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Original Article: Clinical Investigation

Temporary reduction of immunosuppression enhances production of anti-S antibody against severe acute respiratory syndrome coronavirus 2 after vaccination in kidney transplant recipients

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Abbreviations
ANOVA = analysis of variance
ATG = antithymocyte globulin
AUC = area under the concentration-time curve
CI = confidence interval
COVID-19 = coronavirus disease 2019
eGFR = estimated glomerular filtration rate
EVR = everolimus
IgG = immunoglobulin G
MMF = mycophenolate mofetil
OR = odds ratio
RIT = rituximab
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
TAC = tacrolimus

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Abstract:

Objectives: The study identified factors affecting anti-S immunoglobulin G production after vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in kidney transplant recipients.

Methods: Serum samples were prospectively collected from kidney transplant recipients, live kidney donors, and healthy volunteers 1 month after receiving the second dose of SARS-CoV-2 vaccine, and anti-S immunoglobulin G titers were measured. The mycophenolate mofetil dose was reduced before vaccination in some immunologically low-risk recipients.

Results: A total of 151 kidney transplant recipients, 74 live kidney donors, and 50 healthy volunteers were included. Kidney transplant recipients had significantly lower titers of anti-S immunoglobulin G than donors and healthy volunteers (1377 ± 246, 8310 ± 932, and 9908 ± 1040 AU/ml, respectively). Only 67.3% of kidney transplant recipients, compared to 100% of donors and healthy volunteers, were positive for anti-S immunoglobulin G. Among the kidney transplant recipients, the anti-S titer was higher in younger recipients, those with higher peripheral blood lymphocyte counts and glomerular filtration rates, those without a history of antithymocyte globulin use, and those who had discontinued or received a reduced dose of mycophenolate mofetil. Younger age, higher lymphocyte count, glomerular filtration rate, and mycophenolate reduction were significantly associated with anti-S immunoglobulin G > 1000 AU/ml in nominal logistic regression analysis. There were no rejection episodes after mycophenolate modification in kidney transplant recipients.

Conclusions: Anti-S immunoglobulin G production after vaccination was attenuated in kidney transplant recipients. Mycophenolate mofetil cessation or reduction is a modifiable means to enhance anti-S immunoglobulin G production in immunosuppressed kidney transplant recipients.

Key words: antibody, kidney transplant, mycophenolic acid, SARS-CoV-2, vaccination.

INTRODUCTION

Organ transplant recipients have a relatively poor immune response to vaccination.[1] Given the need for immunosuppression, transplant recipients are at a high risk of infection since the coronavirus disease 2019 (COVID-19) pandemic.[2,3] Although recent retrospective studies have shown a reduced incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection after vaccination in solid organ transplant recipients,[4–7] breakthrough infection is possible and SARS-CoV-2 infection in transplant recipients is associated with high rates of morbidity and mortality. Thus, it is important to improve the effectiveness of vaccines against SARS-CoV-2 in this vulnerable population. We conducted a multicenter prospective observational study to identify factors associated with the effectiveness of the SARS-CoV-2 vaccine in kidney transplant recipients. In this study, factors associated with the acquisition of anti-S antibodies early after the second dose of the vaccine were identified in an interim analysis.

METHODS

One hundred and fifty-one kidney transplant recipients that were followed up at our institute, 50 health-care workers serving as healthy volunteer (HV) controls, and 74 live kidney donors serving as chronic kidney disease controls were enrolled in this study. Individuals with a history of previous SARS-CoV-2 infection or a positive anti-S (receptor binding domain) immunoglobulin G (IgG) result before the first vaccination were excluded. Over 95% of the participants received two doses of the BNT162b2 vaccine with an interval of 3 weeks between doses, and the rest received two doses of the mRNA-1273 vaccine with an interval of 4 weeks between doses.

