

Desensitization Protocol in Highly Sensitized Renal Transplant Patients

M.^a Luisa Rodríguez Ferrero¹, David Arroyo¹, Nayara Panizo¹, Javier Reque¹, Jose Luis Vicario², Antonio Balas² and Fernando Anaya¹

¹Nephrology Department, General University Hospital Gregorio Marañón, Madrid, Spain; ²Histocompatibility Department, Transfusion Centre of Madrid, Madrid, Spain

Abstract

Our aim was to analyze the effect of desensitization therapy with plasmapheresis and high-dose intravenous immune globulin on antibody levels and the impact on antibody mediated rejection incidence and renal function in the early period after kidney transplantation.

Methods: We conducted a prospective study of seven deceased donor kidney transplants. Immunosuppressive therapy was performed with steroids, mycophenolate mofetil, and prolonged-release tacrolimus. Five patients received induction therapy with anti-human activated-T rabbit lymphocyte immunoglobulin and one received basiliximab. The study of antibodies was performed with the use of Luminex technology pretransplantation, a week after therapy, and three months after transplantation. Desensitization treatment consisted of six sessions of plasmapheresis and infusion of intravenous immune globulin (total dose 2 g/kg) on alternate days. One patient also received a dose of rituximab.

Results: We did not observe a statistically significant decrease in antibody levels after treatment or at three months after transplantation. Two patients developed an episode of Banff grade I acute rejection without C4d deposition in peritubular capillaries, with good response to methylprednisolone. There was no graft loss and renal function remained stable at three months with serum creatinine 2.12 ± 0.99 mg/dl, glomerular filtration rate estimated by Modification of Diet in Renal Disease-4 36.8 ml/min/1.73 m² (IQR 21.1-52.0 and proteinuria 0.00 g/day (IQR: 0.00-0.14).

Conclusions: In our experience, desensitization therapy with plasmapheresis and high-dose intravenous immune globulin reduces the levels of anti-human leukocyte antigen antibodies in the short term posttransplantation, although not significantly. There was no change in levels of anti-major histocompatibility complex class I-related chain A circulating antibodies. Interestingly, no patient at high immunological risk developed antibody mediated rejection during the study period. (Trends in Transplant. 2013;7:80-3)

Corresponding author: M.^a Luisa Rodríguez Ferrero, mlrodriguezf@senefro.org

Correspondence to:

M.^a Luisa Rodríguez Ferrero
Servicio de Nefrología
Hospital General Universitario Gregorio Marañón
Doctor Esquerdo, 46
28007 Madrid, España
E-mail: mlrodriguezf@senefro.org

Key words

Plasmapheresis. Intravenous immune globulin. Rituximab. Highly sensitized patients. Renal transplantation. Donor specific antibodies. Antibodies against MICA antigens.

Background

In kidney transplant recipients, the presence of preexisting¹ or newly formed² circulating anti-human leukocyte antigen (anti-HLA) antibodies, both donor-specific antibodies (DSA) or non-DSA, or antibodies against major histocompatibility complex class I-related chain A (MICA) antigens³, has been associated with reduced allograft survival. Various therapies have led to successful transplantation of highly sensitized patients, resulting in acceptable allograft survival, including plasmapheresis or immunoadsorption, high-dose intravenous immunoglobulin (IVIg), and rituximab⁴⁻⁶. The presence of DSA is associated with all forms of antibody mediated rejection (AMR)⁷ and this is the major cause of late kidney graft failure. Prevention of antibody mediated allograft damage starts avoiding sensitized events⁸.

Our aim was to analyze the effect of a desensitization protocol with plasmapheresis and high-dose IVIg on circulating anti-HLA titers, and the impact on AMR incidence and renal function in the early period after kidney transplantation.

Methods

We carried out a descriptive prospective study of a cohort of seven highly sensitized (with a mean panel-reactive antibody level, determined by use of the complement-dependent cytotoxicity assay, of $33 \pm 10\%$ and with DSA) renal transplant recipients from deceased donors performed between October and November 2011. All of them were

re-transplants. The immunosuppressive therapy consisted of corticosteroids, mycophenolate mofetil, and prolonged-release tacrolimus with monoclonal antibody basiliximab induction in one patient and rabbit anti-human activated-T lymphocyte immunoglobulin in the other five patients.

The study of antibodies against HLA and MICA antigens was performed by complement-dependent cytotoxicity (extended incubation) with a panel of peripheral blood mononuclear cells, and by bead-array single antigen solid supports (Gen-Probe, CA, USA; Luminex, TX, USA) including HLA class I, class II and MICA antigens. Samples were obtained before transplantation, one week after the desensitization therapy, and three months after transplantation.

Desensitization therapy consisted of six plasmapheresis sessions with 5% albumin replacement on alternate days and IVIg infusion after each plasmapheresis session (total dose 2 g/kg). One patient also received a single dose of rituximab.

