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Comparison of the Immune Response After an Extended Primary Series of COVID-19 Vaccination in Kidney Transplant Recipients Receiving Standard Versus Mycophenolic Acid–sparing Immunosuppressive Regimen

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Background. Two doses of coronavirus disease 2019 vaccination provide suboptimal immune response in transplant patients. Mycophenolic acid (MPA) is one of the most important factors that blunts the immune response. We studied the immune response to the extended primary series of 2 doses of AZD1222 and a single dose of BNT162b2 in kidney transplant patients who were on the standard immunosuppressive regimen compared to those on the MPA-sparing regimen. **Methods.** The kidney transplant recipients who were enrolled into the study were divided into 2 groups based on their immunosuppressive regimen. Those on the standard immunosuppressive regimen received tacrolimus (TAC), MPA, and prednisolone (standard group). The patients in the MPA-sparing group received mammalian target of rapamycin inhibitors (mTORi) with low dose TAC plus prednisolone (MPA-sparing group). The vaccination consisted of 2 doses of AZD1222 and a single dose of BNT162b2. **Results.** A total of 115 patients completed the study. There were 76 (66.08%) patients in the standard group and 39 (33.91%) patients in the MPA-sparing group. The overall median anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S antibody level at 4 wk after vaccine completion was 676.64 (interquartile range = 6.02–3644.03) BAU/mL with an 80% seroconversion rate. The MPA-sparing group achieved higher anti–SARS-CoV-2 S antibody level compared to the standard group (3060.69 and 113.91 BAU/mL, $P < 0.001$). The seroconversion rate of MPA-sparing and standard groups were 97.4% and 71.1%, respectively ($P < 0.001$). The anti-HLA antibodies did not significantly increase after vaccination. **Conclusions.** The extended primary series of 2 doses of AZD1222 and a single dose of BNT162b2 provided significant humoral immune response. The MPA-sparing regimen with mTORi and low dose TAC had a higher ant–SARS-CoV-2 S antibody level and seroconversion rate compared to the participants in the standard regimen.

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Coronavirus disease 2019 (COVID-19), a pandemic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has different clinical presentations, which range from no symptom to pneumonia and respiratory failure, resulting in high morbidity and mortality rates.[1,2] The risk of developing severe disease is high, especially in kidney transplant recipients who have to take immunosuppressive drugs to prevent graft rejection.[3,4] These immunosuppressive drugs do not only impair the natural immune response against infection but also diminish humoral and cellular-mediated immune responses to COVID-19 vaccination.[5,6]

Maintenance immunosuppressive regimens in kidney transplant recipients commonly include a calcineurin inhibitor (CNI) such as tacrolimus (TAC), an antimetabolite such as mycophenolic acid (MPA), and mammalian target of rapamycin inhibitors (mTORi) such as sirolimus. Currently, these medications are widely used in 2 combination regimens. First, the standard regimen consisted of TAC, MPA, and prednisolone. The second regimen, the CNI reduction regimen or also can be called as the MPA-sparing regimen, consisted of mTORi, low dose CNI, and prednisolone.[7] These immunosuppressive drugs are crucial in preventing donor-specific anti-HLA antibody (DSA) production and allograft rejection.

Previous observational studies conducted in kidney transplant recipient population have shown that 2 doses of mRNA, viral vector, or inactivated COVID-19 vaccines provided only suboptimal immunogenicity.[8-10] The vaccine response rate after 2 doses of mRNA vaccine was around 30%–60% in solid organ transplant recipients.[11,12] A third dose of mRNA vaccine can provide another 50% seroconversion among those patients who did not have an immune response to the first 2 doses of the mRNA vaccine.[13] Moreover, the vector-based vaccine yielded lower serological response compared to the mRNA vaccination.[14] Therefore, in August 2021, the US Food and Drug Administration authorized the administration of a third dose of SARS-CoV-2 mRNA vaccine to immunocompromised patients, including kidney transplant recipients.[13,15] Switching the types of vaccines used can improve the serological response in healthy and organ transplant patients.[16-18] In an observational study of solid organ transplant patients, a heterologous vaccination of 2 doses of AZD1222 with a single booster dose of BNT162b2 showed that the immune response was comparable to people who received 3 doses of mRNA vaccine.[19]

Most but not all previous studies showed that MPA, which inhibits the proliferation of both T and B cells is one of the most important factors that blunts the immune response.[8,9,20-24] Studies of comparing the immune response after receiving 3 doses of SARS-CoV-2 vaccine consisting of 2 doses of viral vector vaccines (AZD1222) followed by a single booster dose of mRNA vaccine (BNT162b2) between kidney transplant recipients who used MPA-sparing regimen (mTORi, low-dose TAC, and prednisolone) and the standard immunosuppressive regimen of TAC, MPA, and prednisolone have never been published.

