



HAL
open science

A fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improves serum neutralization against the Delta variant in kidney transplant recipients

Ilies Benotmane, Timothée Bruel, Delphine Planas, Samira Fafi-Kremer,
Olivier Schwartz, Sophie Caillard

► **To cite this version:**

Ilies Benotmane, Timothée Bruel, Delphine Planas, Samira Fafi-Kremer, Olivier Schwartz, et al.. A fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improves serum neutralization against the Delta variant in kidney transplant recipients. *Kidney International*, 2022, 101 (5), pp.1073-1076. 10.1016/j.kint.2022.02.011 . pasteur-03696743

HAL Id: pasteur-03696743

<https://pasteur.hal.science/pasteur-03696743v1>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

A fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improves serum neutralization against the delta variant in kidney transplant recipients

Ilies Benotmane MD^{1*}, Timothée Bruel PhD^{2,3}, Delphine Planas PhD^{2,3}, Samira Fafi-Kremer PharmD PhD⁴, Olivier Schwartz PhD^{2,3}, Sophie Caillard MD PhD¹

¹Department of Nephrology and Transplantation, Strasbourg University Hospital, Strasbourg, France

²Institut Pasteur, Université de Paris, CNRS UMR3569, Virus and Immunity Unit, 75015 Paris, France

³Vaccine Research Institute, 94000 Créteil, France

⁴Department of Virology, Strasbourg University Hospital, Strasbourg, France

*Corresponding author: Ilies Benotmane, Department of Nephrology and Transplantation, Strasbourg University Hospital, 1 place de l'hôpital, 67091 Strasbourg, France

Email: ilies.benotmane@chru-strasbourg.fr

Tel: 0033369550116

Running head: Anti-delta neutralizing antibody titers after four doses of mRNA vaccine

Word count: 1166

Keywords: SARS-CoV-2, kidney transplantation, mRNA vaccine, fourth dose, neutralizing antibodies, delta variant

Introduction

Research has suggested that even three doses of SARS-CoV-2 mRNA-based vaccines might be unable to elicit a sufficient immune response in immunocompromised kidney transplant recipients.^{1,2} While the antibody response mounted by the Pfizer and AstraZeneca vaccines in immunocompetent subjects seems sufficient to neutralize the delta variant,³ the effectiveness appears three- to five-fold lower than that observed against the alpha variant.^{4,5} In addition, standard vaccination schemes are beset by low immunogenicity in immunocompromised subjects – who remain prone to develop severe COVID-19.³ The purpose of this study is to describe the kinetics of the neutralizing antibody response against the delta strain before and after a fourth dose of the mRNA-1273 (Moderna) vaccine in kidney transplant recipients who had experienced a weak antibody response after three previous doses. We also assessed the correlation between this neutralizing activity and levels of IgG against the receptor binding domain (RBD) of the spike (S) protein.

Results

Sixty-seven kidney transplant recipients (median age: 56.6 years; interquartile range [IQR]: 47–64.6 years; 61.2% men) showed a weak humoral response after three doses of the mRNA-1273 vaccine and received a fourth dose. None of these patients had a previous history of COVID-19 and displayed anti-nucleocapsid antibodies. The median interval from transplantation to the fourth dose was 6.1 years (interquartile range [IQR]: 2.2–11.4 years). As for immunosuppressive therapy, 97% of the study patients were being treated with calcineurin inhibitors, 82% with mycophenolate mofetil, 76% with steroids, and 18% with mTOR inhibitors (Table 1). The median interval between the third and the fourth doses was 68 days (IQR: 63–82 days). After the fourth dose, the anti-RBD median titer increased significantly ($p < 0.0001$) from 13 BAUs/mL (IQR: 2.6–66.3 BAUs/mL) to 112.5 BAUs/mL

