Effectiveness of Rabbit Antithymocyte Globulin in Chronic Lung Allograft Dysfunction

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ABSTRACT

Background. Rabbit antithymocyte globulin (rATG) therapy has been shown to be beneficial in lung transplant recipients as induction therapy for treating acute lung rejection; however, its role in chronic lung rejection has been reported only rarely. We evaluated the effectiveness of rATG therapy in slowing the progression of chronic lung allograft dysfunction (CLAD) syndrome.

Methods. We conducted a retrospective review of 25 lung transplant patients with CLAD who received rATG therapy in the Pulmonary Institute of Rabin Medical Center, Israel, between May 2005 and February 2016. Response to treatment was divided into 2 categories: stabilization, defined as a halting of the decline of forced expiratory volume in 1 second (FEV_1) for $\geq$6 months after rATG therapy, and deterioration, defined as showing a continued decline in FEV_1.

Results. Of 25 subjects, 8 (32%) were categorized as part of the stabilization group and 17 (68%) were categorized as showing continued deterioration. The stabilization group was older (61 $\pm$ 8 vs 44 $\pm$ 19 years) and showed longer survival rate after rATG therapy (930 $\pm$ 385 vs 414 $\pm$ 277 days). The stabilization group also demonstrated a lower mean white blood cell count (7.9 $\pm$ 1.8 vs 8.5 $\pm$ 2.9 $\times$ 10^9 cells/L) and lymphocyte count (0.37 $\pm$ 0.1 vs 0.55 $\pm$ 0.3 $\times$ 10^9 cells/L) during rATG treatment. The stabilization group also demonstrated a higher FEV_1 after lung transplantation (91% $\pm$ 21% vs 75% $\pm$ 15.4%), at the beginning of rATG therapy (51% $\pm$ 11% vs 39% $\pm$ 9.6%) and at 6 months after rATG therapy follow-up (51% $\pm$ 9.1% vs 28% $\pm$ 7.6%).

Conclusions. rATG was effective in stabilizing rejection progression in approximately one-third of our patients with CLAD. rATG therapy should be considered early in the course of CLAD. Randomized, controlled studies should be considered to confirm these findings.

CHRONIC lung allograft dysfunction (CLAD) syndrome is a major cause of allograft dysfunction in lung transplant recipients [1]. The course of the disease has a variable presentation. Some individuals experience an accelerated loss of lung function and develop respiratory failure rapidly, whereas others experience a slower progression with intermittent loss of lung function. These subjects may exhibit long periods of relatively stable lung function.

A diagnosis of CLAD requires the absence of other causes of airflow obstruction, which include infection, acute rejection, anastomotic stricture, or bronchomalacia. Therapy for progressive airflow obstruction owing to CLAD is being studied extensively. Potential therapies include pulse corticosteroids [2], methotrexate [3], photopheresis [4], total

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0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.04.024

lymphoid irradiation [5], azithromycin [6,7], cyclophosphamide [8], azathioprine [9], and cytolytic agents [10–12].

Rabbit antithymocyte globulin (rATG) is a polyclonal antibody preparation that may lead to indirect depletion of cytotoxic T cells through depletion of circulating lymphocytes. Multiple mechanisms of rATG action include Fc-dependent, complement-mediated lysis and opsonization with antibody clearance via the reticuloendothelial system [13]. Reports from the International Society of Heart and Lung Transplantation Registry have shown a decreased incidence of bronchiolitis obliterans syndrome and survival benefits in patients who received rATG as induction therapy [14,15]. However, rATG is not a listed therapy for CLAD and has been only rarely studied for this indication. Only 3 studies suggest that rATG may delay the progression of CLAD [10–12]. We therefore evaluated rATG as a therapy to slow CLAD progression in individuals after lung transplantation.

METHODS

Setting

Rabin Medical Center (RMC) is a major tertiary medical facility in central Israel and is the national center for lung transplantation. More than 500 lung transplants have been performed at RMC since the inception of the program. In recent years, between 40 and 50 lung transplant procedures are performed annually.

Patients

A retrospective study of 25 lung transplant recipients was initiated to evaluate the effectiveness of rATG treatment for chronic lung rejection at RMC between May 2005 and February 2016. This study received approval by the RMC Institutional Review Board.

