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BRIEF COMMUNICATION

Immune response to third SARS-CoV-2 vaccination in seronegative kidney transplant recipients: Possible improvement by mycophenolate mofetil reduction

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Abstract

Modification of vaccination strategies is necessary to improve the immune response to SARS-CoV-2 vaccination in kidney transplant recipients (KTRs). This multicenter observational study analyzed the effects of the third SARS-CoV-2 vaccination in previously seronegative KTRs with the focus on temporary mycophenolate mofetil (MMF) dose reduction within propensity matched KTRs. 56 out of 174 (32%) previously seronegative KTRs became seropositive after the third vaccination with only three KTRs developing neutralizing antibodies against the omicron variant. Multivariate logistic regression revealed that initial antibody levels, graft function, time after transplantation and MMF trough levels had an influence on seroconversion ($P < .05$). After controlling for confounders, the effect of MMF dose reduction before the third vaccination was calculated using propensity score matching. KTRs with a dose reduction of ≥33% showed a significant decrease in MMF trough levels to 1.8 (1.2–2.5) μg/ml and were more likely to seroconvert than matched controls ($P = .02$). Therefore, a MMF

Jörg Timm and Johannes Stegbauer contributed equally to this study.

dose reduction of 33% or more before vaccination is a promising approach to improve success of SARS-CoV-2 vaccination in KTRs.

KEYWORDS
antiproliferative agent: mycophenolate mofetil (MMF), dysfunction, immunosuppressant, kidney (allograft) function, vaccine

1 | INTRODUCTION

Vaccination against SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) is the most important and efficient strategy for preventing severe courses of COVID-19 infection.[1–3] However, antibody levels decline within months after vaccination[4,5] which is one of the main factors responsible for lower protection against novel virus variants.[6] Susceptible patients' groups such as kidney transplant recipients (KTRs) demonstrate lower peak antibody values and faster antibody waning compared to the general population.[7–9] To overcome this immunological deficit, intensified vaccination schedules are recommended. Despite this, seroconversion rates remain in a range between 25 and 50%,[10,11] leaving still a large part of KTRs without adequate protection. One of the main factors interfering with the vaccine response is immunosuppressive treatment, especially the use of mycophenolate mofetil (MMF) and belatacept.[7,12,13] In this prospective multicenter observational study, we aimed to determine whether MMF reduction is associated with improved immune response to the third SARS-CoV-2 vaccination.

2 | METHODS

A total of 174 seronegative KTRs after receiving two doses of either BNT162b2 (Biontech/Pfizer) or mRNA-1273 (Moderna) were included in this prospective multicenter observational study (NCT04743947). Study design is presented in Figure S1. Results of the immune response to two vaccine doses have been published previously.[7,14] KTRs included in the study had to be older than 18 years, without previous COVID-19 infection, and able to give informed consent for participation. All KTRs had no signs or history of acute graft rejection within the last 6 months. The study was approved by the ethics committee of the Medical Faculty at the Heinrich-Heine University, Düsseldorf, Germany (study number 2020-1237) and in line with the Declaration of Helsinki, as revised in 2013.

2.1 | Third vaccination against SARS-CoV-2

One hundred and forty eight (85%) patients received a full dose of BNT162b2 (Biontech/Pfizer), nineteen (11%) patients ChAdOx1 (AstraZeneca) and seven (4%) patients Ad26.COV2.S (Johnson & Johnson). The time interval between the second and the third vaccine dose was 76±25 days. Immune response was measured 22±7 days (interquartile range between 19 and 23 days) after the third vaccination. At the visits data on medication and laboratory parameters were obtained from medical records.