There were two study parts. The first was a prospective cohort study, in which the anti-S IgG levels were compared among the three groups. Anti-S IgG was measured 1–6 months before the first dose and 4–8 weeks after the second dose of vaccine, using the SARS-CoV-2 IgG II QUANT assay (Abbott Japan LCC). Anti-S IgG levels <50, 50–1000, and ≥1000 AU/ml were defined as negative, weakly positive, and strongly positive, respectively.

In the second study, factors possibly affecting the anti-S IgG levels in the kidney transplant recipient group were retrospectively compared. All kidney transplant recipients were immunosuppressed with tacrolimus (TAC) and mycophenolate mofetil (MMF), with or without everolimus (EVR) or corticosteroids. Their immunosuppression was concentration controlled with periodic tests of the TAC area under the concentration-time curve ($AUC_{0–24h}$), mycophenolic acid (MPA) $AUC_{0–12h}$, and EVR trough level. The kidney transplant recipients were screened annually for the presence of donor-specific antibodies. Kidney transplant recipients were encouraged to inform their physicians of their vaccine schedule in advance, and the MMF dose was reduced for these participants around the time of vaccination to enhance the effectiveness of the vaccine, at the discretion of their attending physician using the criteria later described. However, 32 recipients did not notify their physicians about their vaccine schedule and they did not undergo MMF modification.

The following criteria for MMF dose modification, based on the latest TAC $AUC_{0–24h}$ and MPA $AUC_{0–12h}$ results, were used (Table 1):

1 In kidney transplant recipients who were ≤6 months post-transplant, with detectable donor-specific antibodies, or had biopsy-proven rejection within the previous year, MMF was suspended for 3 days, starting on the day of vaccination.
2 In kidney transplant recipients who were >6 months post-transplant and receiving TAC, MMF, and EVR, regardless of steroids, MMF was suspended for 7 days starting on the day of each vaccination if the TAC $AUC_{0–24h}$ was ≥100 ng·h/ml and for 3 days if the TAC $AUC_{0–24h}$ was <100 ng·h/ml, followed by a reduced dose for 3 weeks (80–100 ng·h/ml was the target TAC $AUC_{0–24h}$ level for the maintenance of immunosuppression in our institute and recipients with TAC-$AUC_{0–24h}$ > 100 ng·h/ml were considered to have room for longer MMF cessation).
3 In kidney transplant recipients who were ≥6 months post-transplant and receiving TAC and MMF without EVR, regardless of steroids, MMF was withheld for 3 days starting on the day of each vaccination and returned to the original dose thereafter if the MPA $AUC_{0–12h}$ was <30 μg·h/ml; if the MPA $AUC_{0–12h}$ was ≥30 μg·h/ml, suspension of MMF for 3 days was followed by a reduced dose for 2 weeks.
4 MMF reduction after cessation was based on the following doses: 500 to 250 mg/day, 1000–1500 to 500 mg/day, and >2000 mg/day to half the dose.

The rationale for the periods of cessation and reduction was as follows: The basal period for cessation was 3 days; this is because MMF has usually been withheld safely for 3 days during infections in general practice. In recipients on only TAC and MMF immunosuppression, MMF reduction after cessation was considered inadequate when MPA $AUC_{0–12h}$ was <30 μg·h/ml. When MPA levels were higher, MMF reduction was considered safe for 2 weeks. In recipients on TAC, MMF, and EVR immunosuppression, TAC and EVR levels were maintained at a sufficient level to prevent acute

TABLE 1 MMF dose modification based on patients' statuses

Recipient status	Immunosuppression	MMF cessation beginning on the vaccination day	MMF reduction after cessation
<6 months post-transplant	Any	3 days	None
Detectable donor-specific antibody		3 days	None
History of biopsy-proven rejection within 1 year		3 days	None
None of the above	TAC + MMF + EVR (regardless of steroids) TAC $AUC_{0–24h}$ ≥ 100 ng·h/ml	7 days	Until 3 weeks after each vaccine dose
	TAC + MMF + EVR (regardless of steroids) TAC $AUC_{0–24h}$ < 100 ng·h/ml	3 days	Until 3 weeks after each vaccine dose
	TAC + MMF (regardless of steroids, no EVR) MPA $AUC_{0–12h}$ ≥ 30 μg·h/ml	3 days	2 weeks
	TAC + MMF (regardless of steroids, no EVR) MPA $AUC_{0–12h}$ < 30 μg·h/ml	3 days	None

Abbreviations: AUC, area under the concentration-time curve; EVR, everolimus; MMF, mycophenolate mofetil; TAC, tacrolimus.