(IQR: 13.5–260 BAUs/mL, Figure 1A). In parallel, median inhibitory dilution 50 (ID50) titers increased significantly ($p=0.0001$) from <7.5 (IQR : <7.5 –15.1) to 47.1 (IQR <7.5 –284.2). While only 16% of patients ($n = 11$) harbored neutralizing antibodies against the delta strain prior to the fourth injection, this percentage raised to 66% ($n = 44$) afterwards (Figure 1B). Patients with undetectable neutralizing antibodies after the third dose were less likely to have their neutralizing capacity increased after the fourth dose (median fold-change: 1.1 *versus* 6.3, $p=0.01$). Of the nine patients who were seronegative after the third dose, only one displayed a strong anti-RBD IgG response (>143 BAUs/mL) and two were able to neutralize the delta variant after the fourth dose. Additionally, 81% of patients with a weak immune response after the third dose displayed a strong anti-RBD IgG response after the fourth injection. Notably, 63.8% of them were able to neutralize the delta variant after the fourth dose. Interestingly, patients under combined therapy with tacrolimus, mycophenolate mofetil, and steroids displayed lower neutralizing ID50 titers (median ID50 titers: 25.6 *versus* 140.6, $p=0.01$). Neutralizing ID50 titers against the delta variant were positively correlated with anti-RBD titers (Pearson's $r^2=0.54$, $p<0.0001$, Figure 1C). Once the anti-RBD titer exceeded 143 BAUs/mL after the fourth dose, the specificity, sensitivity, positive predictive value, and negative predictive value to detect neutralizing activity were 92.9%, 74.3%, 93.6%, and 72.2% respectively. Neither major adverse events nor graft rejections were observed after the fourth dose. One patient – who lacked neutralizing activity after the fourth injection (ID50 titer: <7.5) – developed symptomatic COVID-19 caused by the delta variant nineteen days after receiving the fourth dose.

Discussion

In this cohort of 67 kidney transplant recipients who showed a low immune response after three doses of the mRNA-1273 (Moderna) vaccine, a fourth dose significantly increased the

neutralizing response against the delta variant. Specifically, the proportion of patients harboring neutralizing antibodies against the delta strain rose significantly from 16% to 66%. In our study, men displayed higher neutralizing ID50 titers than women. While this observation has no obvious pathophysiological explanations, it is in accordance with the results published by Masset et al.⁶ after the third dose. Patients with a history of cellular or antibody-mediated rejection were less likely to display a neutralizing antibody response. This may be attributed to a higher burden of immunosuppression implemented in response to the rejection episodes. Only two published studies have focused on the effect of a fourth vaccine dose in patients who had undergone solid organ transplantation. In a small cohort of 18 solid organ transplant recipients, Alejo et al.⁷ found that eight patients with negative or low response after the third dose developed high antibody titers after the fourth injection – a result in line with our current data.⁷ Moreover, six of the ten patients who already had high positive titers after three doses showed additional boosting after the fourth injection. This report did not provide data on the neutralizing activity – which has been shown to be highly predictive of immune protection against symptomatic SARS-CoV-2 infection.⁸ In another cohort of 37 patients, Kamar et al.⁹ assessed antibody response, neutralizing activity, and T cell response; a slight improvement of humoral response was observed. In the work by Kamar et al.,⁹ 86% of the study patients (32 out of 37) had no immune response after three doses. Conversely, 87% of our study participants (58 out of 67) showed a weak antibody response after three doses. This may at least in part explain the discrepancies between the two investigations. This is, to our knowledge, the first study to assess the effect of a fourth dose vaccine by taking into account the neutralizing activity against the delta variant. Previous research has focused on the response of solid organ transplant recipients after a third vaccine dose.^{1,6} While improvements have been observed for both B and T responses, a significant proportion of non-responders (30–50%) was reported. In a double-blind, randomized, placebo-controlled

trial of a third dose of mRNA-1273 vaccine, Hall et al.² found a higher neutralizing activity in the vaccine group *versus* the placebo group (median percent virus neutralization: 71% *versus* 25%, respectively). These observations suggest the existence of an “antigen dose effect” – indicating that stronger immune stimuli are required to improve vaccine immunogenicity. There have been previous reports of better immunogenicity after additional vaccine doses or higher vaccine dosing in immunocompromised patients.^{S1,S2} Although a consensus threshold for COVID-19 seroprotection has not been defined yet, higher antibody titers have been correlated with a reduced risk of symptomatic infections.^{S3,S4} These data, coupled with our findings, indicate that a fourth vaccine injection is beneficial in transplant recipients who show a weak response after three doses. It is nonetheless concerning that a fourth injection was still unable to elicit neutralizing antibodies against this variant in approximately one third of our study sample. These patients should maintain strict sanitary protection measures and/or be considered as candidates for higher vaccine doses or prophylactic administration of monoclonal anti-SARS-CoV-2 antibodies. While immunosuppressive modulation during vaccination could be another alternative to improve vaccine response, this approach should be weighed against the risk of developing acute rejection. No data are currently available on the cost-effectiveness of this strategy.

In summary, our data indicate that a fourth mRNA-1273 vaccine injection in kidney transplant recipients with a weak antibody response after three previous doses improves serum neutralization against the delta variant.