In the present study, we prospectively examined the immune response of our kidney transplant recipients on either one of these 2 immunosuppressive regimens who received this heterogenous extended primary series of SARS-CoV-2 vaccine with 2 doses of AZD1222 and a single dose of BNT162b2. There is evidence that after the vaccination, there is an increase of anti-HLA antibody[25-27] and mRNA vaccine can induce very strong immunogenicity.[28] Therefore, we assessed the anti-HLA antibody, including panel-reactive anti-HLA antibody (PRA) and DSA before and after BNT162b2 vaccination.

MATERIALS AND METHODS

Study Design

This is a single-center, prospective, cohort study that was conducted at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand, from July 2021 to February 2022. At the time of the study, there was an outbreak of the delta variant. The inclusion criteria were kidney transplant recipients older than 18 y of age who underwent kidney transplantation for more than 6 mo with stable allograft function and were at least 6 wk on either one of the 2 immunosuppressive regimens, the standard regimen (TAC, MPA, and prednisolone) or the MPA-sparing regimen (mTORi, low dose TAC, and prednisolone). Kidney transplant recipients with active rejection or infection within 3 mo before screening or with a history of SARS-CoV-2 infection were excluded from the study.

Most of the enrolled patients were included in the ongoing ODKT trial (Thai clinical trial registry; TCTR20190228005) which is an open label, randomized clinical trial comparing the outcomes between standard immunosuppressive regimen (TAC, MPA, and prednisolone) and CNI reduction (mTORi, low dose TAC, and prednisolone, also called the MPA-sparing regimen). All of the patients in this ODKT trial were ABO-compatible kidney transplant recipients without preexisting or presence of DSA at the time of enrollment. Patients who did not participate in the ODKT trial have been selected to receive immunosuppressive regimens based on many reasons such as risk of rejection, history of cytomegalovirus, or polyomavirus (BK) infection, and CNI nephrotoxicity proven by surveillance allograft biopsy.

Immunosuppressive Regimens

The standard immunosuppressive regimen consists of TAC (Prograf or Advagraf, Astellas, Tokyo, Japan) with a trough level of 4–7 ng/mL, MPA (mycophenolate mofetil [MMF], Cellcept, Roche, Basel, Switzerland; or enteric-coated mycophenolate sodium, Myfortic, Novartis, Basel, Switzerland) 1000–1500 mg/day, and prednisolone (standard group). The MPA-sparing regimen comprised mTORi (sirolimus, Rapamune, Pfizer, New York, NY; or everolimus, Certican, Novartis, Basel, Switzerland) with a trough level of 5–10 ng/mL, low dose TAC (Prograf or Advagraf, Astellas, Tokyo, Japan) with a trough level of 2–4 ng/mL, and prednisolone (MPA-sparing group). The immunosuppressive regimens were not

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changed for at least 6 wk before entering the study and continued throughout the study period. The trough level of TAC, everolimus, and sirolimus were measured every 1–3 mo in every outpatient follow-up visit.

COVID-19 Vaccination and Anti-spike Testing

Patients were randomly tested for baseline anti–SARS-CoV-2 S antibody to screen for unrecognized asymptomatic COVID-19 infection before entering the study. Forty-four patients were tested and none of them had anti–SARS-CoV-2 S antibody.

After enrollment, 2 doses of AZD1222 (AstraZeneca, Cambridge, United Kingdom) were administered 12 wk apart. Four weeks after receiving 2 doses of AZD1222, a full single dose of BNT162b2 (Pfizer, New York, NY) was administered to all recipients. Blood was collected at 4 wk after 2 doses of AZD1222 were administered, and at 4 wk after BNT162b2 was administered. The blood samples were tested for anti–SARS-CoV-2 S antibody level (Elecsys, by Cobas e 411 analyzer; Roche Diagnostics, Basel, Switzerland). According to the cut-off index of the test, anti–SARS-CoV-2 S antibody level ≥ 0.823 binding antibody units (BAU)/mL was considered reactive or seroconverted. Patients were screened for COVID-19 symptoms. The risk factors were assessed from questionnaires and medical history of the patients at every visit. Patients who had either symptomatic or asymptomatic COVID-19 infection during the study period, which was confirmed by a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR), were excluded from the study.

After all patients were vaccinated, they were required to remain in the waiting area for observation for 30 min. All serious side effects were reported directly to their transplant nurse coordinator or nephrologist.