TABLE 2 Background characteristics of study participants

	Kidney transplant recipients (n = 151)	Kidney donors (n = 74)	Healthy controls (n = 50)	p value
Age (mean ± SD)	59.4 ± 14.1	65.8 ± 11.4	43.9 ± 8.9	<0.01*
Female sex (%)	30.5	75.8	74	<0.01*
Time since second vaccination (weeks, average mean ± SD)	5.3 ± 1.6	5.3 ± 1.9	5.1 ± 1.2	0.76*
Time since transplant (years, mean ± SD)	7.7 ± 4.1	NA	NA	NA
Maintenance immunosuppression (%) (TAC + MMF/TAC + MMF + EVR/others)	34/57/9	NA	NA	NA
Chronic steroid use (%)	27.2	NA	NA	NA
Pre-sensitized (%)	13.9	NA	NA	NA
Estimated glomerular filtration rate (%) (<30/30–45/>45 ml/min/1.73 m^2)	21/37/42	3/31/66	0/0/100	<0.01**
History of antithymocyte globulin (%)	15.2	NA	NA	NA
History of rituximab use (%)	37.7	NA	NA	NA
Lymphopenia (<1200/μl) (%)	33.8	0	NA	NA
MMF dose modification (%) (cessation + reduction/cessation only/no modification)	52/27/21	NA	NA	NA

Abbreviations: ANOVA, analysis of variance; EVR, everolimus; MMF, mycophenolate mofetil; NA, not applicable; SD, standard deviation; TAC, tacrolimus. *p values determined using ANOVA. **p value determined using a chi-squared test.

rejection. MMF has been used as an additional prevention of de novo donor-specific antibody production. Therefore, MMF reduction after cessation was considered safe (3-week reduction period was equivalent to an interval of two vaccination doses). When TAC exposure was high, MMF was considered safe to be discontinued for a longer period (7 days).

In this second study involving a retrospective analysis, anti-S IgG levels were compared according to the following factors in the univariate analysis: age, sex, peripheral blood lymphocyte count, MMF cessation with/without reduction, estimated glomerular filtration rate (eGFR), history of antithymocyte globulin (ATG) treatment, and history of rituximab (RIT) treatment, time since transplant, TAC trough levels ($TACC_0$), MPA AUC, EVR trough levels, and maintenance immunosuppression regimen (TAC + MMF vs. TAC + MMF + EVR). Finally, factors associated with anti-S IgG positivity were analyzed using nominal logistic regression analysis.

Statistical analyses were performed using JMP 14.0 (SAS Institute). Statistical comparisons were performed using chi-square tests for categorical variables, and ANOVA for continuous variables. In addition, independent sample t-tests were used for comparisons between two groups, Welch's test was used for comparisons between the three groups, and Wilcoxon rank-sum test was used for comparison between two groups in the three-group analyses. p values <0.05 were considered statistically significant. The digitized data are registered with Mendeley Data (https://doi.org/10.17632/jgd64pbz6j.1).

RESULTS

The demographics of the participants are summarized in Table 2. The average anti-S IgG levels 1 month after the second vaccination in the HV, kidney donor, and kidney transplant recipient groups were 9908 ± 1040, 8310 ± 932, and 1377 ± 246 AU/ml, respectively. Antibody production in the kidney transplant recipient group was significantly attenuated ($p < 0.01$). The antibody levels were negative, weakly positive, and strongly positive in 0%, 0%, and 100% of the HV group; 0%, 1.4%, and 98.6% of the kidney donor group; and 32.7%, 40.6%, and 26.7% of the kidney transplant recipient group, respectively.

