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

Table 1. Characteristics of Highly Sensitized Kidney Transplant Recipients

No.	Age (y)	Sex	MM	Pregnancy	Previous Transplant	PRA (%)	Time on Dialysis (mo)	Time on Waiting List (mo)	DGF	Cold Ischemia Time (h)	ACR	CKD-EPI (mL/min) at 1 Year
1	38	F	1	Yes	Yes	92	250	48	0	10	No	123
2	47	M	4	N/A	No	87	129	9	0	11	No	100
3	50	M	2	N/A	Yes	83	73	47	0	16	No	70
4	40	F	0	Yes	No	100	206	38	1	18	No	92
5	54	F	4	Yes	No	100	210	53	0	16.5	No	80
6	53	F	0	Yes	No	100	78	65	1	16	Yes	10
7	27	M	0	N/A	Yes	94	190	50	0	14	Yes	45
8	58	M	3	N/A	Yes	93	32	22	0	6	No	46
9	56	F	4	Yes	No	93	168	72	0	15	No	95
10	48	F	1	Yes	No	84	54	54	0	2	No	69

Abbreviations: ACR, acute cellular rejection; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DGF, delayed graft function; MM, mismatch; N/A, does not apply; PRA, panel reactive antibody.

cytotoxicity test. There was no cross-test available for flow cytometry. In Colombia, organ allocation does not take into account acceptable antigens for highly sensitized patients, as in European countries.

DISCUSSION

Approximately 15% of patients on awaiting transplantation are highly sensitized (PRA ≥80%) and have a higher risk of graft rejection, and decreased survival [3]. Given that there is little experience with this type of patient in Colombia, this study describes the characteristics and outcomes of highly sensitized transplant recipients based on the lack of antibodies against donor HLA antigens and negative complement-dependent cytotoxicity.

Previous experience with organ allocation strategies based on VXM has been successful with good results in graft survival and an increase in the allocation of kidneys (living and cadaveric donor), for highly sensitized patients, who in another scenario would remain in waiting list [11]. The present study describes the results from our experience with this patient population that includes highly and very highly sensitized patients: PRA ≥80% (n = 6) and PRA ≥94% (n = 4), respectively.

The availability of organs for highly sensitized patients is particularly difficult [12]. In the United States in 2011, United Network for Organ Sharing reported 7908 highly sensitized patients awaiting transplantation, defined as those with a PRA of >80% [13]. HLA antibodies can be formed owing to immunization by blood transfusion, pregnancy, or previous transplants [2].

A viable option for sensitized and highly sensitized patients is living donor kidney transplantation, which includes prior desensitization using treatment schemes that include plasma exchange, intravenous immunoglobulin, rituximab, and/or bortezomib, administered under individual, combined, or sequential protocols [14]. Other options include the use of paired kidney exchange or the combination of these two strategies [15]. However, these patients do not always have a living donor, so they depend on a cadaveric donor kidney transplant. In addition, waiting lists continue to increase with a reduced possibility for sensitized patients, who represent 1 in 3 patients awaiting transplantation. Currently on our waiting list, 20% of patients are highly sensitized (PRA ≥80%), a figure even higher than that reported in published series [3,13,16].

A study conducted by Vo et al. [17] between 2005 and 2007 included 20 sensitized patients with a PRA of 77% ± 19% who received intravenous immunoglobulin and rituximab. The percentage of PRA, dialysis time, crossmatch compatibility, race, comorbidities, graft and patient survival, rejection complications, creatinine levels, adverse events, and immunologic factors were considered. In this registry, 80% of the study population (n = 16) underwent transplantation, of which 62% (n = 10) were transplanted with living donors and 38% (n = 6) with cadaveric donors. The PRA level after the second intravenous immunoglobulin infusion was 44% ± 30%, the mean dialysis time was 144 ± 89 months, the transplant waiting time after desensitization was 5 ± 6 months, creatinine at 12 months posttransplant was 1.5 ± 1.0 mg/dL, and the survival rate for the graft and the patient was 94% and 100% respectively [17]. During the observation period of the present study, 10 patients were transplanted, representing 6.3% of the total population transplanted in our center during the period between 2010 and 2016. The first 4 patients were transplanted without taking into account the SAB, because the test was not available at that time, but the PRA was analyzed by making an approximation to detect antibodies with the donor HLA. Graft and the patient survivals at 1 and 3 years, using VXM, was 100%.