Anti-HLA Antibody, PRA, and DSA

The anti-HLA antibody was evaluated in all participants by solid phase (Luminex bead-based assays) before and 4 wk after receiving BNT162b2. PRA was calculated using Luminex phenotype beads. DSA was determined by matching between anti-HLA antibody and donor HLA typing using a molecular method.

Statistical Analyses

Categorical data were presented as counts and percentages. Continuous data were presented as mean ± SD or median and interquartile range (IQR) as appropriate. The differences between the groups were tested using Chi-square test for categorical data and independent *t* test or one-way ANOVA for continuous data. Antibody levels were log-transformed before *t*-test due to non-Gaussian distribution of the data. All analyses and visualizations were performed using GraphPad Prism version 9.0 for Windows (GraphPad Software, San Diego, CA) and SPSS statistical analysis package (version 28.00; SPSS Inc, Chicago, IL).

Ethical Approval

All participants provided written informed consent prior to their enrollment in this study and medical records were thoroughly reviewed. The study was approved by the Institutional Review Board of the Research Ethics Review Committee for Research Involving Human Research Participants, Health Sciences Group, Chulalongkorn University (Institutional Review Board number 477/64), and was conducted according to the Declaration of Helsinki 1983. The study was registered in the Thai Clinical Trials Registry (TCTR20220402001).

RESULTS

Baseline Characteristics

A total of 138 kidney transplant recipients were enrolled, of which 19 patients did not complete the 3 doses of the vaccination. There were 4 patients who developed SARS-CoV-2 infection, which was confirmed by polymerase chain reaction (PCR) before completing the study (Figure 1). Therefore, 115 patients completed the study, of which 39 (33.91%) and 76 (66.08%) patients were in the MPA-sparing and standard groups, respectively. The mean age (± SD) of the recipients was 50.65 ± 11.40 y, which was not different between the

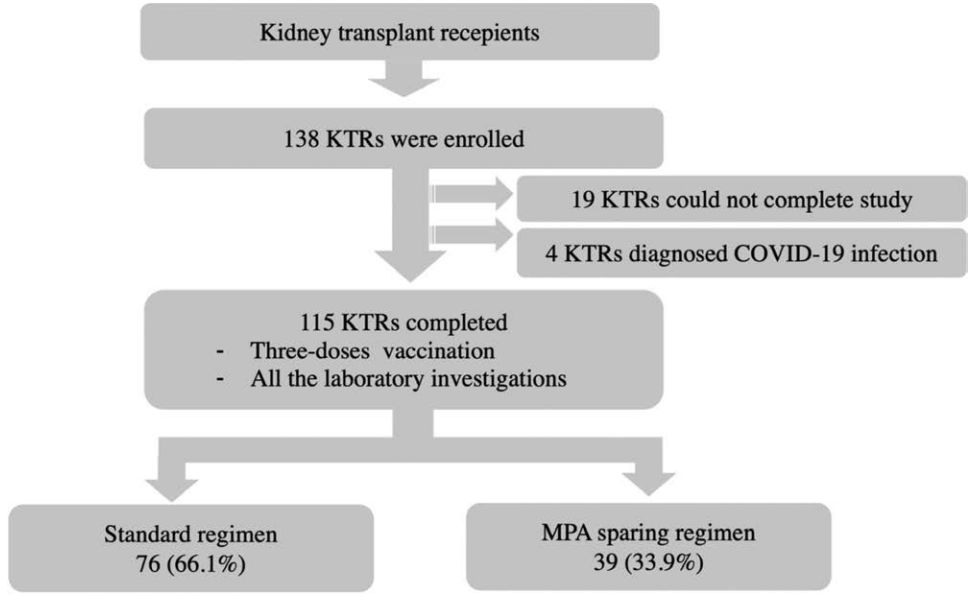

FIGURE 1. Flow diagram of the study participants. COVID-19, coronavirus disease 2019; KTR, kidney transplant recipient; MPA, mycophenolic acid.

2 groups (Table 1). The mean (±SD) transplant vintage of the standard and the MPA-sparing groups were 6.13 ± 5.68 y and 6.52 ± 4.21 y (P = 0.122), respectively. There were lower proportion of female recipients in the MPA-sparing group (35.8%) compared to the standard group (55.2%) (P = 0.049). The mean PRA (±SD) of the standard group was higher than the MPA-sparing group (11.74 ± 3.06% and 1.41 ± 0.81%, P < 0.001). The mean (±SD) total white blood cell counts was comparable between the 2 groups. However, the lymphocyte count of the MPA-sparing group was higher than the standard group (2332.10 ± 1235.91 cells/μL and 1899.55 ± 1284.59 cells/μL, respectively, P = 0.043).