Immunosuppression Protocol

The initial immunosuppression protocol included high-dose intravenous methylprednisone preoperatively with transition to oral prednisone in a tapering dose. All subjects received maintenance immunosuppressive therapy with oral prednisone, mycophenolate mofetil and tacrolimus. Target tacrolimus blood levels were 10–20 ng/mL in the first month after lung transplantation period and 8–12 ng/mL subsequently. Immunosuppressive antibody induction therapy was not used.

Treatment for CLAD was given to patients who developed a $\geq$20% drop in predicted forced expiratory volume in 1 second (FEV_1) in relation to the best FEV_1 obtained post-transplantation in the absence of any other explanation for lung function deterioration. Fiberoptic bronchoscopy, bronchoalveolar cultures, and transbronchial biopsies were performed in all subjects to exclude acute rejection, infection, or airway stenosis.

Therapy for CLAD was initiated with a course of pulse IV methylprednisolone 500 mg/d for 3 consecutive days and lung function was reassessed after 2–3 weeks. If no response to CLAD progression was detected, a repeat steroid course was given and the subject reassessed after a further 2–3 weeks. If this treatment failed to stabilize the decline in lung function, the subject was hospitalized and rATG therapy administered.

The rATG course was given intravenously at a dosage of 1.5 mg/kg/d for 7 days. Before each rATG infusion, the subject was premedicated with intravenous paracetamol 1 g, promethazine 12.5 mg, and methylprednisolone 60 mg to decrease the incidence and severity of adverse effects. During rATG treatment, oral tacrolimus was administered; mycophenolate mofetil and prednisone were discontinued. Daily complete blood counts were obtained to monitor for lymphopenia.

Patient response to rATG treatment was divided into 2 categories: stabilization or deterioration. Stabilization was defined as halting the decline of FEV_1 for $\geq$6 months after rATG therapy and deterioration was defined as a continued decline in FEV_1 in the 6-month period after receiving rATG therapy. We measured the slope of FEV_1 change from the beginning of CLAD to the date of initiation of rATG therapy and compared it with the period after rATG therapy to the end of follow-up.

RESULTS

Of the 25 patients who were treated with rATG after CLAD (Table 1), 8 (32%) responded positively to the treatment and formed the "stabilization" group (Fig 1), and 17 (68%) did not respond to rATG treatment and were categorized as the "deterioration" group (Fig 2). The stabilization group was older than the deterioration group (61 $\pm$ 8 vs 44 $\pm$ 19 years). These subjects survived longer (930 $\pm$ 385 vs 414 $\pm$ 277 days) after rATG therapy. All patients in stabilization group survived during the study period, whereas only 35% of the patients in the deterioration group survived until the end of the follow-up period (Table 1).

Table 1. Demographic Characteristics of rATG-treated Groups

Parameter	Stabilization	Deterioration
Patients (n)	8	17
Male, n (%)	6 (75)	9 (53)
Age (y)	61 $\pm$ 8	44 $\pm$ 19
Transplant type, n (%)		
Single lung	3 (38)	8 (47)
Double lung	5 (63)	9 (53)
Diagnosis, n (%)		
Pulmonary fibrosis	4 (50)	4 (24)
Emphysema	2 (25)	3 (18)
Cystic fibrosis	0	4 (24)
Other	2 (25)	6 (35)
Survival		
Overall (d)	231 $\pm$ 881	1798 $\pm$ 126
n, (%)	8 (100)	6 (35)
Time from		
Transplantation to starting decline FEV_1 (d)	873 $\pm$ 579	1098 $\pm$ 1091
Starting decline FEV_1 to rATG treatment (d)	515 $\pm$ 332	284 $\pm$ 277
rATG treatment to death/end of follow-up (d)	930 $\pm$ 385	414 $\pm$ 277
Before rATG treatment		
FK average level (ng/mL)	10.34 $\pm$ 0.94	10.46 $\pm$ 1.79
WBC count (10^9 cells/L)	8.04 $\pm$ 0.82	9.66 $\pm$ 2.80
Lymphocyte (10^9 cells/L)	1.55 $\pm$ 0.86	1.77 $\pm$ 0.60
During rATG treatment		
FK average level (ng/mL)	10.28 $\pm$ 1.25	14.21 $\pm$ 4.79
WBC count (10^9 cells/L)	7.9 $\pm$ 1.8	8.5 $\pm$ 2.9
Lymphocyte, (10^9 cells/L)	0.37 $\pm$ 0.10	0.55 $\pm$ 0.30

Abbreviations: FEV_1, forced expiratory volume in 1 second; FK, tacrolimus; rATG, rabbit antithymocyte globulin; WBC, white blood cell count.