Effectiveness of Antithymocyte Globulin Induction Dosing Regimens in Kidney Transplantation Patients: A Network Meta-analysis

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ABSTRACT

Background. Antithymocyte globulin (ATG) is an induction therapy in kidney transplantation, but our knowledge about the relation between outcomes and ATG regimens is limited. We compared ATG effectiveness in kidney transplantation according to dosage and administration schedule.

Methods. Reports from 1970 until May 2018 in CENTRAL, MEDLINE, EMBASE, and Science Citation Index Expanded were searched. We performed direct and indirect network meta-analysis using Bayesian models and generated rankings for ATG dosage and injection number variations by generation mixed treatment comparison.We compared ATG dose and schedule in kidney transplantation in relation to all-cause death, graft failure, antibody-mediated rejection, T-cell mediated rejection, biopsy-proven acute rejection, and bacterial and viral infection.

Results. Ten studies (N = 1065) were analyzed by forming 6 groups: ATG alternate doses, 9 mg/kg, 6 mg/kg, and 4.5 mg/kg; single dose, 6 mg/kg, and 4.5 mg/kg; and control. Compared to placebo, ATG regimen variations were not associated with significant differences in survival, viral infection, renal function, or graft survival. ATG regimens 9 and 4.5 mg alternate dosing tended to reduce biopsy-proven acute rejection but without statistical significance. According to the highest rank probability, the 9 mg alternate dosing group had the highest tendency for cytomegalovirus and bacterial infections but without statistical significance.

Conclusions. The rejection frequency tended to be lower for the 9 and 4.5 mg alternate dosing groups. Infections occurred at a higher rate in the 9 mg alternate dosing group, but the differences in the risk of infection among the groups with different ATG regimens were not statistically significant.

INDUCTION immunosuppressants for kidney transplantation reduce the frequency of rejection and increase the survival of patients and graft survival [1]. Most transplantation centers use interleukin 2R Ab (IL-2R Ab) as an induction immunosuppressant, except in cases of very highly sensitized patients or patients with very low immunologic risk. IL-2R Ab can be safely administered to improve graft survival without serious side effects [2].

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However, in the United States, the use of antithymocyte globulin (ATG) as an induction immunosuppressive agent has been increasing in recent years, replacing the IL-2R Ab therapy. In the past, transplantation was not considered in cases of high-sensitized patients, more than 2 transplants, and donations from cardiac death donors. However, there is a current trend of high-risk patients undergoing transplantation after ATG administration to increase the donor pool worldwide.

ATG is an antithymocyte polyclonal antibody produced in rabbits immunized with human thymic tissue that has been used for decades. ATG contains an antibody against T lymphocytes and depletes CD2+, CD3+, CD8+, CD16+, CD25+, and CD45+ in a dose-dependent manner within 24 hours after administration. B cell apoptosis, along with the effect on T cells, interferes with dendritic and natural killer cell function [3,4]. Although there is worldwide agreement on the dosage, duration, and method for IL-2R Ab therapy, ATG treatment regimens still vary widely in dose, duration, and method of administration. In addition, the high price of ATG and the high incidence of opportunistic infections that occur after administration also make it difficult to create treatment protocols in centers using ATG. We therefore conducted this study to identify the most effective method of induction immunosuppression in kidney transplantation by performing a network meta-analysis on the dosing regimens of ATG.

METHODS

Ethics Statement

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses statement (S1 Checklist) [5]. The entire analysis was based on previously published studies; therefore, ethical approval and patient consent were not required.

Data Sources, Searches, and Inclusion and Exclusion Criteria

Two researchers (SDH and JHL) independently performed comprehensive searches of the following databases for studies published from the database inception until March 31, 2017: MEDLINE (via PubMed), EMBASE, CINAHL, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. We applied a highly sensitive search strategy to identify randomized controlled trials using the following search string: (anti-thymocyte globulin [rabbit] OR rabbit ATG OR rabbit antithymocyte globulin OR rabbit anti-human thymocyte globulin OR lapineT lymphocyte immune globulin OR antithymocyte immunoglobulin) AND (renal transplantation or renal transplantations or transplantations, renal or transplantation, renal or grafting, kidney or kidney grafting or transplantation, kidney or kidney transplantations or transplantations, kidney). The study's inclusion criteria were as follows: all studies evaluating the induction therapy of ATG during kidney transplantation, adult patients (>18 years old), and direct and indirect comparisons of the ATG dose frequency.