Postvaccination Anti–SARS-CoV-2 S Antibody and Seroconversion Rate

The median anti–SARS-CoV-2 S antibody level 4 wk after 2 doses of AZD1222 was 8.85 (IQR = 00.00–180.81) BAU/mL and significantly increased to 676.64 (IQR = 6.02–3644.03) BAU/mL at 4 wk after receiving BNT162b2 (Table 2 and Figure 2). The overall seroconversion rates were 69.6% after receiving 2 doses of AZD1222 and 80% after receiving BNT162b2 (Table 3).

The MPA-sparing group had a higher anti–SARS-CoV-2 S antibody level after receiving AZD1222 and higher anti–SARS-CoV-2 S antibody level after receiving BNT162b2 compared to the standard group (Table 2 and Figure 3). The seroconversion rate after receiving 3 doses of the vaccines was 97.4% in the MPA-sparing group and 71.1% in the standard group. The anti–SARS-CoV-2 S antibody level among the MPA-sparing group was higher than the standard group (P < 0.001, Table 3 and Figure 4).

We also evaluated the seroconversion rate after receiving the third dose of BNT162b2 in 35 patients who had negative anti–SARS-CoV-2 S antibody after receiving 2 doses of AZD1222. Twelve (34.3%) patients have seroconverted after receiving the third dose; 7 of 8 (87.5%) patients from the MPA-sparing group and 5 of 27 (18.5%) patients from the standard group seroconverted (P < 0.001, Table 3).

Anti-HLA Antibody, PRA, and DSA

The anti-HLA antibody was measured before and 4 wk after receiving BNT162b2. Eleven of 115 patients were positive for anti-HLA antibody (PRA > 0%) before BNT162b2 vaccination (10 patients were in the standard group and one patient was in the MPA-sparing group), of which 4 patients had DSA and all of them were in the standard group (**Table S1, SDC**, http://links.lww.com/TXD/A467). None of the patients developed de novo DSA after BNT162b2 vaccination. Out of 104 patients, one patient was negative for anti-HLA antibody after receiving 2 doses of AZD1222 but later developed anti-HLA antibody after receiving BNT162b2.

Safety and Efficacy During the Follow-up Period

There were no serious local or systemic adverse events such as bruising, bleeding, chest discomfort, severe headache, vomiting, seizure, or stroke-like symptoms, within 30 min after each vaccination. During a 3-mo follow-up period, 7 (6.1%) of 115 patients developed COVID-19 infection of which 2

TABLE 1.

Baseline characteristics of the patients who received all three doses of the coronavirus disease 2019 vaccines

Baseline characteristics	Total (N = 115)	Standard regimen TAC + MPA + prednisolone (n = 76; 66.09%)	MPA-sparing regimen mTORi + low TAC + prednisolone (n = 39; 33.91%)	*P*
Age, mean ± SD, y	50.65 ± 11.40	50.49 ± 11.28	50.95 ± 11.78	0.720
Female sex, n(%)	56 (48.7)	42 (55.2)	14 (35.8)	0.049
Deceased donor KT, n (%)	69 (60)	46 (60.5)	23 (58.9)	0.872
Living donor KT, n (%)	46 (40)	30 (39.4)	16 (41.0)	
HLA mismatch, mean (±SD)	2.74 (±1.56)	2.91 (±0.18)	2.41 (±0.21)	0.427
PRA, mean (±SD), %	8.23 (±22.35)	11.74 (±3.06)	1.41 (±0.81)	<0.001
Previous KT, n (%)	3 (2.6)	0 (0)	3 (2.6)	0.203
Induction, ATG; IL-2 receptor antagonist; no induction, n (%)	96(83.5); 15 (13.0); 4 (3.5)	60 (78.9); 14 (18.4); 2 (2.6)	36 (92.3); 1 (2.6); 2 (5.1)	0.180
Time after transplantation, mean ± SD, y	6.26 ± 5.34	6.13 ± 5.86	6.52 ± 4.21	0.122
SBP, mean ± SD, mm Hg	129.16 ± 16.66	129.78 ± 17.52	127.95 ± 14.71	0.336
DBP, mean ± SD, mm Hg	76.71 ± 10.88	76.13 ± 11.24	77.85 ± 10.18	0.964
Cr, mean ± SD, mg/dL	1.35 ± 0.71	1.36 ± 0.74	1.33 ± 0.65	0.979
eGFR, mean ± SD, mL/min/1.73 m^2	63.56 ± 18.48	61.48 ± 18.37	67.61 ± 18.25	0.911
Albumin, mean ± SD, g/dL	4.25 ± 0.27	4.25 ± 0.26	4.25 ± 0.28	0.862
Hb, mean ± SD, mg/dL	12.78 ± 1.91	12.51 ± 1.92	13.30 ± 1.81	0.785
White blood cells, mean ± SD, cells/μL	6521.21 ± 2152.17	6048.67 ± 2054.49	7442.05 ± 2061.03	0.551
Neutrophil, mean ± SD, cells/μL	3889.77 ± 1376.96	3739.87 ± 1437.80	4181.90 ± 1214.64	0.805
Lymphocyte, mean ± SD, cells/μL	2047.60 ± 1279.38	1899.55 ± 1284.59	2332.10 ± 1235.91	0.043
Platelets, mean ± SD, per μL	225 147.83 ± 62 592.702	221 855.26 ± 65 857.36	231 564 ± 55 940.66	0.109
C_{trough} TAC, mean ± SD, ng/mL	4.60 ± 1.59	5.32 ± 1.27	3.02 ± 0.95	0.215
C_{trough} mTORi, mean ± SD, ng/mL	8.38 ± 2.04	N/A	8.38 ± 2.04	N/A
Prednisolone, mean ± SD, mg/d	3.97 ± 1.01	4.01 ± 0.88	3.95 ± 1.01	0.74