2.2 | Identification of MMF reduction group

Due to the low immune response rate in KTRs following two SARS-CoV-2 vaccinations and growing evidence that the intensity of MMF therapy negatively affects humoral response rates, in selected cases and when approved by the patient, recommendation to reduce the MMF dose 3 weeks prior to and until 1 week after the third vaccination was given. According to this recommendation, we identified a group of 24 KTRs with MMF dose reduction before the third vaccination (Table 1). In detail, there were eight (33.3%) patients with 50% dose reduction, nine (37.5%) patients with 33% dose reduction and seven (29.2%) patients with 25% dose reduction. After controlling for baseline confounding factors such as antibody levels after the second vaccination, renal graft function, and MMF trough level (Table S2), we have estimated propensity scores for 174 patients who received the third SARS-CoV-2 vaccine dose. These scores were used to match 24 pairs with and without MMF reduction prior to the third vaccination. The representable matches were similar with respect to age, immunosuppression regime, MMF dose and trough levels before reduction, renal graft function, and initial antibody levels (Table 1). Based on the medical records, the immunosuppressive therapy was not significantly changed in any of the KTRs without MMF reduction. MMF trough levels were measured using high-performance liquid chromatography (HPLC). There were 3/24 patients with MMF reduction and 5/24 KTRs without MMF dose reduction taking coated enteric MMF formulation. There were no differences in MMF trough levels among these patients.

2.3 | Evaluation of humoral response

All samples were tested for IgG antibodies against SARS-CoV-2 spike S1 subunit using Anti-SARS-CoV-2-QuantiVac-ELISA (Euroimmun AG, Lübeck, Germany) as well as for SARS-CoV-2 neutralization efficacy (NT) in a BSL-3 facility at the Institute of Virology, University Hospital Düsseldorf, Germany. Antibody levels above ≥35.2 BAU/ml were considered as positive. In addition to antibody level measurement, an endpoint dilution neutralization test with the infectious SARS-CoV-2 B.1 (Wuhan Hu-1, GISAID accession ID: EPI_ISL_425126), SARS-CoV-2

TABLE 1 Characteristics of propensity matched groups with and without MMF dose reduction prior the third vaccination against SARS-CoV-2

Parameter	MMF reduction ($N = 24$)	No MMF reduction ($N = 24$)
Age, year	63 ± 10	60 ± 15
M:F	17:7	17:7
Antibody level (after 2nd vaccine), BAU/ml	0	0
Antibody level (after 3rd vaccine), BAU/ml	8.4 (0–46.8)	0 (0–5.2)*
Seroconversion after 3rd vaccine, N	7 (29%)	1 (4%)*
Time after transplantation, months	30 (21–68)	29 (15–45)
Creatinine (before 2nd vaccine), mg/dl	1.5 (1.1–1.9)	1.6 (1.2–2.1)
eGFR, (before 2nd vaccine) ml/min/1.73m^2	47 (37–60)	45 (30–57)
Creatinine (before 3rd vaccine), mg/dl	1.5 (1.1–2.0)	1.6 (1.2–2.2)
eGFR, (before 3rd vaccine) ml/min/1.73m^2	47 (36–63)	45 (30–56)
MMF trough level, μg/ml (before reduction)	2.9 (1.7–4.0)	2.8 (1.6–4.4)
MMF trough level, μg/ml (after reduction)	2.1 (1.4–2.6)	3.2 (2.2–4.8)*
Tacrolimus concentration, ng/ml	5.4 (5.0–6.3)	5.7 (4.6–6.3)
Immunosuppression		
• CNI	24 (100%)	24 (100%)
• Steroid	23 (96%)	23 (96%)
• Triple therapy	21 (88%)	21 (88%)
• MMF (before reduction)		
.5 g/d	0 (0%)	1 (4%)
1 g/d	7 (29%)	6 (25%)
1.5 g/d	9 (37%)	9 (38%)
2 g/d	8 (33%)	8 (33%)
• MMF (after reduction)		
.5 g/d	6 (25%)	1 (4%)
1 g/d	11 (42%)	6 (25%)
1.5 g/d	7 (46%)	9 (38%)
2 g/d	0 (0%)	8 (33%)

Following variables have been included into matching process: creatinine concentration, MMF trough level, initial antibody level and time after the transplantation. Match tolerance was set to .05. Seroconversion was defined as IgG antibody level against SARS-CoV-2 spike S1 subunit ≥35.2 BAU/ml. Dichotomous data are presented as percentages whereas continuous data as means ± SD or median (Q1 – Q3). *** represent significant difference between the groups with $P < .001$, ** $P < .01$, * $P < .05$ using unpaired t – test, Chi-square test or Mann Whitney test.
Abbreviations: eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor.

