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HLA Matching and Sensitization in Kidney Transplantation

"Do they deserve consideration in regional kidney allocation?"

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A paper prepared for the
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Introduction

The fact that an organ from an identical twin can be transplanted in the absence of immunosuppressive therapy supports a role for matching tissue antigens between donor and recipient. While a number of tissue antigens have been implicated, mismatched donor HLA molecules have long been recognized as the dominant target of the recipient's immune response post-transplant. Early efforts to dissect out the relative impact of matching for various HLA loci in promoting allograft survival were hampered by the availability of serologic typing reagents that not infrequently gave false assignments making definitive conclusions difficult. Nonetheless, these studies demonstrated a benefit to HLA matching such that by 1987 the US created a national kidney allocation program based on a point system that prioritized the sharing of HLA matched organs.

In recent years the growing shortage of donor organs coupled with improvements in immunosuppressive therapy and recognition of the effect of prolonged cold ischemic time on graft survival, has led to a call for re-evaluation of the benefits derived from HLA matching. The first part of this paper will focus on a review of the evidence for or against the continued practice of prioritizing allocation of deceased donor kidneys on the basis of HLA matching.

While the benefits of HLA matching have been recognized over the years, the negative impact of HLA sensitization has also been noted. Indeed, the fact that most programs, up until lately, have considered a positive cross-match a contraindication to transplantation is evidence of the community's limited ability to overcome this barrier. Recognition that sensitized individuals have a more restricted pool of acceptable donors has resulted in kidney allocation protocols assigning additional points to patients who are highly sensitized. In the second part of this paper, the impact of this approach will be reviewed to determine if there is evidence for ongoing support of this practice or whether the practice goes far enough in creating equity of access for this disadvantaged group.

Part I: HLA Matching

Since the inception of the sharing of deceased donor organs on the basis of HLA matching there have been a number of reports detailing the benefits in terms of improved long-term graft survival (Hata, Takemoto, Stegall, Danovitch). At the beginning sharing was limited to HLA A, B, DR identical 6 Ag matches, which resulted in approximately 5% of deceased donor organs being shared. Once this proved beneficial, the criteria were liberalized first to include phenotypically identical then later to zero mismatch (MM) based sharing. Early on it was reported that when allocating 0 MM organs, it was important to allocate 0 MM HLA A or B on the split antigens (e.g., HLA B21 slits into B49 and B50), whereas 0 MM HLA DR could be determined on the basis of the broad DR antigens without negatively impacting graft survival (Hata).

After 10 years of this practice it was reported that shared HLA matched kidneys had superior graft survival as compared to local MM kidneys with an estimated half-life of 12.3 years versus 8.4 years respectively (Hata). This was despite the median cold ischemic time being prolonged with the shared kidneys as compared to the local MM kidneys (25.0 hours versus 21.4 hours) as well as the fact that 25% of shared kidneys were allocated to high risk patients (i.e., sensitized %PRA>80% or retransplants) compared to only 14% when allocated locally to MM patients.

In 2000, it was noted that after 12 years of operation this same pattern of outcomes was observed (Takemoto). Indeed, this paper noted that shared kidneys had better outcomes independent of whether the sharing was based on HLA matching, phenotypic matching or even 0 mismatching between donor and recipient. Moreover, the same observation was made when considering only the most recent six years of UNOS facilitated sharing (i.e., 1994-1999). Interestingly, when they considered the outcomes of kidney pairs they noted that the kidney allocated on the basis of 0MM sharing versus local MM resulted in the shared kidney having a significantly prolonged half-life (17.8 versus 11.3 years). However, it was also noted that the benefit of 0 MM sharing was lost when the cold ischemic time was >36 hours (9.7 years versus 8.6 years).

In a separate report in 2002, these earlier findings where again substantiated (Stegall). This latter report went on to determine whether there was a negative impact to sharing in terms of worse outcome with the payback kidneys as compared to local MM of the paired kidney. While a trend was noted with a poorer 3 year graft survival of payback versus local MM paired kidney, it was not significant. Moreover, this trend was lost once cold ischemic time was accounted for; leading the authors to conclude that there was no decrease in graft survival as a result of voluntary sharing or on the basis of payback. Finally, the authors noted that sharing on the basis of 0 MM led to more highly sensitized patients being transplanted as compared to local MM allocation (7% versus 2%). However, it should be noted that still the majority of 0 MM kidneys are allocated to non-sensitized patients. It has recently been observed that when comparing two Eras of time (1978-1984 versus 1995 - 2000) that the difference in expected graft survival between a 0/6 MM graft and a 6/6 MM graft remained constant at 18% (Danovitch).

As a result of these improved outcomes, 0 MM kidneys continue to have mandated national sharing in the US. Indeed, 36% of all deceased donor kidneys are being shared in the US; 15.6% as mandatory 0 MM and 20.4% as payback or other sharing (Stegall). In comparison, only 2-3% of all deceased donor kidneys were shared prior to the inception of a national program in 1987.

In a study of the UK database, the observed benefits of 0 MM kidney sharing were similar to those observed in the US (Morris). When the UK study looked for benefits beyond 0 MM organs they found that a single mismatch at either the HLA A or HLA B loci was associated with improved short-term outcomes (i.e., 0-3 months post-transplant). However, they did not observe any benefit beyond this early period for even this limited degree of mismatch. These findings corroborate an earlier study of the UK database, which also only reported a benefit to this limited degree of mismatching (Gilks). This is in contrast to smaller single centre studies where it has been reported that even 0 MM HLA DR kidneys have a superior outcome if the cold ischemic time was <26 hours (Connolly). While old studies, two groups reported an independent effect, in terms of short term graft survival, for HLA –B and –DR matching (D'Apice, Opelz). Most notable, both of these groups reported that 0 MM HLA B, DR transplants faired significantly better. More recently, at the 2005 US Kidney Allocation Review Subcommittee hearings, Alan Leichtman reported, on behalf of the SRTR, that DR mismatching was the only HLA locus that affected outcomes in the absence of a 0MM.