Risk of Bias Assessment

Two researchers (SDH and JHL) independently assessed the risk of bias of each trial using the Cochrane Collaboration's Risk of Bias tool [6] during random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, analysis of incomplete outcome data, selective reporting, and in other areas. All these judgments were categorized as "yes" (low risk of bias), "unclear", or "no" (high risk of bias) [6,7].

Quality of Evidence Assessment

We assessed the overall quality of the evidence for our primary outcome using an adapted Grading of Recommendations Assessment, Development, and Evaluation approach [8]. The quality of the evidence for a specific outcome was based on performance vs the limitations of the study design, inconsistency of results, indirectness of evidence, imprecision of results, and publication bias among all studies measuring a specific outcome. The overall quality of the evidence for the outcome was evaluated by combining assessments from all domains [9].

Outcome Measures

The primary outcome was the rate of graft rejection among several groups. The secondary outcomes were patient and graft survival after kidney transplantation and reversal of rejection. We assessed the rate of the side effects leucopenia and thrombocytopenia, which can occur after using ATG. Opportunistic infections such as BK virus infection, cytomegalovirus (CMV) infection, oral candidiasis, herpes infection, and fungal infection were identified.

Statistical Analyses

We compared the effectiveness of patient and graft outcomes and adverse outcomes among 6 types of induction therapies for kidney transplant recipients via the random effect of Bayesian network meta-analysis. We performed direct and indirect network meta-analysis using Bayesian models and generated rankings of the different hypoglycemia agents according to the generation mixed treatment comparison. We compared multiple studies reporting on multiple treatments; therefore, the random effects model of meta-analysis can be extended to a random effects network meta-analysis, which allows the estimation of the pooled effects within each treatment contrast [10]. For multi-arm trials, correlations between the treatment effects among the arms were included in the analysis. Studies with $j+1$ treatment arms can be assessed by modeling the treatment effects relative to the reference treatment using a multivariate normal distribution where the covariance elements $tau^2/2$ are based on the assumption that there are homogeneous between-study variances across the tau^2 treatment contrasts [11,12]. An inconsistency test, homogeneity analysis, and sensitivity analysis were performed using the node analysis method in R software. The inconsistency test was assessed according to the Bayesian value, where $P<.5$ was considered evidence of the existence of significant inconsistency [13,14]. The I^2 test was performed ($I^2>50\%$ was considered an indication for significant heterogeneity) to assess homogeneity. Furthermore, a sensitivity analysis was conducted by comparing the differences between 2 effect models (a fixed effects model and a random effects model). The clinical outcome indicators were evaluated by the mean difference or the odds ratio (OR) with 95% confidence interval (CI) (mean difference for continuous outcomes, OR for binary outcomes) [11,15].

RESULTS

A total of 13,727 records were initially retrieved from the electronic databases and 2862 were removed as duplicate

entries. Of all records, 2168 were excluded based on a review of either the title or abstract and 61 records were selected for full-text review. From those 61 studies, further exclusions were made because some reports publishing hemodialysis and peritoneal dialysis results (n = 23) were duplicates of other publications (n = 16), review articles (n = 6), editorial comments (n = 3), or failed to extract a CMV event (n = 3). Finally, 10 trials reporting outcomes for 1065 patients were included in the analysis and categorized into 6 groups: ATG alternate doses, 9 mg/kg, 6 mg/kg, and 4.5 mg/kg; single dose, 6 mg/kg and 4.5 mg/kg; and control (Fig 1A).

The parameters for the model fit were the deviance information criterion (40.9) and the residual deviance (21.4), which measured a square root for this, and the funnel plot, which measured the publication bias among research papers.

Graft rejection was the primary endpoint among the studies assessed by our network analysis. When each intervention was compared to placebo, the ORs for graft rejection in the ATG dosage groups 9 mg alternate and 4.5 mg alternate were .34 (95% CI, .10–1.2) and .34 (95% CI, .049-2.50), respectively (Fig 1B, C). Although the trend to reduce graft rejection was found in these 2 ATG treatment groups, it was not statistically significant. The rank probabilities for decreased graft rejection showed that the 9 mg alternate and 4.5 mg alternate groups shared the same best probability of 44.9% among the different ATG regimens; the next highest probability, 43.5%, was found in the 6 mg alternate group (Fig 1D).