B1.617.2 (delta variant, GISAID accession ID:EPI_ISL_4471555) and SARS-CoV-2 B.1.1.529 (omicron variant, GISAID accession ID: EPI_ISL_12813299.1) isolates at a tissue culture infectious dose (TCID) 50 of 100 was performed as described previously.[15]

2.4 | Data analysis

Statistical analysis was performed using SPSS version 23 (SPSS Inc., Chicago, USA) and Graph Prism 8 (GraphPad Software, San Diego, USA). Shapiro–Wilk normality test was used to assess if data was normally distributed. Accordingly, continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range expressed as two numbers, Q1–Q3, respectively. Categorical variables are expressed as numbers (percentages). The differences between the groups were assessed using Chi-square, unpaired t-test, Mann-Whitney test or Kruskal-Wallis test. Multivariate logistic regression using backward elimination was used for indicating variables associated with a positive immune response after the vaccination. These co-founding variables were further used for propensity matching process. Receiver operating characteristic (ROC) curve of combination between MMF daily dose and MMF trough concentration was used to predict seroconversion rate after the third vaccination. *P* values less than .05 were considered statistically significant.

3 | RESULTS

One hundred and seventy four previously seronegative KTRs received the third SARS-CoV-2 vaccination and have completed the

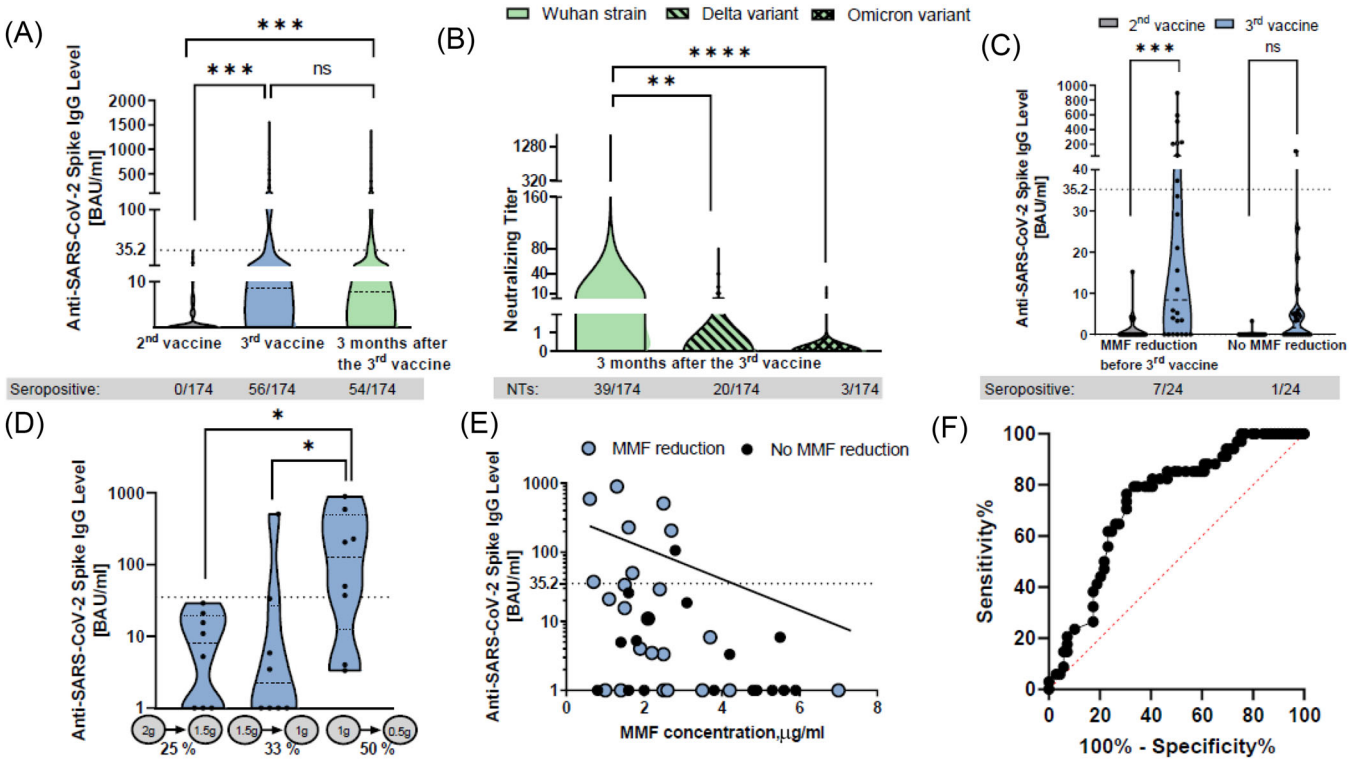

FIGURE 1 Humoral response to third and fourth SARS-CoV-2 vaccination among kidney transplant recipients. (A) Comparison of antibody levels among KTRs after the third vaccination and at 6 months follow-up visit. Dashed line was set at 35.2 BAU/ml to outline seropositive patients. (B) Comparison of neutralizing titer among KTRs after the third vaccination and at 6 months follow-up visit. At the 6 months follow-up visit, patients' serum was tested for neutralizing antibody capacity against various virus strains. 