Comments for Consideration on the Questions Regarding the Use of Erythropoiesis Stimulating Agents (ESA): The Impact on ESA Use on Renal Transplant Survival

The American Society for Histocompatibility and Immunogenetics
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The American Society for Histocompatibility and Immunogenetics (ASHI) appreciates the opportunity to present information that we believe will be useful to the members of the MEDCAC in their consideration of the impact of the use of ESAs on the outcomes of renal transplants. ASHI is comprised of scientists, transplant physicians, transplant surgeons, and histocompatibility technologists who are actively involved in clinical transplantation. Our members believe the issues being considered by the MEDCAC are extremely relevant to our transplant candidates and recipients. As the practitioners who determine the presence of antibodies to the major histocompatibility (HLA) antigens and who evaluate the level of risk conferred to transplantation by such antibodies, we offer the following comments and data regarding the questions under consideration that deal with PRA, or panel reactive antibody, as a measure of sensitization, the impact of HLA sensitization, and the relationship between transfusion and HLA sensitization.

Definition of Sensitization

Although it has been widely used for over fifty years, PRA is an older measure of sensitization that is highly variable and inconsistent. PRA simply measures the reactivity of patient sera against panels of cells with known HLA, or more recently against purified HLA antigens. The magnitude of PRA varies depending upon panel composition and assay method. Furthermore, PRA is determined either for HLA class I antigens (HLA-A, B,C) or class II HLA-DR,DQ,DP) and consequently, often will not reflect the true extent of a patient's sensitization. The older methods for determining PRA were cell based and were substantially less sensitive than current methods which use solubilized HLA antigens attached to solid phase supports. The definition of PRA for listing candidates on the OPTN renal wait list varied considerably across U.S. transplant centers, particularly when some centers began basing PRA on the more current assays that used HLA antigens instead of cells. This inconsistency was a major reason that led to the OPTN implementation of a calculated PRA (CPRA) on October 1, 2009 (1). CPRA represents the frequency of potential donors who would be incompatible based on the presence of HLA specific antibodies. It is calculated using actual frequencies of HLA antigens from the HLA phenotypes of over 12,000 donors in the OPTN registry. CPRA is a more accurate measure of

the extent of sensitization because it includes both HLA class I and II antigens and it has provided consistency across the U.S. in the definition of sensitization. It is important to note, however, that neither PRA nor CPRA alone are predictive of the transplant outcome for a given patient. Both measures are indicative of the breadth of sensitization on a population level, specifically predicting the proportion of potential donors with whom a given candidate will be incompatible due to HLA sensitization. The identification of the presence of *donor* HLA specific antibody is the best predictor for an adverse impact of sensitization on graft survival (2).

Impact of Sensitization

The problem of sensitization among renal transplant candidates is not small. According to OPTN data on May 4, 2009, 39.5 % of active kidney wait list patients were sensitized with PRAs of 10 or greater (Note: there has been insufficient time since its implementation for cumulative data based on CPRA). Notably, 17.2% of these candidates are considered highly sensitized with PRAs of 80 or greater (3). The consequences of sensitization have been well established and include both reduced access to transplantation and reduced graft survival (reviewed in 2, 4, and 5). Importantly, sensitized patients wait significantly longer for transplantation and consequently incur the associated mortality risk from prolonged hemodialysis, which exceeds 20% per year during the first two years after the initiation of maintenance dialysis (6). Access to transplantation is inversely proportional to the level of sensitization, decreasing as the PRA or CPRA increases. The impact of donor HLA specific antibodies is manifested as an increased incidence of antibody mediated rejection (AMR), which has been demonstrated to be 9-fold higher in patients with donor specific HLA antibodies than in patients without such antibodies (7). The increased rate of AMR is further associated with significantly worse graft survival. In addition to the adverse impact of HLA sensitization on patients and graft survival, sensitization results in increased costs associated with prolonged dialysis and clinical management, as well as the costs for desensitization in order to achieve compatible transplantation (8). For young adults and children, transplantation as treatment for their end stage renal disease is more than likely to involve more than one transplant. Loss of a previous graft results in significant increases in sensitization and the associated national costs of re-transplantation are even further expanded by several millions of dollars (9).

