Antibody and T-cell response to a third dose of SARS-CoV-2 mRNA BNT162b2 vaccine in kidney transplant recipients

To the editor: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination has become the standard of care for the prevention of severe coronavirus disease 2019 (COVID-19), with a strongly positive impact in countries in which vaccination has been effectively promoted. In kidney transplant recipients (KTRs), SARS-CoV-2 vaccination has been recommended through international guidelines. Unfortunately, the data reported in KTRs are disappointing, with a low rate of seroconversion after 2 doses, whereas the occurrence of severe infection after vaccination is of concern. In this context, as of April 6, 2021, the French Administration recommends that solid organ transplant recipients receive a third mRNA vaccine dose at least 4 weeks after the second dose. Herein, we report the evaluation of humoral and cellular responses induced after the second and third doses of BNT162b2 (Pfizer–BioNTech) in 80 KTRs (see Supplementary Methods).

Baseline characteristics of the 80 KTRs are described in Table 1. After the second dose, 30 KTRs (37.5%) had anti-spike IgG antibodies; and 49 KTRs (61.2%) had these antibodies after the third injection (P < 0.0001) (Figure 1a). In patients already seropositive after the second dose (Figure 1b), median antibody titers increased from 271.7 arbitrary units (AU)/ml (interquartile range [IQR], 120.2–443.8 AU/ml) to 2238.3 AU/ml (IQR, 1934.4–7220.6 AU/ml; P < 0.0001). Forty-one KTRs (51.2%) displayed a significant number of IFN-γ-producing spike-reactive T cells after the second injection, and 56 (70%) displayed these cells after the third injection (P < 0.0001 compared with the second dose). No response to N, M, ORF3A, and ORF7A was evidenced, excluding a potential SARS-CoV-2 infection between the second and up to 1 month after the third dose. In these 41 patients, the median number of spike-reactive T cells increased from 225 spot-forming cells (SFCs)/106 CD3+ T cells (IQR, 90–355 SFCs/106 CD3+ T cells) to 330 SFCs/106 CD3+ T cells (IQR, 187–610 SFCs/106 CD3+ T cells; P < 0.0001) after the third dose (Figure 2b). Vaccination status after the third dose is summarized in Supplementary Figure S1.

Baseline characteristics and immune response after the third dose, according to baseline immunosuppressive regimen, are described in Supplementary Tables S1 and S2 and Supplementary Figure S2.

Two KTRs presented with symptomatic COVID-19 67 and 72 days, respectively, after the third vaccine injection. One KTR was hospitalized but did not require intensive care. Both KTRs had a low number of spike-reactive T cells after the third dose (65 and 50 SFCs/106 CD3+ T cells), and only the second KTR had a low titer of anti-spike antibodies (145 AU/ml).

We did not report any severe adverse events after the third vaccine dose. None of the patients presented an acute rejection after vaccination. We did not report any de novo donor-specific antibodies until 1 month after the third dose.

We provide herein the largest cohort of KTRs explored for both humoral and T-cell responses after a third dose of BNT162b2 vaccine. The seropositivity rate increased, with an important increase in median antibody titers in responders, reaching levels that have been found associated with the presence of neutralizing antibodies. Our results are in line with other reports in solid-organ transplant recipients. Hall et al., in a double-blind, randomized, placebo-controlled trial of a third dose of mRNA-1273 vaccine (Moderna), found that seroconversion, virus neutralization,

Table 1 | Baseline characteristics of patients and according to the immune response after the third dose of mRNA BNT162b2 vaccine (Pfizer–BioNTech)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire cohort (n = 80)</th>
<th>S+ / E+ (n = 43)</th>
<th>S+ / E+ (n = 6)</th>
<th>S+ / E+ (n = 13)</th>
<th>S+ / E+ (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD</td>
<td>63.6 ± 15.7</td>
<td>60.3 ± 14.9</td>
<td>66.7 ± 15.6</td>
<td>64.3 ± 18.1</td>
<td>70.2 ± 14.6</td>
</tr>
<tr>
<td>Sex (M/F), n</td>
<td>48/32</td>
<td>24/19</td>
<td>5/1</td>
<td>8/5</td>
<td>11/7</td>
</tr>
<tr>
<td>Time from transplantation, yr, median (IQR)</td>
<td>7.3 (3.4–14.1)</td>
<td>10.3 (4.7–16)</td>
<td>6.8 (3.5–17.5)</td>
<td>6.6 (1.6–14.2)</td>
<td>4.4 (1.7–6.8)</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m², mean ± SD</td>
<td>44.8 ± 17.2</td>
<td>50.2 ± 14.2</td>
<td>46.6 ± 17.3</td>
<td>44.0 ± 21.6</td>
<td>32.0 ± 14.8</td>
</tr>
<tr>
<td>IS regimen, n (%)</td>
<td>Tacrolimus (57.5)</td>
<td>22 (51.2)</td>
<td>6 (100)</td>
<td>10 (76.9)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine (17.5)</td>
<td>13 (30.2)</td>
<td>0 (0)</td>
<td>1 (7.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>MMF (76.2)</td>
<td>32 (74.4)</td>
<td>4 (66.7)</td>
<td>13 (100)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td></td>
<td>AZA (11.2)</td>
<td>6 (13.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td></td>
<td>mTOR inhibitors (12.5)</td>
<td>7 (16.3)</td>
<td>1 (16.7)</td>
<td>1 (7.7)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td></td>
<td>Belatacept (15)</td>
<td>1 (2.3)</td>
<td>0 (0)</td>
<td>1 (7.7)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td></td>
<td>Steroids (32)</td>
<td>16 (37.2)</td>
<td>3 (50)</td>
<td>4 (30.8)</td>
<td>9 (50)</td>
</tr>
</tbody>
</table>