In the kidney transplant recipient group, the anti-S IgG levels were significantly higher in younger recipients, who had a higher peripheral lymphocyte count and higher eGFR and had no history of ATG treatment and a history of MMF cessation plus subsequent dose reduction at the time of vaccination (Figure 1a–f). Univariate analyses revealed that the factors that significantly contributed to anti-S IgG positivity in kidney transplant recipients were female sex (51% in positive recipients vs. 31% in negative recipients), eGFR (45.4 ± 1.1 vs. 35.5 ± 1.8), $TACC_0$ (2.8 ± 1.1 vs. 3.3 ± 0.2), MMF cessation and dose reduction (60% vs. 31%), a history of ATG treatment (9% vs. 29%), and history of RIT treatment (31% vs. 53%).

Strong positivity was significantly associated with younger age (52.5 ± 2.0 in strongly positive recipients vs. 62.5 ± 1.3 in weakly positive or negative recipients), higher eGFR (47.1 ± 1.9 vs. 38.7 ± 1.2), higher lymphocyte count (1809 ± 113 vs. 1365 ± 71), MMF cessation and dose reduction (65% vs. 31%), and history of ATG treatment (4% vs. 20%).

In multivariate analyses, IgG positivity was significantly associated with MMF cessation and dose reduction (odds ratio [OR]: 3.78, 95% confidence interval [CI]: 1.59–9.01, $p = 0.003$), no history of ATG treatment (OR: 3.23, 95% CI: 1.02–10.22, $p = 0.046$), eGFR (OR: 16.1, 95% CI: 1.08–238.95, $p = 0.010$), and no history of RIT treatment (OR: 2.56, 95% CI: 1.06–6.17, $p = 0.036$) (Figure 1g). Strong IgG positivity was significantly associated with a lymphocyte count >1200/μl (OR: 13.72, 95% CI: 3.34–56.42, $p < 0.001$), MMF cessation and dose reduction (OR: 8.24, 95% CI: 2.77–24.45, $p < 0.001$), age < 50 years (OR: 5.19, 95% CI: 1.53–17.61, $p = 0.008$), and eGFR (OR: 47.9, 95% CI: 2.20–1044.93, $p = 0.010$) (Figure 1h).

There were no acute or chronic biopsy-proven allograft rejection cases after temporary cessation of MMF, with or without subsequent dose reduction.

