의학석사 학위논문

A prospective, open-label, randomized, non-inferiority pilot study to compare the dose (6.0mg/kg vs 4.5mg/kg) of antithymocyte globulin as an induction therapy in living donor kidney transplantation

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이 논문을 의학석사 학위 논문으로 제출함

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의학과

고영민

고영민의 의학석사학위 논문을 인준함

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A prospective, open-label, randomized, non-inferiority pilot study to compare the dose (6.0mg/kg vs 4.5mg/kg) of antithymocyte globulin as an induction therapy in living donor kidney transplantation

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The optimal dose of rabbit antithymocyte globulin as an induction regimen in Asian living donor kidney transplant recipients has rarely been investigated. Patients were randomly assigned to receive either 4.5 mg/kg (19 patients) or 6.0 mg/kg (17 patients) antithymocyte globulin. All patients had corticosteroid withdrawal within 7 days. The primary end point was a composite of the biopsy-proven acute rejection, development of de novo donor-specific antibody, or graft failure. At 24 months post-transplant, the composite end point rate was 42.1% in the 4.5 mg/kg group and 24.4% in the 6.0 mg/kg group. There was neither graft failure nor mortality during the follow-up period (22 to 40 months). We decided to stop the study earlier than planned because we were concerned about the higher composite end point rate in the 4.5 mg/kg group. Antithymocyte globulin induction at 4.5 mg/kg and early corticosteroid withdrawal increased the rate of de novo donor-specific antibody and biopsy-proven acute rejection.

Abbreviations:

ATG, antithymocyte globulin

NK, natural killer

PRA, panel-reactive antibody

BPAR, biopsy-proven acute rejection

DSA, donor specific antibody

DGF, delayed graft function

CMV. cytomegalovirus

Keywords: kidney transplantation, antithymocyte globulin, induction, dose, biopsy-proven acute rejection, donor-specific antibody, graft failure

목차

표, 그림 목차 및 약어 목록

There has been a significant evolution in the immunosuppressants available for renal transplantation. In the 1980s, the development of cyclosporine dramatically lowered the acute rejection rate and improved the kidney graft survival rate. In the 1990s, the advent of mycophenolic acid and tacrolimus additionally improved the post-transplant outcomes. More recently, newly developed immunosuppressants have made it possible to dramatically improve long-term graft survival compared to the early era of transplantation.[1] The immunosuppressive agents currently used in kidney transplantation can be classified into three groups. The immunosuppressants in the first group are used for induction, those in the second group are used for maintenance regimens, and those in the third group are used for the treatment of rejection. Induction regimens are administered intravenously in the initial phase after kidney transplantation to reduce the risk of acute rejection. The immunosuppressants currently used for maintenance therapy are mammalian target of rapamycin (mTOR) inhibitors, antiproliferative agents, corticosteroids, and calcineurin

inhibitors. Newly introduced maintenance agents consist of protein C kinase inhibitors, Janus kinase (JAK) 3 inhibitors, and co-stimulation blockers.

There are three classes of immunosuppressive agents used for induction therapy: chimeric monoclonal antibodies to the IL-2 receptor, antithymocyte globulin (ATG), and anti-CD3 monoclonal antibodies (OKT3).

Lymphocyte-depleting agents such as the murine OKT3 and polyclonal ATG derived from rabbit (rATG) have been used since the 1980s. Two non-depleting chimeric monoclonal antibodies, Basiliximab and Daclizumab, directed against the IL-2 receptor were introduced in the 1990s.[2]

OKT3 is a monoclonal antibody against CD3 derived from the serum of mouse. It depletes T cells by binding the T cell receptor-associated CD3 complex. As mentioned above, the purpose of using T cell-depleting agents in renal transplantation is to reduce acute rejection in the immediate post-transplantation period. These agents are also used for the treatment of

rejection unresponsive to steroid therapy.[3] The IL-2 receptor antagonist Basiliximab, also called a non-depleting antibody, blocks the function of lymphocytes by binding to cell surface molecules. Polyclonal ATG (thymoglobulin) is derived from the serum of a rabbit immunized with human thymocytes. It acts as a depleting antibody to reduce the number of circulating lymphocytes through direct cytotoxicity. Over the last few decades, rATG has become the most common induction agent used in kidney transplantations worldwide. ATG induces T cell depletion and modulates the cell-surface and adhesion molecules that regulate T cell function and leukocyte endothelial interaction, respectively.[4567] Previous studies demonstrated that ATG is more effective in reducing the incidence and severity of acute rejection compared with anti-IL2 receptors (Basiliximab or Daclizumab).[8] Several studies showed superior outcomes when thymoglobulin was used as induction therapy for patients with a high immunologic risk.[9] Although ATG is effective for preventing acute rejection, it can cause additional short and long-term side effects, such as opportunistic infections by cytomegalovirus (CMV) and malignancy.[10111213] The severity and incidence of infection is

substantially dependent on the total dose of the drug and ATG also increases the incidence of posttransplant lymphoproliferative disease.[14,15]