Transfusion and HLA Sensitization

Given the large body of data that sensitization to HLA antigens decreases renal allograft survival and access to transplantation, questions remain as to whether transfusion results in significant increases in HLA sensitization and whether the use of ESAs reduces the incidence of

sensitization. HLA specific antibodies induced by transfusion are recognized as major factors in the serious clinical complications of blood transfusion, as well as impacting transplant outcomes (10). Today, many blood centers provide leukocyte-depleted (leukoreduced) blood which has been shown to reduce HLA alloimmunization. In an effort to assess whether transplant candidates requiring transfusions are being sensitized today, given the use of ESAs and increased use of leukoreduced blood, the rate of sensitization among males who had not been previously transplanted was examined at two centers. Without prior transplantation, the most likely cause of HLA sensitization among male patients is transfusion. Sensitization was detected by sensitive solid phase immunoassays among 257 non-transplanted males on the John Hopkins Comprehensive Transplant Center renal wait list and among 356 males waiting for hematopoietic stem cell transplants (HSCT) at the MD Anderson Medical Center. Results are given in Table 1. Among the non-transplanted renal patients waiting for a deceased donor transplant, detectable sensitization was found in 23.5% of candidates. The rate was substantially higher among non-transplanted patients with known sensitization who were specifically referred to the Johns Hopkins center for transplantation with a living donor following desensitization or paired donation (57.4%). Among the candidates for allogeneic HSCT, the rate of detectable sensitization was 12.1% among non-transplanted males.

Investigators at the Leiden Medical Center recently investigated the impact of a single, non-leukocyte depleted transfusion among 21 non-sensitized recipients and 20 female recipients sensitized through pregnancy. Respective rates of sensitization among these patients were 9.5% and 35% (11). A similar rate of sensitization was observed among non-transplanted females in the MD Anderson cohort (38.4%). The collective data on the higher rates of sensitization among parous females and patients referred for known incompatibility with a live donor indicate that transfusion can expand the breadth and level of HLA antibodies among patients with some prior sensitization. It has been shown among parous women or male patients with some prior HLA sensitization that up to 50% of patients form HLA specific antibodies after receiving UV treated platelets or leukoreduced blood transfusions (12). Another recent study specifically addressed the impact of leukoreduced blood on HLA allo-sensitization among multiply transfused patients with sickle cell disease (13). An overall 34% rate of sensitization was observed with the strongest correlation to blood transfusion occurring among patients with no history of chronic transfusions. The authors concluded that while the incidence of allo-sensitization may have decreased with the use of leukoreduced blood, the potential for HLA sensitization remains, particularly with multiple immunizing events. It should also be noted that even low levels of HLA sensitization may become problematic for patients

who are waiting for transplantation, as it has been clearly shown that non-HLA inflammatory events, such as infection or trauma, can stimulate both an increase in titer and expansion of HLA specificity (14).

There are limited data available to address the second question of whether ESAs reduce the incidence of sensitization and subsequently, the adverse effects of sensitization on transplant outcomes. There are several early reports that indicated that the use of erythropoietin reduced sensitization and might improve transplant outcomes (15-18). In one example of these studies, Vella et al., observed a 34% decrease in the total number of transfusions administered to hemodialysis patients four years after the introduction of recombinant human erythropoietin. Notably, the number of patients sensitized as a consequence of blood transfusion decreased significantly from 63% in the cohort of patients pre-erythopoietin to 28% in the group post-erythropoietin and the overall incidence of sensitization decreased from 50% to 36.5% (18). As previously mentioned, current methods for detection and identification of HLA specific antibodies are far more sensitive than the techniques employed in earlier studies. Therefore, it is difficult to assess whether the combined usage of ESAs and blood center practices aimed at avoiding allosensitization have appreciably changed the impact of blood transfusions. If patient sera from earlier studies were examined with today's methods it is highly likely that much higher rates of sensitization would result. However, it is clear that even with leukoreduced blood, there is potential for HLA sensitization and even very low levels of pre-exisiting HLA specific antibody may evoke subclinical AMR that ultimately contributes to the pathology of chronic rejection(19). Therefore, it seems prudent to avoid sources of potential allosensitization whenever possible and medically advisable.

The members of ASHI hope that these comments will prove useful to the MEDCAC in the consideration of the use of ESAs in patients with chronic kidney disease.

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Table 1. Detectable HLA sensitization among renal transplant and hematotpoietic stem cell transplant candidates who have no previous transplant. Unpublished data from Johns Hopkins Comprehensive Transplant Center (M.S. Leffell) and the MD Anderson Medical Center (M. Fernandez-Vina).

Male Candidates (N)	**Male Candiates with No PreviousTransplant (N)**	**Sensitized N(%)**
Renal		
DD[1] (266)	196	46 (23.5%)
InKTP[2] (319)	61	35 (57.4%)
HSCT[3] (356)	356	43 (12.1%)

[1] Deceased donor transplant candidates
[2] Candidates for incompatible transplant program through desensitization or paired donation.
[3] Hematopoietic stem cell transplant candidates