AZA, azathioprine; E, enzyme-linked immunosorbent spot; eGFR, estimated glomerular filtration rate; F, female; IQR, interquartile range; IS, immunosuppressive; M, male; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; S, serology.
and specific T-cell counts were statistically higher in the mRNA-1273 group. In our study, the rate of positive T-cell response increased from 51.2% to 70% after the third dose, with a median spike-reactive T-cell number comparable to that observed in the general population after 2 doses. S7

Our results suggest that the immune response to a third BNT262b2 dose is highly influenced by the intensity of the immunosuppressive regimen. As already reported, S8 belatacept-treated patients were the worst responders, developing no antibodies and no or only few specific T cells. Mycophenolic acid by itself appears associated with a lower seroconversion rate. S5 However, in our study, KTRs on cyclosporine were more likely to develop humoral and cellular responses than KTRs on tacrolimus (Supplementary Table S2), regardless of mycophenolate mofetil coadministration.

In addition, the BNT262b2 vaccine appears safe with regard to acute rejection and de novo donor-specific antibodies, a potent risk factors for antibody-mediated rejection and graft loss, S9 up to 1 month after the third dose.

In conclusion, a third dose of the SARS-CoV-2 mRNA BNT162b2 vaccine in KTRs increases the rate of positive antibody and T-cell responses in nonresponsive patients after the second dose and improves the magnitude of these responses in already seropositive patients. In patients without significant response after a third dose, anti–SARS-CoV-2 monoclonal antibodies could be proposed in prophylaxis, S10 as recommended by the French Administration since August 6, 2021.

DATA STATEMENT
All relevant data are within the article.

ACKNOWLEDGMENTS
The authors wish to thank the health care professionals of the University Hospital of Rouen, who were involved in the care of the patients, and the nurse from the kidney transplant team, Manuel Etienne for his help.

AUTHOR CONTRIBUTIONS
SC and DB designed the study; JL performed enzyme-linked immunosorbent spot assays; SC and DB collected data; MHam, SC, and DB analyzed the data; SC and DB wrote the article; and all authors provided feedback and critical review.
SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary Methods.

Figure S1. Flowchart of the humoral and cellular response to the third dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA BNT162b2 (Pfizer–BioNTech) vaccine in kidney transplant recipients (KTRs).

Figure S2. Anti-spike antibody and T-cell responses in kidney transplant recipients (KTRs) following the second and third injections of the BNT162b2 vaccine (Pfizer–BioNTech), according to the immunosuppressive regimen.

Table S1. Baseline characteristics of kidney transplant recipients (KTRs) and the immune response after the third dose, according to the immunosuppressive regimen.

Table S2. Baseline characteristics of kidney transplant recipients (KTRs) and the immune response after the third dose, according to the immunosuppressive regimen tacrolimus (Tac) + mycophenolate mofetil (MMF; n = 32) or cyclosporine + MMF (n = 10).

Supplementary References.


Dominique Bertrand1, Mouad Hamzaoui1, Veronique Lemée2, Julie Lamulle3, Charlotte Laurent1, Isabelle Etienne1, Mathilde Lemoine1, Ludwine Lebourg1, Mélanie Hanoy1, Frank Le Roy1, Dorian Nezam1, Fabienne Farce4, Jean-Christophe Plantier2, Olivier Boyer3,5, Dominique Guerrot1 and Sophie Candon3,5
1Department of Nephrology, Transplantation and Hemodialysis, Rouen University Hospital, Rouen, France; 2Department of Virology, Rouen University Hospital, Rouen, France; 3Department of Immunology and Biotherapies, Rouen University Hospital, Rouen, France; 4HLA Laboratory, Etablissement Français du Sang (EFS) Normandie, Rouen, France; and 5INSERM U1234, University of Rouen Normandy, Rouen, France

Correspondence: Dominique Bertrand, 1 rue de Germont, Rouen University Hospital, 76000 Rouen, France. E-mail: dominique.bertrand@chu-rouen.fr

Kidney International (2021) - - - - ; https://doi.org/10.1016/j.kint.2021.09.014
Copyright © 2021, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.