Therefore, it is important to identify the minimum effective dose of ATG that avoids many of the side effects and allows for early steroid withdrawal. Several studies have been reported on dose optimization of ATG as an induction therapy in kidney transplantation.[16] The minimal doses of ATG ranged from 1.5 to 7.5 mg/kg in these studies. Kho *et al* showed that the rates of patient and graft survival, rejection, and infections did not differ between groups that used different doses of ATG as induction therapy.[13] Wong *et al* found that there was no apparent clinical benefit from using a higher dose of ATG as induction therapy.[17] Airee *et al* suggested that ATG doses no higher than 7.5 mg/kg are efficient and safe as induction therapy for immunologic high-risk renal transplant recipients.[18] However, most of the studies were performed in Western countries and there have been few studies investigating the optimal dose of ATG for Asian kidney transplant recipients. It is also

important to understand the pattern for the depletion and recovery of each subset of lymphocytes after ATG administration.

The aim of this study was to compare the efficacy and safety between 4.5 mg/kg vs 6.0 mg/kg ATG in non-sensitized living donor kidney recipients with early steroid withdrawal in an Asian population.

1. Materials and Methods

A. Study design, patient selection, and randomization

This is a prospective, open-label, randomized, non-inferiority pilot study involving living donor kidney transplant recipients at Asan Medical Center, Seoul, South Korea. Patients above 18 and below 70 years of age scheduled for living donor kidney transplantation were recruited for enrollment. Patients were excluded if they were multi-organ transplant recipients, had a panel-reactive antibody (PRA) above 20% or pre-transplant donor-specific antibody (DSA), were scheduled for ABO- or human leukocyte antigen (HLA)-incompatible kidney transplantation, had a kidney allograft from an HLA-identical donor, had been

diagnosed with malignancy in the last 5 years, had an active infection, or had a known contraindication to the administration of ATG (absolute neutrophil count < 1000/mm^3, platelet count < 75000/mm^3). The study was approved by the institutional review board of our center (Approval Number: 2014-1213) and written informed consent was obtained from all recipients. The study is listed on http://clinicaltrials.gov (NCT02447822) and was performed with full adherence to the principles of the Declaration of Helsinki.

All patients were randomly assigned via a 1:1 variable-block randomization to receive ATG of either 1.5 mg/kg/day x 3 doses (4.5 mg/kg total dose) or 1.5 mg/kg/day x 4 doses (6.0 mg/kg total dose) as induction therapy.

B. Induction and maintenance immunosuppression and prophylaxis against infection

Before ATG was administered (1.5 mg/kg/day given intravenously), chlorpheniramine and acetaminophen were given intravenously as premedication. The ATG dose was reduced by 1/2 for patients with thrombocytopenia (platelet count < 50,000 per cubic millimeter) or neutropenia (absolute neutrophil count 2000-3000 per cubic millimeter). ATG was

discontinued when there was severe thrombocytopenia (platelet count < 50,000 per cubic millimeter) or severe neutropenia (absolute neutrophil count < 2000 per cubic millimeter). The patients were closely monitored during intravenous administration of ATG for signs of anaphylactoid reactions, such as fever, chills, respiratory distress, and hypotension caused by ATG.

The maintenance immunosuppressants consisted of tacrolimus, mycophenolate mofetil, and a 7-day methylprednisolone taper. Tacrolimus was initiated 2 days before kidney transplantation at 0.05 mg/kg twice a day with a target trough level of 6-8 ng/ml for 1 year post-transplant. Mycophenolate mofetil at 750 mg was administered twice a day to both groups. Methylprednisolone was administered intravenously at a dose of 500 mg on day 0, 250 mg on day 1, and 125 mg on days 2 and 3. Thereafter, fast taper was performed with oral prednisone within one week post-transplant.

All recipients took 80 mg trimethoprim and 400 mg sulfamethoxazole orally daily for 6 months for bacterial and *Pneumocystis jiroveci* prophylaxis. Valganciclovir was administered

for CMV prophylaxis for 6 months to seronegative recipients that received a kidney transplant from seropositive donors. For low-to-intermediate risk patients, CMV monitoring was performed on a weekly basis using a CMV-PCR assay for preemptive treatment. If the viral load of CMV exceeded 4.0 log in the CMV-PCR assay, intravenous ganciclovir or oral valganciclovir was given until the CMV viremia was eliminated.