56 KTRs showed neutralizing antibodies against the Wuhan strain with median titer 1:40, 20 KTRs against delta virus variant with median titer 1:20 and three KTRs against omicron virus variant with median titer 1:10. (C) Comparison of antibody level after the third SARS-CoV-2 vaccination between patients with and without temporary MMF dose reduction. The graph represents immune response among 24 matched pairs using propensity score with respect to initial antibody concentration, renal graft function, time after transplantation and MMF trough level prior the dose reduction. (D) The association between MMF dose reduction and the development of IgG antibodies against SARS-SoV-2 Spike S1 protein. Dashed line was set at 35.2 BAU/ml to outline seropositive patients. (E) The association between MMF trough levels and the development of IgG antibody against SARS-SoV-2 Spike S1 protein. Dashed line was set at 35.2 BAU/ml to outline seropositive patients. A negative correlation within MMF reduction group was observed (r −.44, P = .036). (F) Receiver operating characteristics (ROC) curve for MMF daily dose ≤1g/d and low MMF serum concentration with respect to serological patient status with AUC being .872 (95% CI 0.770–.974), P = .001. Differences between antibody levels at different time point and neutralizing antibodies against various SARS-CoV-2 variants were analyzed using Kruskal-Wallis test or Mann-Whitney test. ****represent P value < .0001, ***P < .001, **P < .01, *P < .05.

follow-up period. Baseline characteristics are presented in Table S1. 56/174 KTRs (32%) responded to the third SARS-CoV-2 vaccination with a median antibody level of 119 (76–353) BAU/ml. 39 of these 56 KTRs (69%) developed neutralizing antibodies against the Wuhan type with a median titer of 1:10 (0–1:40) (Figure 1B). Unfortunately, only three out 56 KTRs developed neutralizing capacity against the omicron variant. 5/56 (9%) patients were infected with SARS-CoV-2 (mainly omicron variant) within 6 months after the third vaccination. All of them had a mild disease course. Antibody levels after the second vaccine and time after transplantation were the most relevant factors influencing seroconversion after the third vaccination (OR 1.39 (95% CI 1.09–1.76), P = .006 and OR 1.04 (95% CI 1.02–1.07), P = .001) (Table S2). Daily MMF dose did not have a significant effect in the multivariate backward elimination model, however, in univariate regression analysis, daily MMF dose ≤1g showed 2.5 times higher odds for developing clinically relevant amount of antibodies, P = .016.

