INTRODUCTION

Variants of concern (VOC) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) endanger people through immune-escape, increased fitness, infectivity, and the lack of protective vaccines because of the delay in developing adapted versions. Nevertheless, vaccination in...
immunocompetent people, especially after a booster with the currently available mRNA vaccines, leads to an adequate immune response with reasonable breadth of reactive antibodies, protecting against a severe course of coronavirus disease 2019 (COVID-19), even with emerging VOC. Neutralizing antibodies to SARS-CoV-2 after active and passive immunization have shown a clear association with protection against severe courses of COVID-19. The reduced humoral vaccination response in transplant recipients is in contrast to the strong immune response in healthy individuals. Cellular immunity, which is another barrier against severe disease, has only been demonstrated outside of routine clinical practice. Quantification of neutralizing antispike SARS-CoV-2 antibodies is widely and readily available. At bedside, the presence or absence of these antibodies may be used as a surrogate for immunity and guide clinical decision for the allocation of scarce therapies. We prospectively examined the humoral immune response against the wild type and the omicron variant of SARS-CoV-2 after a third mRNA vaccine dose as a booster dose in 103 stable kidney transplant recipients (KTRs). We also sought to identify factors influencing the humoral vaccine response besides immunosuppressive treatment.

MATERIALS AND METHODS

We initially enrolled 116 KTRs, who were under regular follow-up care at 4 German outpatient centers (Weinheim, Grünstadt, Worms, Heppenheim) (Figure 1). We excluded 6 patients with a history of a previous SARS-CoV-2 infection and positive for SARS-CoV-2–nucleocapsid antibodies (Roche, Mannheim, Germany), another 7 individuals who went back to hemodialysis. All patients had completed a 2-dose SARS-CoV-2 vaccination between February 16 and July 21, 2021. The majority (n = 80 [77.7%]) were vaccinated twice with an mRNA vaccine, n = 8 (7.8%) solely received a vector vaccine (AstraZeneca ChAdOx1-S), and n = 15 (14.6%) a combination of both. A third-dose vaccination exclusively with a mRNA vaccine, either Moderna mRNA-1273 or Pfizer-BioNTech BNT162b2, was administered between September 9 and October 21, 2021, 2–8 mo (median, 5 mo) after the second vaccination. Immediately prior and 4–8 wk after the booster, a blood sample was taken to prospectively examine the progress of the humoral vaccine response. All patients were seen every 4–6 wk on an outpatient basis as part of the transplantation follow-up care. They were instructed to present themselves in the event of possible symptoms of infection, in particular cold symptoms, with and without fever. Additionally, they were asked about symptoms of infection in the previous interval at each presentation. The study was approved by the Ethics Committee II of the University of Heidelberg at the Medical Faculty of Mannheim, Germany (Registration No. 2020-590N). All patients gave written informed consent for study participation.

Serological SARS-CoV-2 Antibody Assays

Immunosassays—electrochemiluminescence double-antigen sandwich immunoassays—for antibodies against the nucleocapsid (Elecsys Anti-SARS-CoV-2) or spike protein (Elecsys Anti-SARS-CoV-2-S) were performed according to the manufacturer’s specifications on a Cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim Germany). The anti-SARS-CoV-2-S antibody electrochemiluminescence double-antigen sandwich immunoassays, further named SARS-CoV-2 spike antibody (SARS-CoV-2-S-Ab) assay, detects all subclasses of immunoglobulins directed against the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2. The measurement range is from 0.4 to 250 U/mL. Higher levels of antibodies were determined by dilution according to the manufacturer’s instructions. According to the manufacturer’s specifications, the cutoff for a reactive test result is defined at ≥0.8 U/mL. In all samples, we also measured SARS-CoV-2–nucleocapsid antibodies to detect asymptomatic infection.

Virus Neutralization Surrogate Enzyme-linked Immunoassay

The enzyme-linked immunoassay–based GenScript SARS-CoV-2 Surrogate Virus Neutralization Test Kit (GenScript Biotech, Piscataway Township, NJ) was used according to the manufacturer’s protocol. The microtiter plates are coated with the “host cell receptor” angiotensin-converting enzyme 2 (ACE-2). The amount of neutralizing antibodies, further named SARS-CoV-2 neutralizing antibodies (SARS-CoV-2-NT-Ab), is measured by the degree of inhibition by using the spike protein RBD-horseradish peroxidase conjugate as binding partner. The RBD represents the wild-type SARS-CoV-2.

