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Session Title : How to Manage Difficult Situations Associated With Antibody-Mediated Rejection in Kidney Transplantation?

Approaches to Management of Refractory Antibody Titers Despite Desensitization

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Approximately 30% of kidney transplant candidates on the UNOS waitlist are human leukocyte antigen (HLA)– sensitized. HLA sensitization is primarily due to pregnancy, blood transfusions, or prior transplants. Sensitization can also occur by exposure to other human tissues such as corneal transplants, bone or skin grafts and heart valve replacements. When broad sensitization to multiple HLA antigens occurs, this poses a significant challenge to kidney transplant in patients with end-stage kidney disease (ESKD). Here, wait times on the list are extensive and for those with the highest levels of sensitization, there may be no possibility for a reasonable match. In addition to prolonged waiting times, preformed donor-specific antibodies (DSAs) are associated with increased mortality and risk of antibody- mediated rejection (AMR) and graft failure in patients who receive transplants. This is especially true for those who have not undergone some form of desensitization prior to transplant and likely speaks to the powerful role for T-cell and B-cell memory and recall responses after HLA-incompatible transplant (HLAi).

The implementation of Kidney Allocation System (KAS)in the US in 2014 increased priority for sensitized candidates and has led to an increased rate of deceased donor kidney transplantation (DDKT) in sensitized patients. Despite this, transplantation rates remain low in the most highly sensitized (HS) candidates (calculated panel reactive antibody [cPRA]: 99.9%1) owing to unacceptable crossmatches. In addition, transplant outcomes for the most highly-HLA sensitized patients show lower grafts survivals than those for non-sensitized patients. Efforts to address the allocation inequities for this group of immunologically disadvantaged patients have emerged and are generally referred to as desensitization. The benefit of incompatible kidney transplant over remaining on dialysis and awaiting an HLA-compatible kidney transplant are well established. Desensitization, aimed at decreasing preformed DSA titers and achieving an acceptable crossmatch, plays a critical role in enabling HLAi kidney transplant and reducing the risk of acute rejection post-transplant.

Initial desensitization protocols primarily involved two protocols that evolved at Johns Hopkins University and Cedars-Sinai Medical Center in Los Angeles. These included the use of plasma exchange (PLEX) + low dose IVIg =+/- anti-CD20 or high-dose IVIg + anti-CD20. Unfortunately, both regimens had limited ability to improve transplant rates for HLA-sensitized patients, especially those who were broadly sensitized with high-titer antibodies. However, in recent years, there have been many advancements in agents that are more specifically focused on addressing multiple targets involved in the allosensitization response. The first advancement was reported in 2017 showing that a novel IgG endopeptidase (Imlifidase) that cleaves IgG molecules into Fc and F(ab)'2 fragments (thus rendering them unable to activate complement (CDC) or mediate antibody-dependent cell-mediated cytotoxicity [ADCC]), could eliminate all HLA antibodies, regardless of titer, within 4-6 hours of a 30min. infusion. This has subsequently led to approval of imlifidase for desensitization by the European Medicines Agency for use in the European Union. However, problems with antibody rebound and single-use application limits use of imlifidase. The second most important advancement was the use of anti-IL-6 in combination with PLEX and IVIg. Here, anti-IL-6 acts directly on B-cells and plasma cells to limit HLA antibody generation and rebound phenomena. Early studies with

clazkizumab (anti-IL-6) in HLA sensitized patients undergoing desensitization showed very encouraging results in improving transplant rates, reducing DSA rebound and de novo DSA development and inducing regulatory T-cells and B-cells that are important in controlling the allo-immune responses. Newer agents aimed at depleting B-cells and plasma cells are likely to improve rates of transplantation for HLA-sensitized patients. These include anti-CD38 (anti-plasma cell) and antibodies aimed at BCMA (B-cell maturation antigen). There is emerging data from human experience with daratumumab (anti-CD38) which are somewhat encouraging, although CD38 is expressed on several immune cells including regulatory T-cells and B-cells whose depletion could increase rejection rates. This does not seem to be a problem with anti-BCMA agents including REGN 5458 and REGN 5459 which are bispecific antibody (one arm of the antigen binding region aimed at BCMA and the other at CD3+). Here, the idea is to bring CD3+ cells into proximity of BCMA+ plasma cells and kill them. This drug appears effective in early trials in patients with multiple myeloma and clinical trials in kidney transplant desensitization are now underway. Another important strategy being borrowed from cancer immunotherapy that is yet to be applied to human desensitization is the use of CAR-T-cells specific for BCMA. Clinical trials of this novel approach will begin soon in an NIH sponsored study. Finally, novel agents consisting of monoclonal antibodies and antibody fragments that are engineered to bind to the Fc-neonatal receptor (FcRn) and inhibit recycling of IgG have already been approved for use in myasthenia gravis. These agents interfere with the body's natural IgG recycling system that allows IgG molecules to maintain structural integrity for ~24 days. In animal models where the FcRn is knocked out (FcRn-/-), the half-life of IgG goes from 24 days to 2 days. Here, the idea of blocking the FcRn is to rapidly degrade pathogenic alloantibodies that prevent successful transplantation in HLA-sensitized patients. This has yet to be examined in kidney transplantation. Of interest, this is the pathway primarily responsible for the efficacy of IVIg.

In summary, allosensitization remains one of the most vexing and,as yet, unsolved problems of transplant medicine. Although, progress has been slow, we are now in a phase of rapid growth and evaluation of newer agents that hold great promise to eliminate the immunologic barriers posed by alloantibodies to successful transplantation.