Approaches for transplanting the sensitized patient: biology versus pharmacology

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Introduction

In 1969, Patel and Terasaki [1] reported that a positive cytotoxic crossmatch between donor lymphocytes and recipient serum was associated with early or immediate graft loss. From this seminal finding it quickly became apparent that the clinically relevant antibodies in a positive lymphocyte crossmatch were those directed against antigens encoded by the human major histocompatibility complex (MHC). These observations helped establish the human MHC as a major factor in allograft rejection. More importantly, this paper and those that followed helped solidify the belief that a positive lymphocyte crossmatch was a contraindication to renal transplantation. As a result, the field of clinical histocompatibility testing was established, driven by the need to identify the MHC proteins (called human leukocyte antigens, HLA) to which many patients possessed antibodies.

It was quickly established that there were two categories of patients awaiting renal transplantation, namely those who are ‘sensitized’ (patients with HLA antibodies) and those who are ‘unsensitized’ (patients devoid of HLA antibodies). Over the next 35 years, physicians practiced with the understanding that a positive crossmatch was a harbinger of poor transplant outcome, and many programs chose not to transplant across a positive lymphocyte crossmatch. The fallout of such decisions was that the ‘sensitized’ patient waited significantly longer for a transplant than the ‘unsensitized’ patient. Currently, in the USA, even though sensitized patients (panel reactive antibody, PRA >10%) comprise a little more than one-third of the deceased donor (DD) waitlist, they only receive ∼19% of DD transplants [2]. As a result of their prolonged time on dialysis, once transplanted, the ‘sensitized’ patient may have shorter graft survival than their ‘unsensitized’ counterparts. Since the majority of transplant candidates do not have a compatible living donor, two approaches (biological and pharmacological) have been implemented to provide these patients with better access to transplantation (Figure 1). Biological approaches, such as the ‘Emory Algorithm’ [3] or ‘HLA Matchmaker’ [4], attempt to identify donor–recipient pairs who will be HLA compatible, while pharmacological approaches focus on eliminating/reducing/managing HLA antibody levels via plasmapheresis and medication. This editorial addresses the pros and cons of these two approaches.

Biological approach

Historically, the detection of HLA antibody was performed using a complement-dependent cytotoxicity (CDC) assay and panels of donor cells, i.e. PRA. This assessment determined the approximate likelihood that a given patient would have a positive (or negative) crossmatch with a random donor from a local pool of potential donors. This assay, although considered the ‘Gold Standard’ for many years, is quickly giving way to the newer, solid-phase testing methods such as those involving ELISA and microparticles [5–9]. Microparticle assays can be performed on two different platforms: standard flow cytometry and the newer Luminex® technology. This latter technology is a multiplex approach permitting simultaneous analysis of up to 100 analytes. For HLA antibody testing, this translates into the ability to test for antibodies against 100 different HLA antigens or alleles. Applying these new technologies, a more complete HLA antibody profile for a sensitized patient can be ascertained including identification of antibodies against HLA—Cw, DR, DQ and DP antigens. By comparison, it was nearly impossible to detect individual antibody specificities in patients with high antibody levels using CDC assays. For large transplant centers with many highly sensitized patients, CDC methods were not an efficient strategy for organ allocation since crossmatch prediction was quite poor. In contrast, more complete HLA antibody identification via solid-phase methods is permitting crossmatch prediction with far greater accuracy, which, in turn, increases organ allocation to sensitized patients [3,4,10–15]. ‘HLA Matchmaker’ [4,13–15] and the ‘Emory Algorithm’ [3] both take advantage of the additional information obtained from solid phase methods.