Virus Neutralization Omicron

CaCo-2 cells (DSMZ, Braunschweig, Germany, no: ACC 169) were cultured in Minimum Essential Medium supplemented with 10% fetal calf serum, 4 mmol/L L-glutamine, 100 IU/mL of penicillin, and 100 μg/mL of streptomycin at 37°C and 5% CO2. All culture reagents were obtained from Sigma (St Louis, MO). For the experimental procedure of the neutralization assay, fetal calf serum supplementation of the culture medium was reduced to 1% and serum samples were inactivated for 30 min at 56°C. Inactivated sera were diluted 1:10 in media and thereafter serially diluted (1:2) and incubated with 4000 TCID50/mL of the Omicron variant (B.1.1.529; BA.1) of SARS-CoV-2 for 1 h before infecting CaCo-2 cells. Seventy-two hours after inoculation, infected CaCo-2 cells were analyzed for cytopathic effect formation by light microscopy to define the neutralization titer. Each serum sample was tested in duplicate, in case of discrepancies the lowest observed titer was chosen.

Statistical Analysis

Data are presented as medians (range) or n% using descriptive statistics. Categorical data were analyzed by 2-sided Fisher’s exact tests. We used ANOVA for the comparison of parametric and Wilcoxon signed rank tests of nonparametric data. We performed logistic regression to evaluate putative influencing variables of the vaccine response. These modulating factors were derived from previously published studies of KTRs after dual and third-dose vaccination. We estimated the glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration equation and...
used eGFR ≥60 mL/min as cutoff of a normal kidney function (10). For a stratified analysis, we created quartiles of age and of the dose of mycophenolic acid (MPA) per kg body weight. Odds ratios (ORs) are displayed with 95% confidence intervals (95% CIs). We also created cumulative incidence curves of symptomatic SARS-CoV-2 infection after booster vaccination according to the Kaplan-Meier method and built up a Cox regression model using age, kidney function (eGFR ≥ 60 mL/
After receiving the third vaccination dose, all patients were clinically observed for the occurrence of infection symptoms until March 31, 2022, as part of regular outpatient transplantation follow-up care (Figure 1). A SARS-CoV-2 infection was confirmed using a rapid antigen test, polymerase chain reaction, or a combination of both from a nasopharynx swab. A total of 24 patients became diseased with SARS-CoV-2 after third-dose vaccination with a median follow-up of 4.6 mo, with a range of 1.4–6.2 mo (Figure 4). By January 11, 2022, 3 patients fell ill with the Delta variant, all of whom were hospitalized and 1 of whom died. At that time, all were treated with casirivimab/imdevimab, 2 in combination with molnupiravir. Hereafter, a further 21 patients fell ill with the Omicron variant. All had mild to moderate cold symptoms only, some with elevated temperatures. Three were hospitalized, none required oxygen therapy. Eleven (52.4%) received a passive immunization with sotrovimab, and 4 (19.1%) received molnupiravir. Patients with a symptomatic SARS-CoV-2 infection were younger (median [range]: 54 [22–75] vs 60 [26–84] y, $P = 0.003$) and more frequently had an eGFR $<60 \text{mL/min}$ (19/24 [79.7%] vs 43/79 [54.4%], $P = 0.03$). Kidney function remained an independent explanatory variable in the multivariable Cox regression analysis, whereas treatment with MPA and the humoral immune response after third-dose vaccination did not affect the incidence of a symptomatic infection with SARS-CoV-2 (Table 3 and Figure 4).