ATG, anti-thymocyte globulin; Cr, creatinine; C_{trough}, trough level; DBP, diastolic blood pressure at first visit; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IL-2, interleukin-2; KT, kidney transplantation; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; PRA, panel-reactive anti-HLA antibody; SBP, systolic blood pressure at first visit; TAC, tacrolimus.

TABLE 2.

Anti–SARS-CoV-2 S antibody after vaccination in standard group (TAC + MPA + prednisolone) and MPA-sparing group (mammalian target of rapamycin inhibitor + low TAC + prednisolone)

	Anti–SARS-CoV-2 S antibody, BAU/mL						
	Total (N = 115)		Standard group (n = 76)		MPA-sparing group (n = 39)		
Vaccination	Median	IQR	Median	IQR	Median	IQR	*P*
Post AZD1222	8.85	00.00–180.81	2.96	0.00–50.84	125.30	4.47–567.69	0.025
Post BNT162b2	676.64	6.02–3644.03	113.91	0.00–1216.04	3060.69	1546.39–11 503.08	<0.001
P	<0.001		<0.001		<0.001		

BAU, binding antibody unit; IQR, interquartile range; MPA, mycophenolic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TAC, tacrolimus.

(5.1%) were in the MPA-sparing group and 5 (6.6%) patients were in the standard group (**Table S2, SDC**, http://links.lww.com/TXD/A467). One of the 5 patients in the standard group who had no seroconversion after receiving 3 doses of the vaccines experienced mild pneumonia while the remaining 4 patients only presented with upper respiratory tract symptoms. None had serious COVID-19 infection. There were no morbidity and mortality in this cohort.

DISCUSSION

The results in the present prospective study demonstrated that the overall seroconversion rate of the extended primary series of 2 doses of AZD1222 followed by a single dose of BNT162b2 in kidney transplant recipients was 80%. The MPA-sparing immunosuppressive regimen group had a higher seroconversion rate compared to the standard regimen group (Table 3). The MPA-sparing regimen group had a higher anti–SARS-CoV-2 S antibody level compared to the standard regimen group. The seroconversion rate of only the third dose of BNT162b2 was 34.3% of which 87.5% were from the MPA-sparing regimen group and 18.5% were from the standard group. In the standard group, the baseline PRA was higher. However, the anti-HLA antibody, PRA, and DSA of both groups remained unchanged after receiving BNT162b2. Seven of 115 patients experienced SARS-CoV-2 infection after completing the vaccination. Only one patient had mild pneumonia.

Immunization is crucial for posttransplant recipients especially in the COVID-19 era. Many vaccines, including COVID-19 vaccine, yielded poor response in immunocompromised and kidney transplant recipients.[5,15,29] The third dose of mRNA