‘HLA Matchmaker’ evaluates the degree of epitope matching between a given donor and recipient to predict cross-match compatibility while the ‘Emory Algorithm’ uses...
information from detailed antibody analysis to select candidates with the highest probability of a negative crossmatch with a specific donor. While both approaches have been successful in increasing allocation to the sensitized patient, there are some key differences. The system employed in the United States tends to ‘push’ incompatible patients away from transplantation while ‘HLA Matchmaker’ tends to ‘pull’ acceptable/compatible matched patients to a transplant. The use of such a ‘pull’ system is best illustrated by the ‘Acceptable Mismatch Program’ within the Eurotransplant–Kidney Allocation System (ET-KAS) [15]. Utilizing the ‘Acceptable Mismatch Approach’, ET-KAS has significantly increased allocation to highly sensitized patients, reduced wait times and increased graft survival within this challenging group of patients. One important aspect of the ‘biological’ approach is that acceptable long-term graft survival can be attained without modifications or additions to standard immunosuppression. Several published studies in renal and cardiac transplantation have shown that appropriate selection of compatible donors for highly sensitized recipients results in survival statistics comparable to those of unsensitized patients [3,10–14]. If there is a drawback to the ‘biological’ approach it is that it is driven by HLA compatibility. Predicted compatibility between donor and recipient is a function of the antibody specificities possessed by a recipient and the frequency of HLA antigens distributed in his or her local donor population. For the highly sensitized patient, the wait may still be substantial unless more organs are made accessible via sharing over larger geographical distances. Two recent ‘biological’ approaches gaining in popularity are ‘Paired Donor Exchange’ and ‘Proxy Donation’ [16–18]. With the former approach, a cohort of potential recipients, each with incompatible donors, forms a pool from which compatible combinations are derived. Altruistic donors can also be added to this pool. In the latter approach, an incompatible donor donates to the deceased donor list and his or her designated recipient becomes the highest ranked candidate for a deceased donor organ (with the exception of a pediatric recipient or a 6 antigen-matched/0 antigen-mismatched recipient). In either situation, the end result is transplantation with a negative lymphocyte crossmatch. While this approach is feasible, it requires significant resources at the local center and, more importantly, a large enough pool of donor–recipient pairs to make finding crossmatch compatible pairs likely. Typically, more than one center must participate. A common theme among all ‘biological’ approaches is the ability to clearly and completely identify HLA antibody specificities in the recipients. Without such antibody identification, it is not possible to accurately predict crossmatch results and, hence, allocate organs.

**Pharmacological approach**

For highly sensitized patients who have a low probability of finding a compatible match, transplantation may still be a viable treatment option. The issue for these patients is how best to deal with the presence of HLA antibodies. Once again, there are two basic approaches: (1) transplant across a positive crossmatch with modified immunosuppression and (2) desensitization. Transplanting across a positive crossmatch is predicated on the presumption that low levels of donor-directed HLA antibodies can be tolerated by the recipient with appropriate immunosuppression. It involves modification to standard immunosuppressive regimes to include such drugs as Thymoglobulin (rabbit) [19,20], antilymphocyte globulin (horse) [19,20], anti-IL-2 receptor antibodies [21], anti-CD52 (Campath-1) [22] and/or rituximab [20,22] or a combination of Thymoglobulin induction followed by post-transplant intravenous immune globulin (IVIG) therapy [23]. For patients with a high PRA% but low titer antibodies, such therapies have been quite successful. However, early antibody-mediated rejection rates are higher and long-term outcomes have not yet been established [23]. In contrast, among patients with high PRA% and high-titer donor-specific HLA antibodies (DSAs), immunosuppression alone is insufficient. Antibody levels must be dealt with prior to transplantation. The practice of ‘desensitization’, that is, the physical removal or reduction of DSA prior to transplantation, has been quite successful. Two basic approaches have been employed: (1) plasmapheresis alone or in combination with low doses of IVIG and (2) high doses of IVIG. For antibodies with intermediate titers, administration of high dose (2 gm/kg) intravenous immunoglobulin (IVIG) has been extremely effective [24,25]. While successful, this approach is not routinely applicable to patients with high titers of antibody. For such patients, protocols to physically remove or reduce antibody titers have been employed. These protocols employ plasmapheresis in combination with low dose (i.e. 100 mg/kg) IVIG [26–31]. One downside to plasmapheresis/IVIG treatment is that it is not always possible to predict how many treatments will be required to reduce the antibody titer. Some reports have indicated that >20 cycles of plasmapheresis/IVIG may be needed to effectively reduce/eliminate HLA antibody. These procedures are extremely expensive and not risk free. Patients can become hypo-coagulable during treatments and require close monitoring during the process. Additionally, some patients cannot physically tolerate these therapies, and certain HLA specificities may be more difficult to remove than others [32]. How much antibody should be removed is debatable and numerous questions still need to be