Next, we identified 24 KTRs who have been advised to reduce the daily MMF dose from 3 weeks prior until 1 week after the third vaccination (Table 1). The reduction in daily MMF dose resulted in a significantly decline in MMF serum concentrations (2.9 (1.7–4.0) μg/ml before reduction versus 2.1 (1.4–2.6) μg/ml after reduction, P < .001). Within the MMF reduction group, there were 3/24 patients on cyclosporine and the rest were taking tacrolimus. After MMF reduction, no fluctuations in CNI levels were observed (5.6 (5.0–6.4) ng/ml before and 5.4 (5.0–6.3) ng/ml after MMF reduction, P > .05). Patients with MMF dose reduction had no alterations in graft function (Table 1) and there were no donor specific antibodies detected through the observation period. To analyze whether a temporary reduction in the daily MMF dose influences the immune response to the third SARS-CoV-2 vaccination, we used propensity score matching. After controlling for confounding factors (Table S2), we matched 24 pairs with and without MMF reduction (Table 1). Of note, before reduction, MMF

trough levels were similar between both groups. After MMF reduction, 7/24 (29%) KTRs developed antibody levels ≥35.2 BAU/ml in the MMF reduction group, whereas in the matched group (with no MMF reduction) only 1/24 (4%) developed antibody levels ≥35.2 BAU/ml ($P = .020$, Figure 1C). A detailed analysis of these patients has showed that all seroconverted KTRs have received at least 33% MMF dose reduction (Figure 1D). As a result, these patients had significantly lower MMF trough levels than KTRs with 25% dose reduction (1.8 (1.2—2.5) μg/ml vs. 2.5 (1.5–4.2) μg/ml, $P = .05$). More importantly, in the MMF reduction group, KTRs who developed antibodies ≥35.2BAU/ml had lower MMF trough levels (1.6 (.7–2.5) μg/ml) as compared to the 17 seronegative KTRs (2.3 (1.5–3.3) μg/ml, $P = .059$). There was as well a small but negative correlation between antibody levels after the third vaccination and MMF concentration in the serum (r −.44, $P = .036$, Figure 1E). The combination of low MMF trough level <2μg/ml and MMF dose concentration ≤ 1g/d were able to predict seroconversion among patients receiving the third SARS-CoV-2 vaccination (AUC .872, 95% CI .770–.974, $P = .001$, Figure 1F)

4 | DISCUSSION

We were able to show that 32% of KTRs seroconverted after the third vaccination which is in line with previously published studies representing smaller KTRs cohorts.[10,11,16–18] Similarly to the observations after the first two SARS-CoV-2 vaccinations, immune resistance was related to immunosuppressive drugs, especially MMF.[7,9,19] Recently, it has been shown that repetitive vaccination can increase seroconversion among patients with MMF therapy.[20] In addition, the present study and recent other studies in solid organ transplanted patients show evidence that the actual MMF daily dose has a significant impact on vaccination success.[7,21,22] Our results show that MMF daily dose ≤ 1g/day as well as lower MMF trough levels are associated with development of antibodies after the vaccination. Indeed, an increase in concentration by 1μg/ml was associated with up to 60% lower possibility to have antibody levels above >35.2 BAU/ml.