**DISCUSSION**

The use of a third vaccine dose as a booster dose, either mRNA-1273 or BNT162b2, resulted in an overall seroconversion rate of 71.8% assessed with the Anti–SARS-CoV-2-S-Ab immunoassay. The majority of the transplant patients had also a marked increase of the antibody concentrations by $>2$ powers of 10 (Figure 2). The observed seroconversion rates and increases in antibody concentrations are comparable to those reported by others.\textsuperscript{5,6,8–12} Around 50% only had functional activity against the wild type of SARS-CoV-2 even after the booster vaccination. By correlating the SARS-CoV-2 antibody concentrations with the inhibitory power for binding of the wild-type spike protein to the ACE-2 receptor, we derived a cutoff value for a 30% virus neutralization that may be clinically meaningful for patients after kidney transplantation (Figure 3). The cutoff value largely corresponds to that in a recently examined dialysis cohort\textsuperscript{13} and in the normal population as provided by the manufacturer.\textsuperscript{14} However, not entirely unexpectedly and as far as comparable because 2 different test methods were used, the respective cutoff on basis of the live virus neutralization test for inactivation of the Omicron variant was 53 times higher. Only 11.6% of our patients had neutralizing antibodies against omicron, which is in line with 2 recent smaller vaccination studies in KTRs from Toronto, Ontario, and from Boston, MA.\textsuperscript{15,16} This is also why patients after kidney transplantation are still considered a subgroup at high risk in the COVID-19 pandemic. Many of them have a high level of comorbidity, which predisposes them to a potentially more severe course after SARS-CoV-2 infection.

There is broad evidence for antibodies as a protective correlate for COVID-19 vaccine.\textsuperscript{17} Antibody titers might be good biomarkers for the protective efficacy of neutralizing antibodies and a successful vaccine response.\textsuperscript{18} In the present study, we identified various influencing factors that were independent from one another associated with the humoral immune response after SARS-CoV-2 vaccination. Unlike a more advanced age or an impaired graft function,\textsuperscript{8,10,19} treatment
with MMF/MPA is basically a modifiable risk factor for seroconversion failure. It seems plausible to reduce or pause therapy with MMF/MPA for stable patients. On the other hand, patients with impaired renal graft function, in whom the response rate could theoretically be increased the most, probably also had a more complicated immunologic course after transplantation. An alloimmune reaction against a predamaged graft would likely impair its function more severely in the further course or even cause a graft loss. Furthermore, our study impressively shows that despite detectable antibodies against the spike protein in the immunoassay, only a limited number of patients produced sufficiently neutralizing antibodies. In contrast to patients with rheumatic and musculoskeletal diseases, in whom immunosuppressive therapy can be temporarily stopped completely, KTRs off MMF/MPA usually have to remain on calcineurin inhibitors ± steroids. This will per se limit the vaccination response. In our cohort, any antibody formation after booster vaccination in patients off MMF/MPA was 78%, which is still below the virus specific seropositivity of >90% that is achieved in the normal population after 2 doses of BNT 162b2. Regardless of this, our data in no way challenge the usefulness of the COVID-19 vaccination in KTRs. However, taking in account the risk-benefit ratio speaks against a strategy of reducing immunosuppressive therapy, because the vaccine response is also largely influenced by nonmodifiable factors other than MMF/MPA treatment. Another argument comes from the to-date lack of a specific vaccine directed against the Omicron variant. Furthermore, the clinical course after infection with Omicron is seemingly less severe also in solid organ transplant recipients and can be attenuated by passive immunization without major side effects. This point of view might

### TABLE 1

Baseline characteristics and serological vaccination results before and after third-dose vaccination

|                          | Median | Range  |
|--------------------------|--------|--------|
| Age, y                   | 58     | 22–84  |
| Sex                      |        |        |
| Female                   | 46 (447)|        |
| Male                     | 57 (55.3)|       |
| Serum creatinine, mg/dL  | 1.44   | 0.6–5.1|
| eGFR, mL/min             | 52     | 12–131 |
| Transplanted organs      |        |        |
| Kidney only              | 98 (95.1)|      |
| Kidney and pancreas      | 2 (1.9) |        |
| Kidney and liver         | 2 (1.9) |        |
| Kidney and heart         | 1 (1.0) |        |
| Immunosuppressive therapy|        |        |
| MMF/MPA                  | 76 (73.8)|      |
| Tacrolimus               | 69 (67.0)|      |
| Cyclosporine             | 31 (30.1)|      |
| mTOR-inhibitor           | 9 (8.7) |        |
| Belatacept               | 3 (2.9) |        |
| Azathioprine             | 6 (5.8) |        |
| Steroids                 | 97 (94.2)|      |
| Time since transplantation, y | 8.9 | 0.6–33.6|
| SARS-CoV-2-S-Ab before third vaccination, U/mL | 16.6 | 1.0–2737|
| SARS-CoV-2-S-Ab before third vaccination, seroconversion | 59 (57.3)| |
| SARS-CoV-2-S-Ab after third vaccination, U/mL | 1307 | 1.0–117375|
| SARS-CoV-2-S-Ab after third vaccination, seroconversion | 74 (71.8)| |
| SARS-CoV-2-NT-Ab before third vaccination, % inhibition | 47 | 28–96|
| SARS-CoV-2-NT-Ab before third vaccination, ≥30% | 16 (15.5) | |
| SARS-CoV-2-NT-Ab before third vaccination, ≥70% | 8 (7.8) | |
| SARS-CoV-2-NT-Ab after third vaccination, % inhibition | 94 | 30–97|
| SARS-CoV-2-NT-Ab after third vaccination, ≥30% | 56 (55.4) | |
| SARS-CoV-2-NT-Ab after third vaccination, ≥70% | 50 (48.5) | |
| Omicron-PRNT after third vaccination, titer (NT50) | 10 | 10–40|
| Omicron-PRNT after third vaccination, seroconversion | 12 (11.6) | |

