Safety and Efficacy of Immunoadsorption in Heart Transplantation Program

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ABSTRACT

Background. Antibody-mediated rejection (AMR) is a serious complication of organ transplantation, and its treatment is complex. The aim of this study was to assess immunoadsorption (IA) for treatment-immunized patients before heart transplantation (HTX) and as the first step of AMR treatment after HTX.

Methods. The cohort consisted of 10 patients (8 men, 2 women; age range, 20–57 years). For 3 of these patients, IA was included in the desensitization protocol before HTX; for 7 patients, IA was the first step of the treatment protocol. One patient underwent IA before and after HTX.

Results. A comparison of values before IA and after the last procedure showed a decrease in immunoglobulin subgroups (G, M, and A). In patients before HTX, a decline was noted in panel reactive antibodies. After HTX, IA procedures led to a significant decrease in donor-specific antibody (DSA) class I; DSA class II fell in 6 of 7 patients, with 51% falling below the detection limit.

Conclusions. IA in patients during HTX is safe procedure for reducing DSA. The removal of antibodies is the first step in comprehensive treatment and must be followed by a procedure that prevents their further development.

ANTIBODY-MEDIATED rejection (AMR) is a serious complication of organ transplantation. After heart transplantation (HTX), AMR occurs in 10% to 15% of cases and is often accompanied by impaired graft function, which represents a risk factor for coronary disease and deterioration of prognosis [1,2]. There has recently been significant progress in the diagnosis of AMR, which is based on histologic and immunohistochemical examinations of endomyocardial biopsy samples [3]. This diagnosis is supported by the occurrence of donor-specific antibodies (DSA) in the serum of the recipient. This type of rejection is often accompanied by impaired graft function. Treatment of AMR is a complex process, the first step of which is the elimination of antibodies. The classic cleaning method of choice is plasmapheresis, but immunoadsorption (IA) has been used more recently.

The aim of the present study was to assess IA by using staphylococcal protein A. We used this method to treat immunized patients before HTX and as the first step of AMR treatment after HTX.

PATIENTS AND METHODS

A total of 243 HTX procedures were performed at our institute between November 1, 2008, and March 31, 2014. The study cohort

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consisted of 10 patients (8 men, 2 women; age range, 20–57 years) in whom the IA method was used. For 3 of these patients, IA was included in the desensitization protocol before HTX; for 7 patients, IA was the first step of the treatment protocol. One patient underwent IA before and after HTX. The relevant data are listed in Table 1.

Analysis of Endomyocardial Biopsy Specimens

Specimens were taken from multiple sites of the right ventricle and stained with hematoxylin-eosin for histologic examination. Immunohistochemistry was performed by using an immunoperoxidase-based method. Polyclonal rabbit antihuman antibodies (Ventana Medical System, Tucson, Ariz, United States) were used for complement C3d and C4d fragment detection. Acute celluar rejection was graded according to the Banff classification [4].

The presence of anti-HLA antibodies was screened before transplantation by using a microlymphotoxicity assay and a lymphocyte panel. Panel reactive antibodies (PRAs) were expressed as percentages of the positive test results. PRAs were tested at a minimum of 6-month intervals. A prospective cytotoxicity-dependent cross-match was performed in cases in which pretransplantation PRAs were $\geq$10%.

Antibody Detection

Serum samples were frozen at −700°C. The specificity of HLA antibodies was defined by using LABScreen mixed and single antigen class I and class II beads (One Lambda, Inc, Canoga Park, Calif, United States). After incubation, the samples were analyzed by using the Luminex 200 flow analyzer (Luminex Inc, Austin, Tex, United States). A mean fluorescence intensity of 1000 was the cutoff point for class I and class II patients. Patients and donors were typed for HLA, which enabled identification of DSA in individuals with positive HLA antibodies.

IA was performed by using an 8-F dialysis catheter. Plasma separation was conducted on COM.TEC separators (Fresenius Kabi, Mihla, Germany) and IA was performed on Citem 10 (Fresenius HemoCare, Bad Homburg, Germany) and ADAsorb (Medicap Clinic GmbH, Ulrichstein, Germany) IA systems. Both systems use 2 columns with staphylococcal protein A binding (Immunosorba; Fresenius Medical Care, Bad Homburg, Germany). Citrate anticoagulant agents (acid citrate dextrose solution A) were applied continuously throughout the procedure.

Graft function was assessed by transthoracic echocardiographic examination. Dysfunction was defined as a decrease in left ventricular ejection fraction (LVEF) <40%.

RESULTS

There were no complications observed in the 84 IA study procedures conducted. A comparison of values before IA and after the last procedure showed a decrease in immunoglobulin (Ig) levels; IgG fell by 64.1%, IgM by 25.6%, and IgA by 16.3%. Before HTX, a decline in PRAs was noted from 92%, 96%, and 99% to 36%, 23%, and 10%, respectively. After HTX, IA procedures led to a decrease in DSA class I in 7 patients, with 74% falling below the detection limit. DSA class II fell in 6 of 7 patients, with 51% falling below the detection limit (Table 2). None of the patients died of graft failure, and clinical improvement and amelioration of graft function were achieved in all patients.

DISCUSSION

The main result of the present study is its documentation of the safety and efficacy of IA in patients during HTX. Compared with plasmapheresis, IA has the obvious advantage of not leading to the unwanted depletion of plasma components, such as albumin and blood-clotting factors. In plasmapheresis, there is also the risk of allergic reactions and the possibility of transmitting viral infections during replacement of the removed plasma. In general, IA is considered to be a safe procedure, which was confirmed by our experience.

We reported a reduction in DSA, which often fell under the detection limit. However, IA is only the first step in comprehensive treatment. The removal of antibodies must be followed by a procedure that prevents their further development. To this end, intravenous immunoglobulin (IVIG), the monoclonal antibody rituximab, and the

Table 1. Basic Characteristics of Study Group

Patient No.	Sex/Year Born	Time Since HTX	No. of IA	Rejection			Graft Dysfunction	Treatment	Follow-up (mo)	Status	Last Control LVEF (%)
				ACR	pAMR	CM					
Desensitization protocol											
1	M/1957	Before	4	−	−	−	−	−	−	−	−
2	F/1969	Before	6	−	−	−	−	IA, IVIG	2	Dead	−
3	M/1956	Before	7	−	−	−	−	IA, IVIG, R	11	Dead	−
Treatment protocol											
1	M/1957	6 wk	2	−	+	+	−	IA, IVIG	62	Alive	58
4	M/1958	44 mo	3	−	+	+	+	IA, IVIG, MP, ATG, R	44	Dead	60
5	M/1962	3 mo	11	−	−	+	+	IA, IVIG, MP, R	9	Alive	53
6	M/1986	17 mo	9	+	−	+	+	IA, IVIG, ATG, R, B	16	Dead	60
7	M/1967	63 mo	4	−	+	+	−	IA, IVIG, MP, R	21	Alive	60
8	M/1953	72 mo	7	−	+	+	+	IA, IVIG, R	104	Alive	50
9	F/1991	9 d	23	−	+	+	+	IA, IVIG, MP, R, B	22	Alive	60
10	M/1982	18 mo	8	+	−	+	+	IA, IVIG, MP, R, B	2	Alive	50

Abbreviations: ACR, acute celluar rejection; ATG, antithymocyte globulin; B, bortezomib; CM, cross-match (follow-up since 1st); IA, immunoadsorbtion; IVIG, intravenous immunoglobulin; LVEF, left ventricular ejection fraction (graft dysfunction LVEF <40%); pAMR, pathologic antibody–mediated rejection; MP, methylprednisolone; R, rituximab.