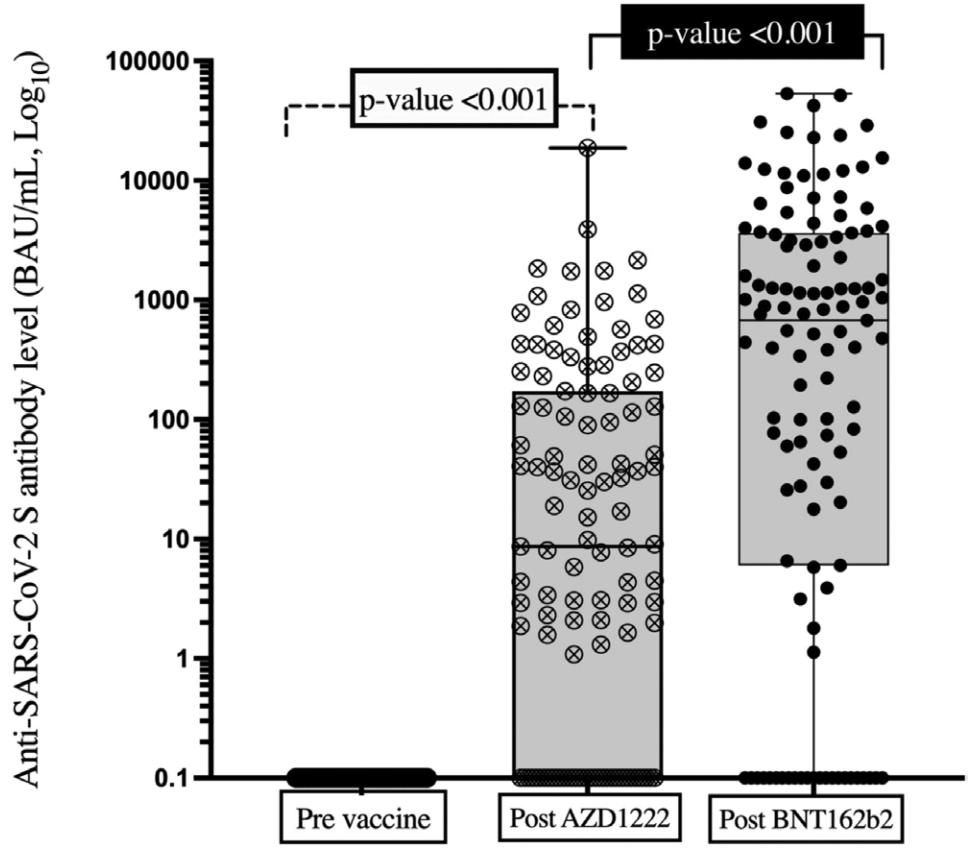

FIGURE 2. The median, interquartile range (box), and range (whisker) of anti–SARS-CoV-2 S antibody level after vaccination with 2 doses of AZD1222 and a single dose of BNT162b2 in a total of 115 patients. BAU, binding antibody unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 3.

Comparison of the seroconversion rate between the standard and MPA-sparing groups after receiving two doses of AZD1222 and a single dose of BNT162b2 in all patients as well as in patients without seroconversion after AZD1222 administration

	Positive for anti–SARS-CoV-2 S antibody			
Vaccination	Total, n(%)	Standard group, n(%)	MPA-sparing group, n(%)	*P* (χ^2test)
Post AZD1222	80 of 115 (69.6)	49 of 76 (64.5)	31 of 39 (79.5)	0.098
Post BNT162b2	92 of 115 (80)	54 of 76 (71.1)	38 of 39 (97.4)	<0.001
Post BNT162b2 in AZD1222 nonseroconversion	12 of 35 (34.3)	5 of 27 (18.5)	7 of 8 (87.5)	<0.001

MPA, mycophenolic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

COVID-19 vaccine improved immune response compared to the standard 2 doses.[13,15,30,31] The heterologous COVID-19 vaccination with vector-based and mRNA vaccines improved the immune response in transplant recipients.[32,33] The priming with vector-based vaccine prior to mRNA vaccination might result in higher SARS-CoV-2-specific CD4 and CD8 T-cell levels in healthy individual compared to mRNA vaccination alone.[32] However, the distinction of these cellular immunity activation between vector-based and mRNA vaccines could not be demonstrated in the organ transplant patients.[32] Further studies are needed to understand the mechanism of the immune response to heterologous vaccination in transplant recipients. The present study demonstrated the efficacy of this extended primary series of 3 doses of heterologous vaccination, which had an 80% seroconversion rate compared to previous homologous vaccination using 3 doses of mRNA regimen. The 3-doses homologous vaccination had a seroconversion rate between 62.3% and 68.0%.[13,34,35]

Immunosuppressive drugs have been considered as the major factor that blunt the immune response; MPA is the most recognized agent to reduce immune response to vaccination.[8,20-23] The present prospective cohort study enrolled patients on standard and MPA-sparing regimens. We found that patients from the MPA-sparing regimen group had significantly higher seroconversion rate (97.4% versus 71.1%) and median anti–SARS-CoV-2 S antibody level (3060.69 BAU/mL versus 113.91 BAU/mL) compared to the standard group. A study from Osmanodja et al had similar results.[24] Patients with reduced MPA dose or had temporary stopped using MPA during the fourth dose of the vaccination provided better immune response compared to patients with unchanged MPA dose.[24] There were 2 recent studies published comparing the immune response between CNI + MPA and CNI + mTORi.[36,37] However, there were some differences in the levels of the immunosuppressive drugs between the present study and the 2 previous studies. In addition, the protocol of

