highly sensitized patients is achieved by relaxing the requirement for a completely compatible donor. Allowing the presence of low-strength donor-specific antibodies by eliminating the corresponding epitopes from the list of unacceptable antigens is the key to getting high PRA patients transplanted. The database is then searched for genotypes that include HLA molecules with low-strength antibodies. The clinician can decide what threshold to use in determining an acceptable strength of reactivity. It might be at a positive flow cytometric cross-match level or even below. The patient can then receive minimal desensitization or be monitored for antibody rebound. Our laboratory eliminates from the list of unacceptable antigens any antibodies with antibody strength at the level of a low titer (<2) AHG CDC cytotoxic cross-match.

The best immunologic donor for a highly sensitized recipient is rarely their original donor. By eliminating low-strength antibodies for the list of unacceptable antigens a better matched but not completely compatible donor can usually be found. The patient is then desensitized against the exchange donor with a minimal amount of desensitization and a higher probability of success. At Johns Hopkins the majority of KPDs are now performed with desensitization (Fig. 2). This approach has both increased our transplantation and success rate for highly sensitized patients.

Conclusion

Kidney-paired donation remains the most economically and immunologically sound modality for transplanting patients with willing but incompatible live donors. However, highly sensitized patients have match rates in KPD pools which are below 15%. This rate can be improved but not overcome by mathematical matching optimization, expanding the size of the pool, including nondirected donors, allowing multiway KPDs or chains (DPD or NEAD), and encouraging the participation of compatible pairs. The low match rate of highly sensitized patients is due to blood type skewing and competition for the same rare HLA genotypes in KPD pools. Desensitization is another alternative that can enable transplantation of

Figure 2 Growth in the Johns Hopkins program of the use of a hybrid modality combining kidney-paired donation and desensitization



This strategy involves permitting the presence of low-level donor-specific antibody in kidney-paired donation (KPD)-matching algorithms. In other words, unacceptable antigens are eliminated if the strength of antibody reactivity is low. Recipients are then desensitized against matched donors with fewer plasmapheresis treatments and better results. Because the Hopkins KPD pool has matured and is enriched with hard-to-match pairs, this strategy is essential to increasing transplant rates.

hard-to-match highly sensitized patients. Unfortunately, many patients have a high strength of reactivity to their donor and are not good candidates for desensitization using current protocols. For patients who are both hard to match and difficult to desensitize, a hybrid modality can be offered in which the donor/recipient pairs are placed in a KPD with the goal of finding a better immunologic match rather than a completely compatible pairing. The recipient can then be desensitized against their KPD-matched donor with fewer treatments and lower risk.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 451–452).

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