While it is clear that HLA matching is of benefit in specific circumstances the down-side of matching is that patients with rare HLA phenotypes or those who do not share the ethnic origin of the majority of the donor pool will be disadvantaged. Indeed, in the US ethnic minorities – African American in particular – do not receive deceased donor kidneys in proportion to their representation on the waitlist. This has led to a call in a reduction in points for HLA matching in the UNOS/OPTN local kidney allocation system. Indeed, apart from 0 MM kidney, this resulted in only

0 and 1 MM for HLA DR continuing to receive points (2 and 1 respectively) in the modified 2003 kidney allocation scheme.

Feasibility of HLA Matching at the Regional Level in Canada

A series of studies in the UK and US have examined the effects of recipient pool size on being able to achieve the desired level of HLA matching (Gilks, Cicciarelli, Mickey). Consistent across all studies is the fact that a recipient pool size (within a given blood group) must be approaching 1000 before even 10% of the recipients can achieve 0 MM for HLA A, B, DR antigens. This recipient pool size will require the entire recipient pool of Canada to be listed together. Even in Ontario, the largest province which shares its deceased donor organs currently, could only expect at most 8% of Blood Group O recipients to receive a 0 MM kidney. Outside of Ontario, most regional programs in Canada would have a recipient pool of 50 to 150, and they could at best expect 2 to 3% of recipients to receive a 0 MM kidney. Therefore, while most regional programs may invoke mandatory allocation for 0 MM kidney only a minority of patients will receive such a kidney.

Allocation may also be mandated for 1A/1B + 0DR or 0 BDR MM kidneys but here again the frequency of events will be limited by the small recipient pool size – occurring in 2 to 3% of deceased donor transplants. However, unlike 0 MM kidney transplants, which have proven long term benefits, these lesser degrees of matched kidneys have only proven short-term benefits. Therefore, other competing factors are likely to trump or come into play when weighing the relative merits of potential recipients for a given deceased donor kidney, rather than mandating that these organs be allocated on the basis of HLA matching alone.

What is clear is that 0 DR matching has a benefit in terms of outcomes and it is something that can be achieved with regular frequency even within a small recipient pool size. Indeed, based on broad DR antigens it has been modeled that up to 60% of recipients could receive a 0 DR MM kidney with a recipient pool size of 100 (*). While one would not expect the same impact as a 0 MM kidney, it would be reasonable to assign some priority for a 0 DR MM recipient that would be weighted against other competing factors. Indeed, given that the current trends in immunosuppression are heading in the direction of drug avoidance or minimization, a foundation of at least 1 or 0 DR MM may facilitate such an approach.

Part II: HLA Sensitization

The impact of HLA sensitization has been discussed previously as part of the CCDT sponsored "Assessment of Immunologic Risk in Transplantation: A Consensus Forum" (www.ccdt.ca). In a recent cross-Canada survey of HLA labs, on average 16% of patients on the waitlist are highly sensitized (i.e., %PRA ≥80%) and yet these patients receive only 0.8% of all deceased donor kidneys. Clearly, this is a disadvantaged group. In recognition of this fact, a CCDT Task Force developed a discussion document outlining the development of a Canadian Highly Sensitized Patient Registry. Subsequently, stakeholders were consulted by the CCDT and there was general endorsement of a Highly Sensitized Registry across Canada based on documented success of such programs in other jurisdictions at increasing transplantation in this disadvantaged group. With the establishment of such a registry, highly sensitized patients (i.e., %PRA ≥80%) will have first priority for an acceptably mismatched deceased donor kidney from across Canada. This will start to address the equity of

allocation that is currently denied to this subgroup of patients who reside on all the waitlists in Canada.

Distribution of deceased donor kidney transplants based on the degree of sensitization at the time of transplant (CORR 1998 to 2002)

	1998	1999	2000	2001	2002
PRA 0-19%	678	538	675	672	617
PRA 20-79%	32	23	35	28	24
PRA 80%	5	5	8	4	6

**Excludes cases where PRA is missing.*

What remains to be determined is whether patients with lesser degrees of sensitization should receive any priority. It is estimated that 10-13% of waitlisted patients have %PRA of 20 to 79% yet this group receive only 4.2% of all deceased donor kidneys in Canada (see table). While not as disadvantaged as those patients with %PRA ≥80%, these patients still have restricted access to deceased donor organs. Therefore it would seem reasonable that they would have some degree of priority assigned perhaps in proportion to their degree of sensitization.

Summary

HLA is the principal target of de novo and memory immune responses by the host – both of which will shorten graft survival. It therefore seems logical to attempt to minimize the size of this target via HLA matching of the donor and recipient. However, given the limited recipient pool size in any given region, optimal HLA matching is unlikely to play a dominant role in the allocation of deceased donor organs. Rather, a minimal level of HLA matching is more feasible and the priority it is assigned will have to be determined in relation to other competing factors. Nonetheless, it may be to the patient's advantage to achieve this minimal level in order to potentially minimize the total immunosuppression required over the lifetime of the graft. The caveat is to ensure that groups of individuals (i.e., ethnic minorities) are not disadvantaged specifically because of a major priority being given to HLA matching.

At the other end of the spectrum there is the cohort of sensitized patients on the waitlist who are at present significantly disadvantaged in terms of equity of access to deceased donor kidneys. This group clearly needs some priority to be given for their degree of sensitization if justice is to prevail.

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