C. End points

The primary efficacy end point was a composite of biopsy-proven acute rejection (BPAR), de novo DSA, or graft failure. BPAR was determined from pathological evidence interpreted using the Banff criteria.[19202122] Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation, excluding a single session for the treatment of hyperkalemia. Kidney graft failure was defined as the need for a transplant nephrectomy or retransplant, or to recommence dialysis. The secondary efficacy end points were renal function determined based on the estimated glomerular filtration rate (eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation) at 1 and 6 months

as well as 1 and 2 years post-transplantation. The safety end points were infection, leukopenia, thrombocytopenia, and malignancy. Leukopenia was defined as a white-cell count of less than 2500 per cubic millimeter and thrombocytopenia was defined as a platelet count of less than 80,000 per cubic millimeter.

D. Statistical analysis

Categorical variables are presented as absolute and relative frequencies. Quantitative variables are presented as mean and standard deviation (SD). The Student's t-test or Mann-Whitney U test was used to analyze differences between means, as appropriate. Categorical variables were compared using the chi-squared test. Survival rates related to the composite outcomes were calculated using the Kaplan-Meier method and compared using the log-rank test. P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

2. Results

A. Characteristics of enrolled patients

From the initiation of this study in January 2016 to the early cessation of enrollment in September 2017, a total of 36 patients were enrolled in the study. However, one patient assigned to receive 4.5 mg/kg ATG was excluded due to poor compliance and subsequent graft failure. Therefore, 35 patients were enrolled in the study. Of these patients, 18 were randomly assigned to receive 4.5 mg/kg ATG and 17 were randomly assigned to receive 6.0 mg/kg ATG. Follow-up data were collected until June 2019 with a mean follow-up period of 31 months. There was no significant difference in the baseline characteristics of the recipients and donors in the two groups including the number of HLA-ABDR, DR, and DQ mismatches (Table 1).

B. Efficacy end points

At 24 months post-transplant, the composite end point rate was 42.1% in the 4.5 mg/kg group and 24.4% in the 6.0 mg/kg group (Table 2). Kaplan-Meier analysis revealed that the composite rate of outcomes was significantly higher in the 4.5 mg/kg group than in the 6.0 mg/kg group (Figure 1). There was no delayed graft function during the first week post-

transplant. DSA was developed by one patient in the 6.0 mg/kg group (5.9%) and by four in the 4.5 mg/kg group (22.2%) (P=0.452). On the other hand, three patients in the 6.0 mg/kg group (18.8%) and five in the 4.5 mg/kg group (27.7%) had BPAR (P=0.661). There was only one death-censored graft failure in the 4.5 mg/kg group (5.5%) and none in the 6.0 mg/kg group. There was no mortality during the follow-up period (22 to 40 months) and there was no difference in renal function determined with eGFR in both groups.

Table 1. Baseline characteristics according to the dosage of antithymocyte globulin

Variables	**Antithymocyte globulin 6.0 mg/kg (N=17)**	**Antithymocyte globulin 4.5 mg/kg (N=19)**	**P-value**
Recipient			
Age, y [range]	42.4 [30.4-54.4]	46.6 [32.6-60.6]	0.186
Female gender, n (%)	10 (58.8)	12 (63.2)	0.827
Body mass index, kg/m^2 [range]	24.1 [19-29.2]	23.1 [18.4-27.8]	0.300
Hypertension, n (%)	16 (94.1)	17 (89.5)	0.827
Diabetes, n (%)	3 (17.6)	5 (26.3)	0.661
Primary cause of ESRD, n (%)			0.531-
Hypertension	2 (11.8)	2 (10.5)	-
Diabetes	3 (17.6)	4 (21.1)	-
Glomerulonephritis	2 (11.8)	2 (10.5)	-
IgA nephropathy	2 (11.8)	5 (26.3)	-
Unknown	5 (29.4)	5 (26.3)	-

