# Highly HLA Sensitized Kidney Transplant Patients in a Transplant Center

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ABSTRACT

Introduction. Approximately 10% to 30% of patients on renal transplant waiting lists are sensitized, which gives them more time on the waiting list. Transplantation in this setting has a greater risk of rejection and decreased graft survival. New strategies of donor allocation through virtual crossmatching and optimization of immunosuppressive therapies in induction and maintenance have allowed the allocation of organs for this population, which in other circumstances would not be chosen for a kidney transplant.

Objective. To describe the experience of renal transplantation in highly sensitized patients with a panel reactive antibody of >80% in a transplant center, through virtual crossmatching, discarding unacceptable antigens, and without desensitization treatment.

Methods. An observational, descriptive, retrospective case series study was conducted on highly sensitized kidney transplant patients with a panel reactive antibody of ≥80% from 2010 to 2016.

Results. A total of 10 highly sensitized transplant patients were identified. Six patients were women, all of whom had a history of pregnancy; all patients had undergone blood transfusions, and 40% had undergone a first transplant. Average time spent on dialysis was 148.5 months, and on the waiting list, 45.8 months. Average follow-up was 42 months (range, 10–84 months). The estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration method at year 1 was 75 mL/min/1.73 $m^2$ body surface. Nine patients at 1 year posttransplantation had graft and patient survivals of 100%, as did 5 patients at >3 years posttransplantation.

Conclusions. Renal transplantation based on virtual crossmatching is a good alternative for highly sensitized patients.

KIDNEY transplantation is the preferred treatment for patients with advanced chronic kidney disease [1]. Approximately 30% of patients on transplant waiting lists are sensitized, with a panel reactive antibody (PRA) of ≥20% [2]. Highly sensitized patients, defined as those with a PRA of ≥80%, may represent ≤15% of patients enrolled, conferring an increased risk of graft rejection and decreased survival [1,3]. This, in turn, means they spend more time on waiting lists, even with the possibility of having a living donor [4,5].

Determining the presence of anti-HLA antibodies is clearly one of the most important factors in evaluating immunological risk before transplant. The single antigen bead assay (SAB; Luminex Corporation, Austin, TX) provides precise detection and profiling of donor-specific HLA antibodies (DSA) in sensitized kidney transplant candidates [6].

Many centers, like our hospital, use the Luminex platform to identify antibodies semiquantitatively and report them as the mean fluorescence intensity (MFI). Therefore, a lower level of signal, a lower level of circulating antibodies and a higher value of MFI, a higher antibody titer and a risk of

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graft rejection [7]. The reference value for an acceptable antibody level in our transplant group must be <2000 MFI U before a virtual crossmatch (VXM) can take place.

Antibodies are classified as unacceptable if they have a greater value than that set for the HLA antibody MFI units. And, in such cases, recipients are not selected for these potential donors; consequently, recipients are automatically excluded from the VMX process [8]. This allows the "VXM" to predict the results during organ assignment [9].

A useful strategy that can improve the possibility of organ transplant outcomes in highly sensitized patients is based on the desensitization of waiting list candidates. This strategy makes them available for acceptable matches procured from living and deceased donors while on the waiting list. Desensitization is carried out under protocols that include the use of plasmapheresis, intravenous immunoglobulin, rituximab, and/or bortezomib [10]. However, desensitization is not possible in many settings, because of the unavailability of a living donor, the high costs of therapy, and the reappearance of high titers of DSAs.

An alternative to desensitization is renal transplantation based on a VXM, accepting a donor whose HLA antigens do not present antibodies in the recipient, based on SAB results. In this way, the probability of acute rejection mediated by antibodies is reduced and patient survival is improved.

## METHODS

We performed a retrospective, observational study that included all highly HLA-sensitized patients (PRA ≥80%) who had received a living or deceased donor kidney between January 2010 and December 2016. All patients were ≥18 years of age, had undergone transplantation with a negative VXM, and had negative complement-dependent cytotoxicity test results for T and negative B lymphocytes. The maximum limit for antibodies to donor antigens was set at 2000 MFI U (unacceptable antigens). All patients were ABO compatible.

## RESULTS

Within the study population of 158 patients, 10 highly sensitized transplant patients with a PRA of >80% were identified. Six of the 10 patients were women, the average patient age at the time of kidney transplantation was 49 years (range, 27–56 years), time spent on dialysis averaged 148.5 months (range, 32–250 months), and on the waiting list, 45.8 months (range, 9–72 months).

Among the factors of sensitization, it was found that all the women in the study had previous pregnancies; 4 had undergone a previous renal transplant and all patients had been transfused before transplantation. The average HLA mismatch (MM) was 1.9; 3 patients had 0 MM. Eight patients had 0 MM in HLA DR. Based on the availability of the study, only the last 5 transplanted patients took into account the absence of antibodies against HLA DQ.

All patients underwent induction treatment with thymoglobulin and continued maintenance therapy with tacrolimus, mycophenolate mofetil, and an oral steroid. The goal set for tacrolimus levels was from 6 to 8 ng/mL.

The average follow-up was 42 months (range, 10–84 months). Nine patients were analyzed 1 year posttransplantation, at which time both renal allograft and patient survival were 100%. Likewise, 5 of the 10 patients were 3 years posttransplant and had 100% graft and patient survival.

Two of the 10 patients developed biopsy-proven acute rejection at 5 and 9 months after transplantation. Both patients responded favorably to treatment with methylprednisolone. To date, no antibody-mediated rejection episodes have been reported.

Three patients had a polyomavirus infection diagnosed by positive viral load. Only 1 of the 3 patients had positive findings for polyomavirus in renal biopsy. Two of the 3 patients had previously received treatment for acute cellular rejection and all had a PRA of >90%. One patient had cytomegalovirus infection, which was treated with valganciclovir until 2 negative viral loads were present, and no other opportunistic infections were present.

The average proteinuria at 1 year posttransplant was at 99 mg in 24 hours. Two patients experienced delayed graft function, with recovery of renal function. The mean serum creatinine at 1 year posttransplant was 1.37 mg/dL, the estimated glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration method at the end of the first year was 75 mL/min/1.73 $m^2$. Three patients had an estimated glomerular filtration rate of <60 mL/min/1.73 $m^2$, two of whom had a PRA of 100%, longer cold ischemia times compared with the rest of the patients, and had undergone treatment for acute graft rejection, polyoma virus–induced nephropathy, or both (Table 1).

One patient received a graft from an extended criteria cadaveric donor. This was considered because he had 100% PRA, >5 years on waiting list, and a MM of 0, including DQ. At posttransplant month 5, he presented with a viral load for positive polyomavirus and renal biopsy with SV40 positive staining, which made a diagnosis of polyomavirus nephropathy. Treatment consisted of decreasing the dose of mycophenolate mofetil and tacrolimus. At 9 months after transplantation, an acute rejection episode was managed with steroids. At 12 months, he had a negative viral load for polyomavirus. Currently, it continues with negative viral load and decreased renal function (17 mL/min/1.73 $m^2$).

One patient received an allograft from a living donor with 1 MM and without donor-specific anti-HLA. At month 10 posttransplant, the patient has a serum creatinine level of 0.97 mg/dL.

The first transplanted patient in the series was in 2010; at that time, no tests were available for detection of specific antibodies against the donor (SAB). In 2012, this test became available to us. Six of the 10 patients underwent SAB testing and were transplanted, taking into account that they did not have specific anti-HLA antibodies against the assigned donor. The first 4 patients in the series were transplanted taking into account complement-mediated