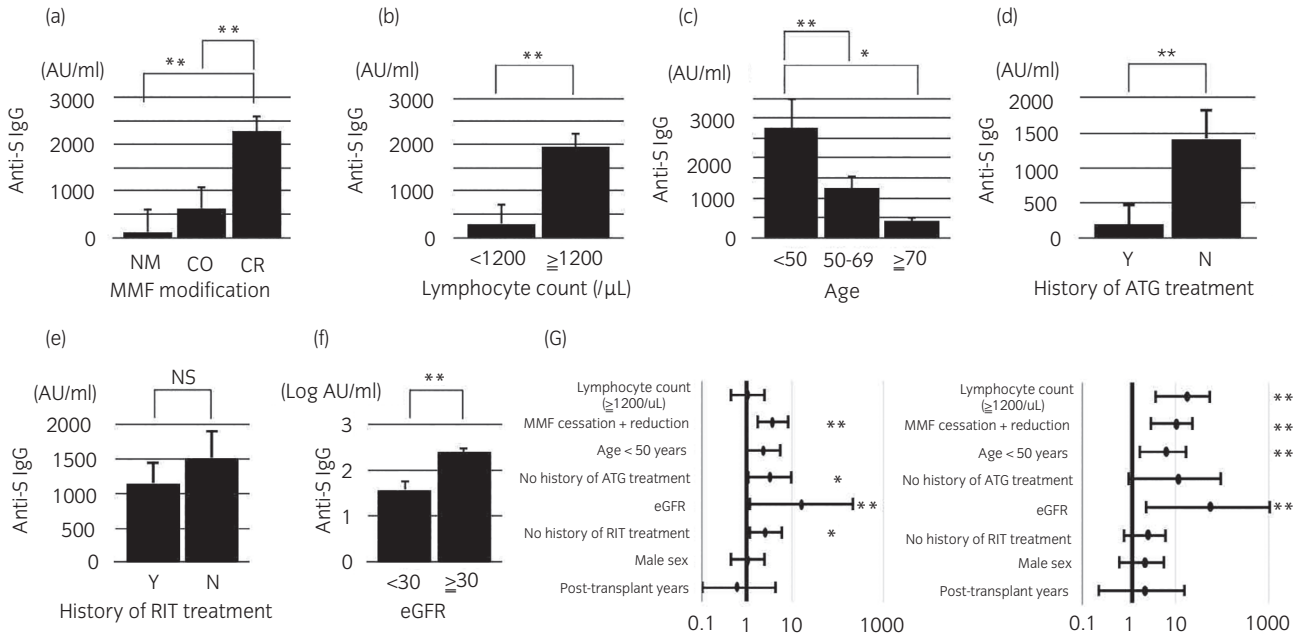

FIGURE 1 Differences in anti-receptor binding domain antibody titers among each factor in the kidney transplant recipient group. (a) Mycophenolate mofetil (MMF) modification. (b) Peripheral blood lymphocyte counts (/μl). (c) Age at second vaccination. (d) History of antithymocyte globulin (ATG) treatment, where Y = yes and N = no. (e) History of rituximab (RIT) treatment. (f) Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2). Statistical comparison was performed using independent sample *t*-tests for comparison between two groups, Welch's test for three groups, and Wilcoxon rank-sum test for comparison between two groups in the three-group analyses. (g, h) The results of logistic regression analysis for factors affecting positivity of anti-spike immunoglobulin G (anti-S IgG). (g) Odds ratio (closed circle) for positive anti-S IgG. MMF cessation, eGFR, history of ATG treatment, and history of RIT treatment were significantly associated with antibody positivity. The bars represent the 95% confidence interval. (h) Odds ratio for strong positivity (anti-S IgG level ≥ 1000 AU/ml). Lymphocyte count, MMF cessation + reduction, age, and eGFR were significant factors for strong positivity. *$p < 0.05$, **$p < 0.01$. ATG, antithymocyte globulin; CO, cessation only; CR, cessation + subsequent reduction; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; MMF, mycophenolate mofetil; NM, no modification; NS, not significant; RIT, rituximab.

DISCUSSION

Transplant recipients on immunosuppressant therapy show severely attenuated antibody production even after mRNA vaccines, which are highly effective in healthy individuals.[5,8] Significant morbidity and mortality related to SARS-CoV-2 infection have been reported in transplant recipients.[2,3] Nevertheless, the kidney transplant recipients in our study showed a wide variety of anti-S IgG production levels. Some of them showed robust production comparable to that in non-immunosuppressed individuals. Despite an impaired response to the vaccine in recipients, the proportion of kidney transplant recipients with negative results in this study was lower than that reported in previous studies.[8]

Most previous studies have only reported binary data of antibody positivity,[5,8] but post-vaccination antibody levels may be correlated with a virus-neutralizing ability or cellular immunity. Although it has been reported that anti-SARS-CoV-2 T-cell immunity can be detected after vaccination even in organ transplant recipients without detectable antibodies,[9] organ transplant recipients with weakly positive serology might have reduced immune responses insufficient to prevent diseases. Although the relationship between antibody levels and susceptibility to SARS-CoV-2 infection is unclear, anti-S antibody levels have been shown to correlate with neutralization activity in vitro.[9] Therefore, we analyzed the factors associated with the level of antibody production and categorized antibody levels as negative, weakly positive, and strongly positive. The cutoff for strong positivity was set at 1000 AU/ml because all participants in the HV group had antibody levels >1000 AU/ml. Notably, the factors associated with overall positivity and those associated with strong positivity differed. The absence of antibody treatment with ATG or RIT was significantly associated with overall positivity but not strong positivity. In contrast, a higher lymphocyte count was associated with strong positivity.