Others	3 (17.6)	1 (5.3)	
Preemptive transplant, n (%)	5 (29.4)	6 (31.6)	0.612
ABDR mismatch, mean [range]	3.29 [2.57-4.01]	3.42 [2.69-4.14]	0.900
DR mismatch, mean [range]	1.23 [0.94-1.52]	1.15 [0.86-1.44]	0.754
DQ mismatch, mean [range]	1.05 [0.67-1.44]	1.00 [0.67-1.32]	0.827
Follow-up period, months, mean [range]	31.7 [26.38-37.03]	31.0 [25.16-36.84]	0.481
Donor			
Age, y, mean [range]	48.71[38.35-59.07]	47 [35.21-58.79]	0.650
Female gender, n (%)	9 (52.9)	9 (47.3)	0.778
Body mass index, kg/m^2, mean [range]	24.11 [22.94-25.19]	24.15 [22.55-25.75]	0.925
24-hour creatinine clearance, mg/day, mean [range]	108.6 [97.21-119.99]	111.6 [100.15-123.04]	0.684
24-hour protein clearance, mg/day, mean [range]	81.14 [67.72-94.57]	87.87 [73.11-102.64]	0.573

Table 2. Clinical outcomes according to the dosage of antithymocyte globulin

Dosage of antithymocyte globulin	**Antithymocyte globulin 6.0 mg/kg (N=17)**	**Antithymocyte globulin 4.5 mg/kg (N=18)**	**P-value**
Recipient			
Delayed graft function, n (%)	0	0	1.000
Presence of de novo DSA, n (%)	1 (5.9%)	4 (22.2%)	0.452
Biopsy proven acute rejection, n (%)	3 (18.8%)	5 (27.7%)	0.661
Death censored graft failure, n (%)	0 (0%)	1 (5.5%)	0.802
Mortality, n (%)	0	0	1.000

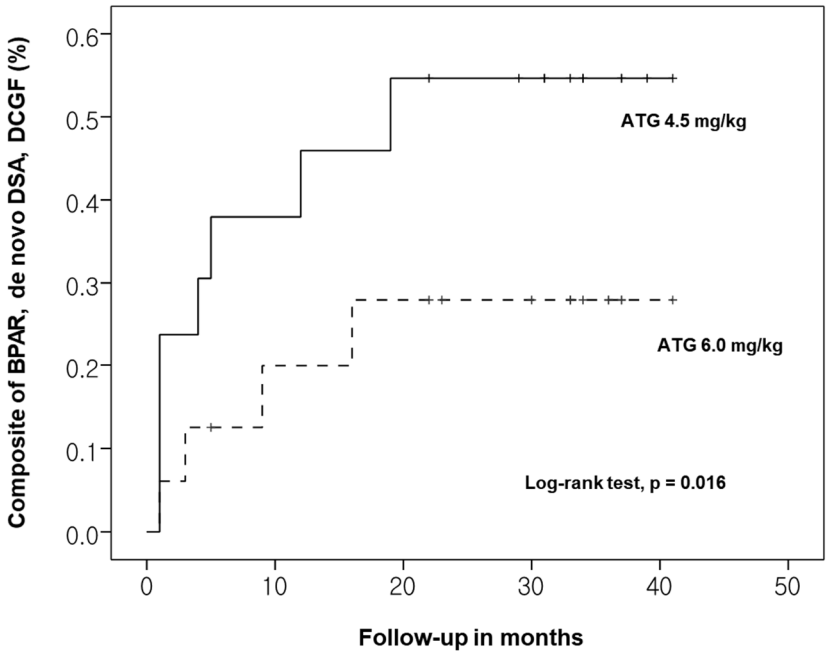

Figure 1. Comparison of composite outcome rates for the groups

C. Comparison of adverse outcomes

There was no significant difference in adverse events between the two groups (Table 3). Nine cases of leukopenia (52.9%) were observed in the 6.0 mg/kg group and 10 cases (55.5%) were observed in the 4.5 mg/kg group. There were two cases of thrombocytopenia in the 6.0 mg/kg group and none in the 4.5 mg/kg group. There were more cases of CMV infection in the 6.0 mg/kg group than in the 4.5 mg/kg group with marginal significance

Table 3. Adverse outcomes according to the dosage of antithymocyte globulin

Adverse Event	Antithymocyte globulin 6.0 mg/kg (N=17)	Antithymocyte globulin 4.5 mg/kg (N=18)	P-value
Leukopenia, n (%)	9 (52.9)	10 (55.5)	1.000
Thrombocytopenia, n (%)	2 (11.7)	0 (0)	0.552
Infection			
Cytomegalovirus, n (%)	6 (35.2)	2 (11.1)	0.078
Polyomavirus, n (%)	0 (0)	1 (5.5)	0.344
Bacterial infections, n (%)	3 (17.6)	3 (16.6)	0.925
Malignancy, n (%)	0 (0)	0 (0)	1.000

* Leukopenia was defined as a white-cell count of less than 2500 per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 80,000 per cubic millimeter. Values for each type of infection do not sum to the total number of infections because some patients had more than one type of infection.