In the 1980s, Claas et al. [18] created a strategy to increase the opportunity for access to transplantation to highly sensitized patients, called the Eurotransplant Acceptable Mismatch program, who before that, could take >10 years in the waiting list. Therefore, an alternative initially consisted in the identification of HLA-A and HLA-B antigens for which the patient had never formed

antibodies, and was called acceptable antigens as a parameter for kidney assignment [19]. In the 25 years experience of the program in Europe, with the implementation of the acceptable antigen, >1000 highly sensitized patients have undergone transplantation, representing ≥3% of cadaveric donor transplant recipients in Europe [19].

The average waiting time in our study was 45.8 months. In Europe, with the Eurotransplant program of acceptable antigens, approximately 60% of highly sensitized patients are transplanted within 2 years of enrollment, but represent only 2% of those awaiting transplantation [18].

In a study by Johnson et al. [20], patients waited an average of 32 months and highlighted the importance of virtual XM for kidney allocation in patients with a PRA of >80% at their transplant center. The greater duration on dialysis results in an annual mortality rate of 16.1 per 100 patient-years [21]. Patients in our study were on dialysis for an average of 148.5 months (12 years) before undergoing transplantation (range, 32–250 weeks); consequently, this has been recognized as a factor that affects patient survival.

VXMs can be used reliably to predict results for complement-dependent cytotoxicity crossmatch and that a large number of transplants can be performed, causing each center to establish criteria for assignment of unacceptable antigens and acceptable crossmatches [3].

In the pair matching program in Australia, VXM is used to assign suitable or permissible HLA donors to sensitized recipients. The matching is based on acceptable MM, and donors are excluded for recipients with a DSA of >2000 MFI. In this program, patients were not desensitized and about 39% of transplant recipients had a PRA of >90%. The results show that transplantation with paired kidneys and VXM are a valid and effective solution for highly sensitized patients [22].

The new organ allocation system in the United States, the Kidney Allocation System, has succeeded in increasing the possibility of transplanting highly sensitized patients, with a system of point assignment between a greater calculated PRA, based on unacceptable HLA antigens [4,23,24].

The options available for these patients include desensitization protocols, which use plasma exchange, intravenous immunoglobulin, rituximab, and/or bortezomib with variable results, and at the expense of increased treatment costs [1,3,10,12–14]. The rates of optimal graft survival are even lower in this group of patients, without completely eliminating the development of antibody-mediated rejection episodes [1,13]. In our center and in our country, we do not routinely perform desensitization given the increased costs, which greatly reduces the opportunity to transplant patients.

In a 17-year follow-up study by Redfield et al [25], the combination of sensitization factors such as pregnancy or blood transfusion increased the risk of allograft loss by ≤23%, and the combination of a previous transplant in a highly sensitized patient increased the risk of allograft loss by ≤58.1%. Our study population was exposed to ≥1 sensitization factor: 100% of our participants had undergone blood transfusion, all 6 women had been pregnant, and 40% had a previous transplant. During the observation period, no patient presented with a loss of graft; however, the follow-up time was short to identify this outcome.

A study by Bielmann et al. [26] suggested that VXM is associated with very low risk of rejection mediated by anti-HLA antibodies owing to the absence of DSA. This finding is in contrast with what has been observed in other studies, where highly sensitized patients undergo a desensitization protocol, and the incidence of antibody-mediated rejection may be ≤50%, as reported in a study conducted in Barcelona [1]. In our study, no patient has had an antibody-mediated rejection episode to date.

In our country, there is no special allocation system for highly sensitized patients, which does not allow a VXM considering acceptable antigens. Currently, once allocation is initiated, if a highly sensitized patient is favored, HLA antibodies are checked for that donor by SAB and a cross test is performed. VXM does not increase costs and favors this group of patients, increasing the likelihood of a transplant with good results in terms of rejection and survival.

In conclusion, highly sensitized patients who underwent renal transplantation showed good renal function and graft and patient survival. Renal transplantation based on VXM is a good alternative for highly sensitized patients.

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