Baseline characteristics of the study population and serological vaccination results before and after third-dose vaccination.

eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; NT50, 50% virus neutralization; NT-Ab, neutralizing antibody; PRNT, plaque reduction neutralization test; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-Ab, spike protein antibody.
be supported by our observation that 21 individual patients infected with the Omicron variant had a symptom-poor clinical course. Although we cannot exclude to have missed asymptomatic infections, it is unlikely that a considerable number of patients with symptomatic disease remained undetected, due to a close monitoring of our patients with regard to fever and cold symptoms as described previously. Notably, impaired kidney function appeared to affect also the incidence of symptomatic infection with COVID-19 after third-dose vaccination (Figure 4B), which, however, requires further confirmation in a larger study base. Treatment with MMF/MPA was not a significant explanatory variable of symptomatic SARS-CoV-2 infection with the Omicron variant in our study cohort. These considerations however would need to be reweighed in a future, more clinically aggressive VOC, such as Delta was. With expected severe COVID-19 from future VOCs and availability of an already adapted vaccine, perhaps a reduction in MMF/MMA could be beneficial if no passive immunization option is available. On the other hand, seroconversion failure is usually found precisely in those patients

FIGURE 2. Dot plot after the third immunization in KTRs of (A) anti-SARS-CoV-2-S-Ab (ECLIA, Elecsys, Roche Mannheim), (B) inhibition of binding of SARS-CoV-2-spike wild-type protein (SARS-CoV-2-WT-NT-Ab) (GenScript Biotech) to the ACE-2 receptor, and (C) live virus neutralization against omicron (PRNT-O) (Wilhelm et al). Values represent reciprocal dilutions of SARS-CoV-2 Omicron microneutralization titers resulting in 50% virus neutralization (NT50). ACE-2, angiotensin-converting-enzyme 2; ECLIA, electrochemiluminescence double-antigen sandwich immunosassays NT-Ab, neutralizing antibody; PRNT, plaque reduction neutralization test; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-Ab, spike protein antibody; WT, wild type.

FIGURE 3. ROC analysis of anti-SARS-CoV-2-S-Ab level indicating the presence of neutralizing antibodies. (A) The presence of neutralizing antibodies against wild-type SARS-CoV-2 was defined as an inhibition of ≥30% within the SARS-CoV-2-NT-Ab assay. (B) Prediction of anti-SARS-CoV-2-S-Ab for virus neutralization against Omicron (PRNT-O). AUC, area under the curve; CI, confidence interval; NT-Ab, neutralizing antibody; ROC, receiver operating curve; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S-Ab, spike protein antibody.
at high risk of rejection who require a more intense immunosuppressive therapy. It is in this group that controlled clinical trials will be needed to weigh the benefit of an adjusted or reduced immunosuppression before vaccination against the risk of graft loss. Another strategy, which was recently pursued especially for risk groups, is based on the administration of a fourth vaccination. However, a fourth vaccination generated an adequate humoral immune response in a very limited number of Ab-negative patient only\textsuperscript{30} and failed to induce neutralization against the Omicron variant.\textsuperscript{31}