(35.2% vs 11.1%, P=0.078). Only one patient in the 4.5 mg/kg group (5.5%) developed BK virus infection. The incidence of bacterial infection requiring hospital admission was 17.6% in the 6.0 mg/kg group compared with 16.6% in the 4.5 mg/kg group. There was no malignancy in both groups during the follow-up period.

3. Discussion

Most medical centers use interleukin-2 receptor antibody or ATG as an induction agent, and subsequently use a triple immunosuppressant regimen (consisting of a calcineurin inhibitor, mTOR inhibitor, antimetabolite, and corticosteroid) as a maintenance immunosuppressive regimen after kidney transplantation. Although triple therapy allows for the administration of a low dose of corticosteroid, there may be some adverse events caused by corticosteroid administration.

Corticosteroid therapy is associated with impaired glucose metabolism, hypertension, osteopenia, weight gain, etc. Consequently, there have been many attempts to find new and

potent immunosuppressive agents for induction therapy that allow for the early withdrawal of the steroid after kidney transplantation.

The immunosuppressive agents used as induction therapy typically include a biological antilymphocyte agent, IL-2 receptor antibody, or ATG. Lymphocyte-depleting agents such as the murine anti-CD3 monoclonal antibody and polyclonal ATG have been used since the 1980s and IL-2 receptor antibodies were introduced in the 1990s. Numerous studies have been conducted to identify appropriate immunosuppressive agents for induction therapy. The important findings of those studies are as follows: (A) There is no benefit from the use of IL-2 receptor antagonist induction compared to no induction in patients with respect to acute rejection or graft survival.[23] (B) ATG induction has an advantage in reducing the risk of acute rejection compared to IL-2 receptor antibody, but has no effect on overall graft survival.[232425] (C) In the event of steroid withdrawal, alemtuzumab was associated with a 47% reduction in the risk of acute rejection compared to IL-2 receptor antagonist and a 27% increased risk of graft

loss.[26] ATG is currently used in the majority of kidney transplantations (>60%) in the United States whereas the IL-2 receptor antibody is used in approximately 20% of kidney transplantations.[2]

Thymoglobulin plays a major role in immunosuppressive therapy in kidney transplantation. It targets a wide range of T cell surface antigens and leads to profound, long-lasting T cell depletion. Induction therapy with thymoglobulin may be preferred for immunologic high-risk patients who receive grafts from donors with a high risk of DGF. Induction with thymoglobulin is also helpful for low-risk patients that desire early steroid withdrawal or minimization of the use of calcineurin inhibitors. In the early stage of kidney transplantation, the standard dose of thymoglobulin is 1-1.5 mg/kg/day for 7-10 days, with a total dose of 10-15 mg/kg. Administration of a high dose of ATG frequently leads to complications such as cancer, infection, and hematological abnormalities. Therefore, some trials have been conducted to evaluate the effects of low doses of ATGs on patients with low immunologic risk. Two trials compared the standard dose of ATG with lower doses of ATG (total doses of

3.75 and 2.75 mg/kg). The studies demonstrated favorable outcomes in terms of acute rejection rates (17% and 10%) and less postoperative opportunistic viral infection.[4]

In our center, we usually use thymoglobulin as induction therapy for high-risk patients with a dose of 6-7.5 mg/kg. However, there is no standardized minimum dose of thymoglobulin for induction in Asian patients that undergo kidney transplantation.

We designed this study to compare the efficacy and safety between 4.5 and 6.0 mg/kg ATG in non-sensitized living donor kidney recipients with early steroid withdrawal in an Asian population.

We found that 4.5 mg ATG induction with early steroid withdrawal increased the composite rate of de novo DSA, BPAR, and graft failure compared to 6.0 mg/kg ATG induction, but there was no significant difference in adverse events between the two groups. CMV infection in the 6.0 mg/kg ATG induction group was higher than that in the 4.5 mg/kg ATG induction group with marginal significance.

There were some limitations to this study due to the small number of enrolled patients.

Additionally, comparison of the long term outcomes for the groups was not possible because of the relatively short follow-up period.

We decided to stop this study earlier than initially planned because we became concerned about the higher composite end point risk in the 4.5 mg/kg group. Though the P-value indicated no significance, 4.5 mg/kg ATG induction and early corticosteroid withdrawal increased the rate of de novo donor-specific antibody and biopsy-proven acute rejection.

4. Conclusion

Among patients at low risk for acute rejection who received a kidney transplant from a living donor, 4.5 mg/kg ATG induction and early corticosteroid withdrawal increased the rate of de novo DSA and BPAR.

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