The importance of MMF affecting the vaccination response in KTRs was further analyzed in 24 KTRs in whom the attending nephrologists had temporarily reduced the MMF dose. Since this group was rather small, we used propensity score matching to address the effect of MMF reduction. As expected, KTRs in the MMF reduction group had significantly lower MMF serum concentrations prior to the third vaccination than patients without dose reduction. MMF trough values tend to fluctuate individually and inter-individually and therefore measuring MMF trough levels for monitoring KTRs in general is not recommended[23,24] However, it is an additional tool to monitor KTRs in situations where MMF dose reduction might be indicated. The analysis of the matched cohort demonstrated that patients with 33% dose reduction (equal to MMF 1g/day) with an average MMF trough level < 2 μg/ml were more likely to seroconvert. This suggests a cut-off for MMF reduction to achieve an immune response. Beside MMF reduction, a temporary stop of MMF is another option to increase immune response in KTRs, mostly performed in the treatment of KTRs suffering from life-threatening infections.[25] Recently, several studies have shown that pausing MMF increases the immune response to SARS-CoV-2 vaccination but did not guarantee seroconversion.[26–28] Therefore, it remains a dilemma whether MMF dose reduction or pausing is the optimal approach to improve humoral response as alterations of the immunosuppressive therapy also bare the risk of acute or chronic rejection. The decision should be taken individually. Patients with low rejection risk and higher risk to develop severe COVID-19 course as elderly KTRs would benefit from MMF free immunosuppression regime. In other cases, temporary MMF reduction might be a better option.

In addition to the description of seroconversion following the third vaccination, we were able to analyze neutralizing antibody levels, predictive for the immune response in symptomatic SARS-CoV-2 infection.[29] KTRs had the lowest neutralizing capacity against the omicron SARS-CoV-2 variant compared to the wild-type and the delta variant. More importantly, the neutralizing antibody levels are much lower compared to the general population.[6,30]

The present study has some limitations which have to be addressed. The observation that MMF negatively affects immune response to SARS-CoV-2 vaccination should require a dose reduction with randomized approach. However, due to the individual risk of rejection this process is not feasible. Therefore, we cannot exclude a bias in the process of MMF reduction as each decision was made by the treating nephrologist after considering each case individually. Another relevant point is that our initial MMF reduction group was relatively small with different categories of dose reduction.

In summary, we showed that third vaccination against SARS-CoV-2 improves humoral immune response in previously seronegative patients. However, neutralizing capacity against the novel virus variants remains very poor. Thus, many KTRs are still insufficiently protected and additional vaccinations are necessary. Our results suggest that a moderate, MMF dose reduction could be a safe approach to improve vaccination success in KTRs.

AUTHOR CONTRIBUTIONS

Conceptualization: Thilo Kolb, Katrin Ivens, Hans Martin Orth, Ortwin Adams, Lars C. Rump, Jörg Timm, Johannes Stegbauer Formal analysis: Marta Kantauskaite, Lisa Müller, Joshua Lamberti, Svenja Fischer Investigation: Marta Kantauskaite, Lisa Müller, Jonas Hillebrandt, Joshua Lamberti, Svenja Fischer, Thilo Kolb, Katrin Ivens, Nadine Lübke, Michael Koch, Michael Schmitz, Claudia Schmidt, Torsten Feldt, Marcel Andree, Hans Martin Orth, Eva Königshausen, Margarethe Kittel, Ortwin Adams, Jörg Timm, Johannes Stegbauer Validation: Lisa Müller, Heiner Schaal, Jörg Timm Writing - original draft preparation: Marta Kantauskaite, Lars C. Rump, Jörg Timm, Johannes Stegbauer Writing - review and editing: Marta Kantauskaite, Lisa Müller, Jonas Hillebrandt, Joshua Lamberti, Thilo Kolb, Katrin Ivens, Michael Koch, Heiner Schaal, Nadine Lübke, Michael Schmitz, Claudia Schmidt, Torsten Feldt, Marcel Andree, Hans Martin Orth, Ortwin Adams, Tom Luedde, Eva Königshausen, Margarethe Kittel, Lars C. Rump, Jörg Timm, Johannes Stegbauer Resources: Tom Luedde Supervision: Jörg Timm, Johannes Stegbauer.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Raw data were generated at University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany. The data that support the findings of this study are available at: doi:10.17632/g3wpr3xtpx.1.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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