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Official Title: Longitudinal Dynamics of Angiotensin II Type 1 Receptor Antibodies and Their Impact on Kidney Transplantation Outcomes

NCT Number: pending

Document Date: 2024-12-09

Study Protocol

1. Study Objectives

The primary objective of this study was to evaluate the impact of longitudinal changes in AT1R-Ab levels during the first year after transplantation on clinical outcomes in kidney transplant recipients. The initial analysis focused on characterizing the trajectory of AT1R-Ab concentrations over time.

Secondary outcomes included the incidence of de novo donor-specific antibody (DSA) formation and changes in renal function by AT1R-Ab group. Renal function was evaluated using serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) at 2 weeks, 3 months, and 1-year post-transplant.

2. Study Design

Design: Retrospective cohort study.

Study Population: Kidney transplant recipients between 2016 and 2022 at Seoul National University Hospital

3. Inclusion Criteria:

Eligible patients were those who had serum samples collected at pre-transplant and at 2 weeks, 3 months, and 1-year post-transplant, with a minimum follow-up of 1 year

4. Exclusion Criteria:

Exclusion criteria were simultaneous multi-organ transplantation and age younger than 18 years.

Statistical Analysis Plan

Group comparisons were performed at four time points: pre-transplant, and at 2 weeks, 3 months, and 1-year post-transplant. Continuous variables were summarized as means with standard deviations and compared using one-way analysis of variance (ANOVA) or Kruskal–Wallis tests, as appropriate. Categorical variables were expressed as frequencies and percentages, and differences between groups were assessed using chi-square tests or Fisher's exact tests.

To visualize longitudinal changes in AT1R-Ab group classification, Sankey diagrams were constructed to illustrate dynamic transitions between antibody groups over time.

The associations between AT1R-Ab groups and post-transplant outcomes, including biopsy-proven acute rejection (BPAR) and de novo donor-specific antibody (DSA) development, were analyzed over follow-up periods of 1 and 3 years using Marginal Structural Cox Models (Cox-MSM). This approach accounted for time-varying confounding and exposure misclassification, and all available time-varying variables were incorporated into the model.

Stabilized inverse probability weights were estimated based on the probability of remaining in a given antibody group at each time point. Covariates included age, sex, body mass index (BMI), pre- and postoperative angiotensin receptor blocker (ARB) use, pre- and postoperative hypertension, donor type, preemptive transplantation, kidney replacement therapy (KRT), donor–recipient relationship, compatibility, and desensitization.

Although the HIGH group became very small by the 1-year time point, the IPW estimates did not diverge. To prevent potential instability due to small cell sizes, stabilized weights were calculated as the product of inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW).

For secondary outcomes, boxplots were generated to visualize the distribution of eGFR and SCr at 2 weeks, 3 months, and 1-year post-transplant by AT1R-Ab group. These graphical analyses illustrated variability, medians, and outliers within each group. Statistical comparisons were performed using parametric or nonparametric tests depending on data distribution. These analyses aimed to evaluate whether higher AT1R-Ab groups were associated with impaired kidney function as reflected by eGFR or SCr levels.