The kidney transplant recipients in this study had precise concentration control of TAC, MPA, and EVR doses, with levels measured at 6 months and 1, 2, 3, and 5 years after the transplant, and otherwise as necessary. This strategy enabled us to safely reduce immunosuppression and enhance the effectiveness of the SARS-CoV-2 vaccines. One-third of the kidney transplant recipients were on conventional immunosuppressive regimens consisting of TAC and MMF. The latter was withheld for only 3 days as per usual practice during episodes of infectious disease in general practice. Most of the other kidney transplant recipients were on TAC-based and EVR-based regimens plus additional MMF to prevent de novo donor-specific antibody production; MMF cessation for 7 days was safe in kidney transplant recipients on this triple-drug regimen. Although MMF withdrawal for prolonged period increases the risk of rejection and

deterioration of graft survival,[10] cessation of MMF for 3 to 7 days did not result in any rejection episode within the 6 months after the second vaccination. However, the limitation of this interim analysis is that the long-term effect on the production of de novo donor-specific antibodies is unclear and still under investigation in our ongoing study.

As expected, lower graft function, older age, and compromised immunity after depletive antibody treatment had a negative effect on vaccine-induced antibody production. Notably, temporary cessation and reduction of MMF was associated with significantly enhanced antibody production. Another recent study found that patients who received mTOR inhibitor-based immunosuppression showed better development of neutralizing antibodies and T-cell-mediated immune responses than patients who received MMF-based immunosuppression.[11] The results of this study suggest that the omission of MMF is more useful for enhancing antibody production than including an mTOR inhibitor in the immunosuppressive regimen. Another study on the humoral immune response after SARS-CoV-2 vaccination in kidney transplant recipients found that an MMF-free immunosuppression regimen was strongly associated with seroconversion. Furthermore, the negative effect of MMF on antibody development was dose-dependent and concentration-dependent.[12]

This study suggests that MMF dose modification could lead to improved response after vaccination. To our knowledge, this is the first study to show a favorable effect of MMF dose modification at the time of SARS-CoV-2 vaccination in kidney transplant recipients. Moreover, MMF dose modification has been reported to have a favorable effect on the immune response to the rabies vaccine.[13]

A recent report from Europe showed that serum samples from vaccine recipients 5 months after the second dose had very weak neutralizing activity on the Omicron variant using a neutralization assay, and that serum samples collected from vaccine recipients 1 month after a booster dose showed greater neutralization activity. However, the neutralization activity against the Omicron variant was much lower than that against the Delta variant.[14] A higher antibody titer is needed to protect against infection with the Omicron variant; thus, it is important to find ways to enhance antibody production in kidney transplant recipients. Approaches for achieving effective antibody production after additional doses of vaccine may also be important, and our strategy of MMF dose modification is useful in this regard. Furthermore, this strategy may effectively enhance the immune response to other currently used vaccines or vaccines that will be developed in the future against possible new variants of SARS-CoV-2 or other emerging pathogens in organ transplant recipients.

AUTHOR CONTRIBUTIONS

Masayoshi Miura: Conceptualization; methodology; investigation; formal analysis; writing – original draft. Maiko Fukumoto: Data curation; investigation. Natsumi Komatsu: Investigation. Reimi Shuto: Investigation. Hiroshi Harada: Review and editing. Hajime Sasaki: Project administration; Conceptualization; methodology; review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The protocol for this research project has been approved by the Sapporo Hokuyu Hospital Institutional Review Board (approval number 210408.02) and by Sapporo City General Hospital Ethical Committee (approval number R02-060-802), and it conforms to the provisions of the Declaration of Helsinki.

INFORMED CONSENT

Written consent was obtained from all participants.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

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