Efficacy and Safety of Induction Therapy in Kidney Transplantation: A Network Meta-Analysis

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ABSTRACT

Background. Rejection and infection can occur after kidney transplantation and are important factors in preserving graft kidney function. The use of immunosuppressant agents in transplantation is therefore important, and the question of which induction therapy should be used as an immunosuppressant is controversial.

Objective. The goal of this study was to assess the comparative benefits and harms of various maintenance immunosuppressive induction agents in adults undergoing kidney transplantation by using a network meta-analysis and to generate rankings of the different immunosuppressive regimens according to their safety and efficacy.

Methods. CENTRAL, MEDLINE, EMBASE, Science Citation Index Expanded, World Health Organization International Clinical Trials Registry Platform, and trial registers were searched until May 2017 to identify randomized controlled trials on immunosuppression for kidney transplantation.

Results. Twenty-seven studies involving 4484 participants were eligible for analysis. Induction and maintenance treatments were administered for 12 months. There was no evidence of differences in outcomes between therapies on all-cause mortality, graft loss, cytomegalovirus, BK virus, neutropenia, thrombocytopenia, and biopsy-proven acute rejection. However, compared with intravenous basiliximab (an interleukin-2 receptor antagonist [IL-2RA]), the most effective treatments to decrease biopsy-proven acute rejection were intravenous alemtuzumab and rabbit antithymocyte globulin (rATG). The odds ratios were 0.45 (95% confidence interval [CI], 0.29–40.78) and 0.63 (95% CI, 0.42–0.95), respectively. As a side effect, rATG was accompanied by more bacterial infection than the IL-2RA (OR, 1.8 [95% CI, 1.01–2.8]).

Conclusions. The determination of induction in kidney transplantation is important for future prognosis of the graft kidney. Alemtuzumab and rATG exhibited lower biopsy-proven acute rejection than the IL-2RA. As a side effect, rATG produced frequent bacterial infections.

KIDNEY transplantation is an optimal treatment for improving survival rate and quality of life in patients with end-stage renal disease [1,2]. Although there are many factors that determine the survival rate of grafts, acute graft rejection is closely related to early and long-term survival rates. In particular, the risk of graft rejection increases, especially in the early stages of transplantation, within 2 months after the operation [3].

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Therefore, the importance of immunosuppressive therapy to reduce the risk of rejection and to increase the survival rate of grafts has been emphasized [4]. Perioperative induction therapy strategies are used to provide fast and effective protection against acute allograft rejection [5].

In the past, interleukin-2 receptor antagonists (IL-2RAs) were mostly used for the prevention of acute rejection and are associated with excellent results [6,7]. Recently, a variety of induction therapies, including alemtuzumab, rabbit antithymocyte globulin (rATG), daclizumab, and rituximab, have been used. There are many studies comparing IL-2RAs with rATG, alemtuzumab, daclizumab, and rituximab. However, the superiority of these therapies in kidney transplantation remains controversial, and there is no direct or indirect comparative study on the prevention of rejection and the infection rate for all medicines. We therefore conducted a network meta-analysis to compare the efficacy and safety of various induction therapies for kidney transplantation.

MATERIALS AND METHODS

Ethics Statement

The present review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses [8] statement. All the analyses were based on previously published studies; ethical approval and patient consent were therefore not required.

Data Sources, Searches, and Inclusion and Exclusion Criteria

Two researchers (S.D.H. and J.H.L.) 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. Using a highly sensitive search strategy to identify randomized controlled trials (RCTs), we searched for: "hemodialysis" or "peritoneal dialysis" or "kidney transplantation" or "end stage renal disease" and "antithymocyte globulin" or "alemtuzumab" or "basiliximab" or "daclizumab" or "rituximab," or "campath" or "ATG" or "antithymocyt*" or "thymocyt*". The criteria we chose for including studies were as follows: RCTs and adult patients (>18 years old). Reviews, observational studies, and clinical trials that did not clearly define outcomes or that did not have thrombosis as an outcome were excluded [9]. The search was limited to human studies but was not restricted to any particular language or publication date. Reference lists from all available review articles and RCTs were searched manually.

Study Selection

The abstracts and full texts found were checked by 2 researchers independently. We resolved disagreements by discussing and consulting with another researcher. Included criteria for the papers in the analysis were: (1) RCTs; (2) kidney transplant recipients with induction (3) studies referring to at least 2 of the following eligible inductions: alemtuzumab, daclizumab, rituximab, IL-2RAs, control, and rATG; and (4) studies containing the main or adverse outcomes (Fig 1A).

Risk of Bias Assessment

Two researchers (S.D.H. and J.H.L.) independently assessed the risk of bias of each trial using the Cochrane Collaboration's Risk of Bias tool [10]. The risk of bias was assessed 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 of these judgments were categorized as "yes" (low risk of bias) or "unclear" or "no" (high risk of bias) [10,11].

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 [12]. 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 particular outcome. The overall quality of the evidence for the outcome was produced by combining assessments from all domains [13].

Outcome Measures

The goal of the present study was to determine the effectiveness of alemtuzumab, daclizumab, rituximab, IL-2RAs, control, and rATG induction graft outcomes in patients. We also investigated the potential for adverse outcomes associated with these medications. The efficacy of the medications on patient and graft outcomes were measured through 1-year biopsy-proven acute rejection, 1-year patient death, delayed graft function, thrombocytopenia, viral and bacterial infection, all infection, and 1-year graft loss. The adverse outcomes included thrombocytopenia, viral and bacterial infection, all infection, and malignancy.

Statistical Analyses

We compared the effectiveness of patient and graft outcomes and adverse outcomes among 6 kinds of induction therapies for kidney transplant recipients through the random effect of a Bayesian network meta-analysis. Network meta-analysis were performed by using Bayesian models, and rankings of the different hypoglycemia agents were generated by mixed treatment comparisons. We performed multiple studies that were recorded on multiple treatments, and the random effects of the meta-analysis model can be extended to a random effects network meta-analysis, which allows estimation of the pooled effects within each treatment contrast [14]. For multi-arm trials, correlations between the treatment effects between arms were included in the investigations. For studies i with $j + 1$ treatment arm, this can be achieved by modeling the j treatment effects relative to the reference treatment using a multivariate normal distribution in which the covariance elements tau-2/2 are based on the assumption that homogeneous between-study variances across tau-2 treatment contrasts [15,16].

Inconsistency test, homogeneity analysis, and sensitivity analysis were performed by using the node analysis method in R software (R Foundation for Statistical Computing, Vienna, Austria). Inconsistency test was assessed according to the Bayesian P value, where $P < .5$ is considered as evidence for the existence of significant inconsistency [17,18]. An I^2 test was analyzed ($I^2 > 50\%$ is considered as the existence of significant heterogeneity) to assess homogeneity. Furthermore, the sensitivity analysis was conducted by comparing the differences of 2 effect models (fixed effects model and random effects model).