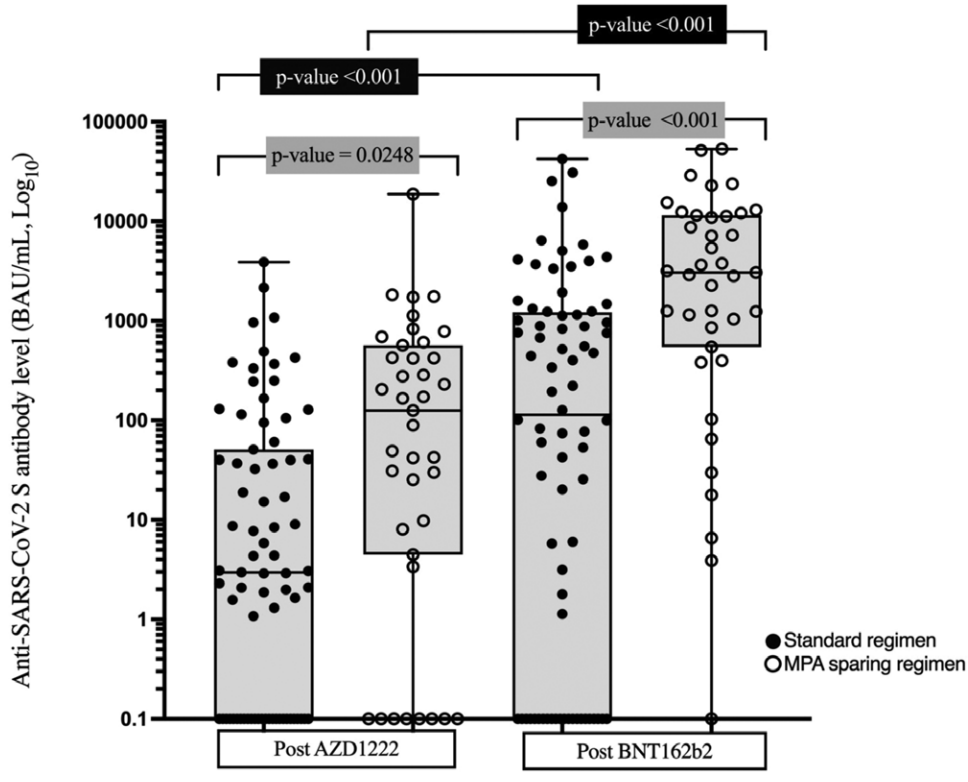

FIGURE 3. The median, interquartile range (box), and range (whisker) of anti–SARS-CoV-2 S antibody level after vaccination with 2 doses of AZD1222 and single dose of BNT162b2 in the standard group vs MPA-sparing regimen group. BAU, binding antibody unit; MPA, mycophenolic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

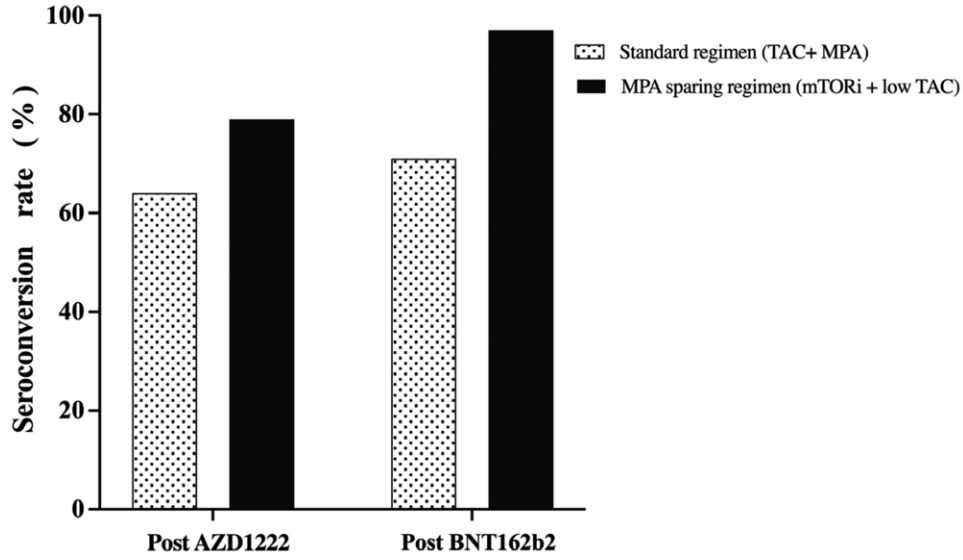

FIGURE 4. The seroconversion rate (%) after 2 doses of AZD1222 and single dose of BNT162b2 in the standard group and MPA-sparing regimen group. MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; TAC, tacrolimus.