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**Fig. 1.** Approaches for transplanting the sensitized patient. ALG = anti-lymphocyte globulin; IVIG = intravenous immune globulin; PP = plasmapheresis.
applied. For example, should all DSA be removed (i.e., a negative crossmatch) or is it sufficient to reduce the antibody titer until the crossmatch is weakly positive? Should plasmapheresis/IVIG procedures always be performed immediately after transplantation in these patients? What additional immunosuppression, if any, should be given? How long after the transplant must a patient be monitored for the development or reemergence of DSA? Are HLA antibodies the only antibodies to consider (e.g., MICA and endothelial cell) [33–34]? What is the long-term survival of these patients compared to DSA negative sensitized patients? Lastly, are the costs for such individualized procedures balanced against the overall costs of transplantation for all patients?

Summary

Providing equitable access to transplantation for the highly sensitized patient is a formidable challenge as HLA antibodies represent the single most significant impediment to transplantation among AB0 compatible pairs. As discussed above, there are now many successful approaches for transplanting the sensitized patient. However, it is clear that no single approach will be effective for all patients. Depending on laboratory and clinical factors, each patient will require a customized approach, and transplant programs that have significant numbers of sensitized patients on their waitlist should consider utilizing all approaches (Figure 2). A key element in transplanting the sensitized patient is the complete identification of HLA antibodies (specificity and titer) both pre- and post-transplant [35]. Comprehensive HLA antibody characterization to identify appropriate donors and guide clinical therapies will help the transplant community provide the equity and utility that these disadvantaged patients deserve.

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Cancer in patients on dialysis and after renal transplantation

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Introduction

During the past few years, it has become evident that standardized mortality rates for patients on dialysis and for renal transplant recipients are greatly increased not only due to excess cardiovascular disease and infection but also from malignancy related to malignancies, i.e. solid organ cancers and lymphomas [1]. However, relative risks vary between dialysis and transplant patients and with ongoing efforts to further reduce cardiovascular morbidity, malignancy-related morbidity and mortality are of increasing importance. Due to different clinical implications one may differentiate between

- Malignancy in dialysis patients
- Donor-derived malignancy
- De novo malignancy after renal transplantation

Malignancy in dialysis patients

Almost 10 years ago, a large international registry analysis demonstrated a significant increase in cancer mortality for dialysis patients. Among European patients, the most frequent malignancies were located in the genitourinary and haematopoietic system and 73.9–16.7 deaths per 10 000 patient-years respectively were attributed to these malignancies [1]. As curative treatment allows transplantation after a waiting period to minimize recurrence, it is not surprising that 13% of patients evaluated for a transplant and 10% of patients on waiting list carry the diagnosis of a malignancy [2]. Thus, the increased prevalence of malignancy of the dialysis population persists in patients on the transplant waiting list despite cancer screening [3].

Donor-derived malignancy

Transmission of malignancy with the transplanted organ is an old yet very infrequent and does not substantially contribute to post-transplant cancer incidence [4]. This is illustrated by a review of the UNOS database with 35 503 deceased donors free from malignant melanoma or high-grade CNS tumour. Only nine of these donors transmitted tumours to 12 of 109 749 recipients during a median follow-up period of 30 months [5]. Nevertheless, under certain