Our study has several limitations, the relatively small sample size and the lacking data on T-cell immunity following vaccination. Furthermore, we assessed only the peak levels of the SARS-CoV-2 antibodies, which usually occur between 4 and 8 wk after vaccination and tend to fall during the ongoing follow-up.\textsuperscript{32} The latter and observational nature risking unbalanced groups for comparisons, limited to some extent the ability of our study collecting truly robust data on the vaccine effectiveness during the further clinical course. Hence, that our study failed to show a clinical correlate of protection should be considered with some caution. Although the determination of antibodies targeting the S1 RBD of the spike protein is technically simple and highly standardized, they seem to be less apt in predicting clinical immunity to omicron. Therefore, the here-presented and highly reliable cutoff of 166 U/mL capable to inhibit the interaction of the wild-type SARS-CoV-2–spike protein with ACE-2 may have lost some of its meaningfulness. The 53 times higher cutoff indicating the presence of neutralizing antibodies against Omicron may indicate how far this variant is serologically distant from the wild type and Delta variant (B.1.617.2).\textsuperscript{15,31,33,34} Furthermore, the breadth of vaccine induced antibodies may be narrowed in organ transplant recipients.\textsuperscript{35} Nevertheless, a very high antibody titer may reflect an immune system that is not relevantly impaired despite immunosuppressive medication and may guide the clinician to dispense with scarce treatment options for COVID-19. At the other end of the spectrum, there is agreement that seronegative patients need a maximum effort in the prophylaxis and treatment to avoid a complicated course in case of infection with SARS-CoV-2, including passive immunization.\textsuperscript{7}

In conclusion, KTRs show a significantly reduced humoral immune response after SARS-CoV-2 vaccination compared with the general population. This refers both to the formation of antibodies in general and to the formation of neutralizing antibodies. In addition to immunosuppressive therapy, the humoral vaccination response in KTRs is significantly influenced by nonmodifiable factors such as advanced age and a

| Variable                  | SARS-CoV-2-S-Abs (≥0.8 U/mL), before booster | SARS-CoV-2-NT-Abs (≥30%), after booster |
|---------------------------|---------------------------------------------|---------------------------------------|
|                           | Univariable analysis                         | Multivariable analysis                |
|                           | OR (95% CI) P                                | OR (95% CI) P                         |
| Age quartiles             |                                              |                                       |
| Q1, median 40 y (22–49)   | 0.64 (0.44-0.93) 0.02                       | 0.60 (0.39-0.91) 0.02                 |
| Q2, median 56 y (51–58)   | 0.40 (0.12-1.30) 0.13                       | 0.54 (0.14-2.09) 0.37                 |
| Q3, median 63 y (59–66)   | 0.30 (0.09-1.00) 0.05                       | 0.20 (0.05-0.83) 0.03                 |
| Q4, median 73 y (67–84)   | 0.24 (0.07-0.79) 0.02                       | 0.20 (0.05-0.84) 0.03                 |
| eGFR ≥60 mL/min           | 3.76 (1.58-8.99) 0.003                      | 5.96 (2.12-16.8) 0.001                |
| Dose quartiles of MPA     | 0.60 (0.41-0.87) 0.007                      | 0.45 (0.28-0.71) 0.001                |
| Q1, median 0 mg/kg        |                                              |                                       |
| Q2, median 7.2 mg/kg (3.3–8.8) | 0.74 (0.22-2.48) 0.63     | 0.89 (0.23-3.39) 0.87 |
| Q3, median 10.5 mg/kg (9.0–12.2) | 0.28 (0.09-0.88) 0.03 | 0.20 (0.05-0.78) 0.02 |
| Q4, median 16.5 mg/kg (12.6–33.5) | 0.25 (0.08-0.82) 0.02 | 0.10 (0.02-0.45) 0.002 |

\textsuperscript{a}According to the Chronic Kidney Disease Epidemiology Collaboration equation.

Logistic regression of SARS-CoV-2 antibody production before and after third SARS-CoV-2 vaccination.

CI, confidence interval; eGFR, estimated glomerular filtration rate; MPA, mycophenolic acid; NT-Ab, neutralizing antibody; OR, odds ratio; S-Ab, spike protein antibody.
compromised kidney function. This puts into perspective the possibilities to significantly enhance the vaccination response just by reducing or temporarily discontinuing proliferation inhibitors. It appears questionable that such a strategy under the leading Omicron variant can significantly enhance the protective efficacy of the currently available vaccines without the inherent risks of a late rejection with subsequent decrease in graft function.

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