vaccination for both previous studies was 2 doses of mRNA vaccine. A study from Netti et al showed that recipients who received 2 doses of BNT162b2 and were on immunosuppressive regimen of TAC (trough level 5–7 ng/mL) + everolimus (trough level 3–5 ng/mL) + prednisolone had a higher anti–SARS-CoV-2 IgG, higher percentages of anti–SARS-CoV-2 S1/RBD Ig, and SARS-CoV-2-specific T cell–derived IFN-γ release compared to the standard regimen group of TAC (5–7 ng/mL) + MMF (1000 mg/day) + prednisolone.[36] A randomized study conducted by de Boer et al compared the immune response between 16 patients on TAC (5–8 ng/mL) + MMF (1000 mg/day) + prednisolone and 16 patients on low dose TAC (1.5–4 ng/mL) + everolimus (3–6 ng/mL) + prednisolone; SARS-CoV-2 anti-spike receptor binding domain IgG antibody level after receiving 2 doses of mRNA vaccine was significantly higher in the low dose TAC + everolimus + prednisolone group.[37] However, there were no differences in the T-cell response to SARS-CoV-2 in both subgroup of patients who had tested for T-cell response.[37] These findings support the benefit of MPA-sparing regimen in both humoral and cellular immune responses to vaccination.

The difference in lymphocyte counts between the 2 groups may contribute to the difference in the immune response to vaccination.[38] The lower lymphocyte count of the standard group may lead to lower anti–SARS-CoV-2 S antibody level. The difference in white blood cell numbers between the 2 immunosuppressive regimens has been previously reported in the randomized control trials.[39,40] A higher incidence of leukopenia has been found in the MPA with CNI group.

The present study also found that none of the previously anti-HLA antibody negative patients developed anti-HLA antibody during the follow-up period. Moreover, the PRA levels in anti-HLA antibody positive patients remained stable without developing any DSA. This finding shows that this vaccination strategy was safe among patients using different immunosuppressive regimens. This vaccine strategy is also effective. Only one out of 115 patients developed mild COVID-19 pneumonia.

There were certain strengths in the present study. The 2 specific immunosuppressive regimens used in this study were strictly controlled for target C_{trough} level. Because the low intensity immunosuppression can lead to de novo DSA, our study monitored for anti-HLA antibody, PRA, and DSA. We found that there were no elevated levels of anti-HLA in our transplant patients. More than one-third of our patients were randomly tested for unrecognized asymptomatic COVID-19 infection by screening for anti–SARS-CoV-2 S antibody prior entering the study. Furthermore, the patients who had COVID-19 infection during the study were also excluded from the final analysis. As a result of this, we were able to minimize the confounder of anti–SARS-CoV-2 S antibody level. Admittedly, there were some limitations in the present work. This study only measured the anti–SARS-CoV-2 S antibody level. However, it has been shown that anti–SARS-CoV-2 S antibody level together with neutralizing antibody could prevent the acquisition of SARS-CoV-2 infection and had a good correlation.[41] As one-third of the patients have been screened for anti–SARS-CoV-2 S antibody before entering the study, we should keep in mind that two-thirds of the patients may acquire asymptomatic COVID-19 infection before enrollment. Since vaccination against COVID-19 infection is crucial for our vulnerable transplant patients during the outbreak, we used the cohort study design instead of the randomized controlled study, in which patients may require a washout period of the immunosuppressive regimen before vaccination. Further studies of immunosuppressive regimen switching from the standard TAC with MPA to mTORi with low dose TAC during immunization should be conducted. As the PRA of the MPA-sparing group was lower, long-term administer of the regimen in high immunological risk patients cannot be recommended. The long-term efficacy and outcome of the heterologous vaccination and the MPA-sparing regimen should be further studied.

CONCLUSIONS

The present study demonstrated the efficacy and safety of the extended primary series of the 2 doses of AZD1222 and a single dose of BNT162b2 vaccination in kidney transplant recipients. The MPA-sparing regimen (mTORi, low dose

TAC, and prednisolone) provides favorable humoral immune response. Studies with a greater number of patients and randomized controlled studies should be carried out in the future to confirm the benefit of the regimen.

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