The CMV infection is the most common side effect of ATG induction therapy. A comparison among the treatment groups and the placebo control found an OR of 2.2 (95% CI, .33–21.2) for the ATG treatment group 9 mg alternate; this group showed the highest tendency for CMV infections and the highest rank probability, but without statistical significance. The ATG treatment group 6 mg alternate had the second highest prevalence of CMV infections, 1.0 (95% CI, .11–8.0). Furthermore, the 9 mg/ alternate group also had the highest infection risk with an OR of 1.2 (95% CI, .35–4.9), which was not associated with statistical significance. Among the other groups, the ORs were in the range of .61-.95 without statistically significant differences.

DISCUSSION

Several studies have shown that the dosage and administration schedule of ATG as induction immunosuppressant

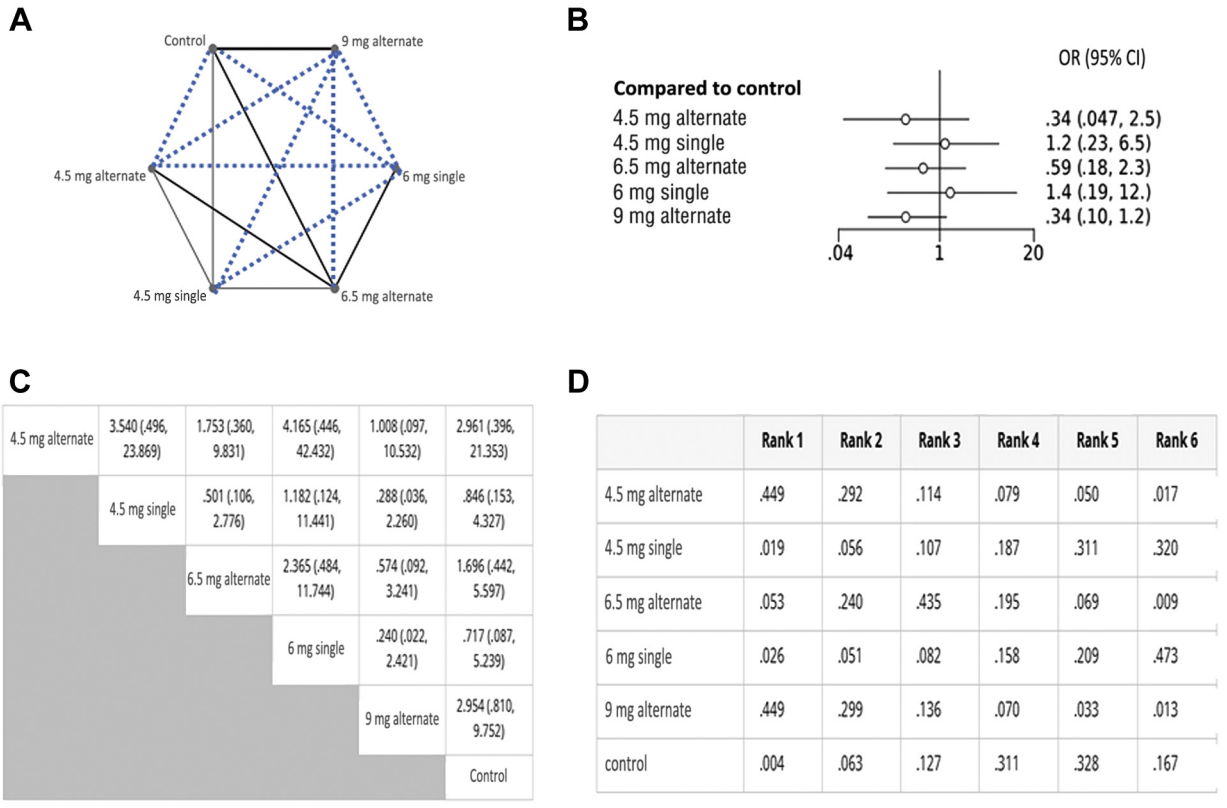

Fig 1. A network meta-analysis was used to assess the effectiveness of ATG induction therapy in kidney transplantation. **(A)** Network flowchart for ATG dose and administration frequency. **(B)** Calculated odds ratios of ATG treatment groups relative to the control in biopsy-proven acute rejection. **(C)** Calculated odds ratios among ATG treatment regimens. **(D)** Calculated rank probability in biopsy-proven acute rejection. CI, confidence interval; OR, odds ratio.

for kidney transplantation vary widely. In this network meta-analysis, the lowest incidence of rejection was observed in the groups treated with the ATG regimens 9 or 4.5 mg/alternate. Both ATG treatment groups were also co-located at the highest position of the podium in rank probabilities. The most frequent complication of CMV infection was 2.2-fold higher in the 9 mg/alternate dose group, with first-rank probabilities. Therefore, the ATG dose and administration frequency with the highest effectiveness and lowest infection rate is estimated to be the 4.5 mg/alternate regimen.