Statistical analysis

Discrete variables were compared by Fisher exact test, and continuous variables by Mann-Whitney U test.

Values were expressed as percentages and mean values and standard deviations or median values and interquartile (IQR) range. All analyses were performed using SPSS version 15 software. A value of $p < 0.05$ was considered to be statistically significant.

Table 1. Antibodies and renal function evolution during the study period

	Before transplantation	After therapy	p value	At 3 months	p value
Max DSA I*	3,000 (0-12,000)	0 (0-2,400)	0.068	0 (0-6,200)	0.068
Max DSA II*	15,000 (0-19,000)	10,000 (0-18,000)	0.893	15,000 (0-21,000)	0.498
Max non-DSA I*	3,000 (0-17,000)	2,800 (0-5,500)	0.068	3,600 (0-6,800)	0.273
Max non-DSA II*	10,000 (0-19,000)	6,000 (0-15,000)	0.144	13,500 (0-21,000)	0.713
Max MICA*	0 (0-4,750)	0 (0-6,000)	0.317	0 (0-6,000)	0.317
Serum creatinine (mg/dl)		2.14 ± 0.96		2.12 ± 0.99	0.866
Proteinuria (mg/d)*		0 (0-0.13)		0 (0-0.14)	0.655
MDRD-4*		32 (22.8-59.3)		36.80 (21.1-52.0)	0.753

*Data are expressed as medians and interquartile ranges (IQR).

Max: maximum level; DSA: donor-specific antibodies; I: HLA antibodies class I; II: HLA antibodies class II; MICA: antibodies against MICA antigens; MDRD-4: glomerular filtration rate estimated by Modification of Diet in Renal Disease-4 formula.

Results

The study included seven kidney transplant recipients from deceased donors (all re-transplants). Donor mean age was 53.00 ± 19.63 years, and 42.9% (3) were male. Recipient mean age was 51.29 ± 14.06 years, 71.4% (5) male. Mean cold ischemia time was 17.21 ± 4.01 hours. Four patients (66.7%) suffered delayed graft function, with a mean time of 5.25 ± 2.63 days. Univariate analysis showed no significant difference in the decrease of maximum antibody levels or in renal function (based on serum creatinine, proteinuria and glomerular filtration rate [GFR] estimated by the Modification of Diet in Renal Disease MDRD-4 formula), either after desensitization therapy or three months after transplantation (Table 1). One patient developed *de novo* low titers of non-DSA class I circulating anti-HLA after the therapy, and another one developed *de novo* low titers of non-DSA class II circulating anti-HLA three months after transplantation. Only one patient had preexisting antibodies against MICA antigens, and showed no modification after desensitization therapy. Two patients developed an episode of Banff grade I acute rejection without C4d deposition in peritubular capillaries, and were successfully

treated with methylprednisolone. No graft loss was observed. Renal function remained stable at three months, with serum creatinine 2.12 ± 0.99 mg/dl, GFR estimated by MDRD-4 36.8 ml/min/1.73 m² (IQR: 21.1-52.0) and proteinuria 0.00 g/day (IQR: 0.00-0.14).

Discussion

We report seven highly sensitized renal transplant recipients from deceased donors, with high levels of preformed anti-HLA and/or anti-MICA antibodies. All of them were re-transplants. When transplantation is performed in such patients, the incidence of AMR is high, with unacceptable rates of graft loss⁹. There are clinical and laboratory data that suggest that IVIg therapy administered to these patients may reduce allosensitization and acute rejection episodes and result in better long-term outcomes for recipients of cardiac or renal allografts¹⁰. Other investigators have shown that plasmapheresis and administration of IVIg may also improve the success of transplantation in this group. However, rejection rates are high and this approach is effective only in patients awaiting transplants from living donors¹¹. High-dose IVIg has been shown to

be effective as a desensitization agent for patients receiving transplants from either living or deceased donors¹², but it requires monthly infusions over a four-month period for optimal results. In our smaller, nonrandomized study, all seven patients underwent desensitization with plasmapheresis and high-dose IVIg and one of them also received a single dose of rituximab (375 mg/m²). In our experience, this therapy reduces the levels of anti-HLA DSA and non-DSA antibodies in the early posttransplant period, but not significantly. We found no modification of anti-MICA circulating antibodies. We showed no significant difference in renal function either after desensitization therapy or three months after transplantation.

It is remarkable that the occurrence of newly formed low non-DSA antibodies titers did not affect renal function. Its role should be weighed after long-term monitoring. It is also noteworthy that no patient had AMR during the study period despite their high immunological risk, perhaps due to the effect of the desensitization protocol. We believe that a study with a larger population and a longer follow-up might be more conclusive of the benefits of such a desensitization protocol over circulating anti-HLA titers and graft survival.

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