Current formulations of ATG contain purified IgG fraction from the serum of rabbits immunized with human thymocytes. ATG contains various polyclonal antibodies related to immune response antigens, adhesion molecules, and molecules involved in the heterogenous pathway [16]. ATG was initially known as a treatment for acute rejection. Mariat et al compared muromonab-CD3 (OKT3) with ATG in steroid-resistant acute rejection in kidney transplant recipients [17]. In this study, the success rate and recurrence of rejection had a more effective tendency for ATG but without statistical significance. Graft survival rate, infection rate, and malignancy were not significantly different between the 2 groups. However, cytokine release syndrome (fever, chills, myalgia, and headache) occurred more frequently in OKT3 than in ATG. In a study published by Daoud et al, ATG (1.5 mg/kg/d for 9 days) showed more effective results in the treatment of acute rejection with resistance to other treatments [18]. In addition, infectious complications were not observed in 90% of the patients even after 3 months of treatment. Other studies have also shown that ATG is effective in reversing acute rejection and its use was not associated with infection or other side effects. The efficacy of ATG was subsequently proven and it was then used as induction therapy as well as in the treatment of rejection. The use of ATG as induction therapy could increase graft survival by preventing rejection. ATG has been used in various types of transplantation, including transplantation of the pancreas, liver, heart, lungs, and kidneys. Brennan et al conducted an randomized controlled trial to compare the efficacy of rabbit and equine ATG as the induction therapy in kidney transplantation [19]. The rejection rate was significantly lower and graft survival was significantly higher in the rabbit ATG group as compared to those in the equine ATG group. In addition, ATG functions in reducing ischemic reperfusion injury by down-modulation of leukocyte adhesion molecules and inhibition of chemokine receptors [20]. These ATG effects reduce the frequency of delayed graft function (DGF) and acute rejection commonly associated with deceased donor kidney transplantation, resulting in increased patient survival and graft survival. Furthermore, studies have shown that the administration of ATG during operation rather than post-operation reduces the DGF frequency [21]. The use of ATG during operation has been shown to maintain better renal function and reduce the length of hospital stays. Interestingly, in the case of deceased-donor kidney transplantation, research has been published that suggests that ATG reduces rejection and the frequency of DGF. In a 5-year observational study in the United States, the rates of acute rejection, graft loss, and death were significantly lower in patients treated with ATG compared to those in patients receiving basiliximab, while the occurrence of CMV infection did not increase significantly in patients receiving ATG [22]. Therefore, ATG is widely used as induction therapy for sensitized or repeated transplantation, or transplantation with high risk for DGF. Recent studies with long-term follow-up examinations have demonstrated that ATG therapy is not associated with an increased risk of infection or malignancy.

This study has some limitations. Firstly, it is well known that an increased ATG dose is positively correlated with the risk of infection. Because of this risk, very low doses of ATG (ie, 2 mg/kg or 3 mg/kg) are currently being investigated. These studies were not included in this study. Although very low doses of ATG are very likely to have a lower rate of infection than high doses, further observations are needed as to whether they effectively reduce rejection. Secondly, the frequency of DGF is high when the donor is elderly, has various underlying diseases, or ischemic time is long. However, DGF not only increases the frequency of rejection but also causes hematologic abnormalities such as leucopenia and thrombocytopenia. In those cases, the adverse effects of ATG are difficult to distinguish from the side effects of drugs. This bias may obscure the overall incidence of acute rejection or the outcome of infection rates.

In conclusion, ATG as an induction immunosuppressant used in high-risk kidney transplantation is effective and does not have a high risk of infection. Our network meta-analysis indicated that induction therapies using ATG with a dose and frequency of 4.5 and 9 mg/alternate were the most effective regimens in preventing rejection. The risk of infection was also the lowest. These results may be helpful in determining the dose and frequency of induction therapy for using ATG in high-risk cases, especially for deceased-donor kidney transplantation, rather than selecting a combination of basiliximab and ATG according to the immunologic risk factors.

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