References

1. Benotmane I, Gautier G, Perrin P, et al. Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses. *JAMA*. Published online July 23, 2021. doi:10.1001/jama.2021.12339
2. Hall VG, Ferreira VH, Ku T, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. *N Engl J Med*. 2021;0(0):null. doi:10.1056/NEJMc2111462
3. How do vaccinated people spread Delta? What the science says. Accessed September 14, 2021. <https://www.nature.com/articles/d41586-021-02187-1>
4. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*. 2021;596(7871):276-280. doi:10.1038/s41586-021-03777-9
5. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med*. 2021;385(7):585-594. doi:10.1056/NEJMoa2108891
6. Masset C, Kerleau C, Garandeau C, et al. A third injection of the BNT162b2 mRNA COVID-19 vaccine in kidney transplant recipients improves the humoral immune response. *Kidney Int*. 2021;100(5):1132-1135. doi:10.1016/j.kint.2021.08.017
7. Alejo JL, Mitchell J, Chiang TPY, et al. Antibody Response to a Fourth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Transplantation*. Published online November 16, 2021. doi:10.1097/TP.0000000000003934
8. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(7):1205-1211. doi:10.1038/s41591-021-01377-8
9. Kamar N, Abravanel F, Marion O, et al. Assessment of 4 Doses of SARS-CoV-2 Messenger RNA–Based Vaccine in Recipients of a Solid Organ Transplant. *JAMA Netw Open*. 2021;4(11):e2136030. doi:10.1001/jamanetworkopen.2021.36030

Table 1. General characteristics of the study patients according to the neutralizing ID50 titers after the fourth dose

	Entire cohort (n=67)	Neutralizing ID50 below 30 (n=28)	Neutralizing ID50 above 30 (n=39)	p
Age (years)	56.6 (47–64.6)	53.1 (45-64.6)	57.6 (50.6-64.6)	0.29
Male sex, n (%)	41 (61.2%)	12 (42.9%)	29 (74.4%)	0.01
BMI (kg/m ²)	25.6 (22.3–29.6)	24.3 (22.2-28.9)	26.6 (22.7-29)	0.48
Comorbidities, n (%)				
Cardiovascular disease	19 (28.4%)	8 (28.5%)	11 (28.2%)	0.59
Diabetes	27 (39.3%)	10 (35.7%)	17 (43.6%)	0.61
Hypertension	53 (79.1%)	21 (75%)	32 (82%)	0.56
Time from kidney transplantation (years)	6.1 (2.2–11.4)	5.1 (1.8-11.1)	7.5 (2.5-11.3)	0.32
First transplantation, n (%)	54 (80.6%)	23 (82.1%)	31 (79.5%)	1
Deceased donor, n (%)	55 (82.1%)	22 (78.6%)	33 (84.6%)	0.54
CNI, n (%)				0.2
Tacrolimus	51 (76.1%)	24 (85.7%)	27 (69.2%)	
Ciclosporin, n (%)	14 (20.9%)	3 (10.7%)	11 (28.2%)	
No CNI, n (%)	2 (3%)	1 (3.6%)	1 (2.6%)	
MMF/MPA, n (%)	55 (82%)	24 (85.7%)	31 (79.5%)	0.74

mTOR inhibitors, n (%)	12 (17.9%)	4 (14.3%)	8 (20.5%)	0.74
Steroids, n (%)	51 (76.1%)	24 (85.7%)	27 (69.2%)	0.15
Tacrolimus + MMF/MPA + steroids, n (%)	35 (52.2%)	19 (67.9%)	16 (41%)	0.05
Serum creatinine ($\mu\text{mol/L}$)	132 (106.2–162.5)	131.3 (100.2-157.8)	132 (115.3-162.6)	0.61
History of graft rejection, n (%)	15 (22.4%)	12 (42.8%)	3 (7.7%)	0.002

Data are expressed as medians (interquartile ranges) unless otherwise indicated.

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitors; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.

Figure 1A. Anti RBD antibody titers after the third and fourth doses of the mRNA-1273 (Moderna) vaccine in 67 kidney transplant recipients. A titer >7.1 was regarded as positive (dotted line), whereas a titer <143 BAUs/mL was considered to reflect a weak humoral response (black line). The percentages of patients with titers above 143 BAUs/mL before and after the fourth dose are shown in the graph. Blue lines represent patients with a titer >143 BAUs/mL, whereas red lines denote patients with a titer <143 BAUs/mL.

Figure 1B. Neutralizing ID50 against the delta variant after the third and fourth doses of the mRNA-1273 (Moderna) vaccine in 67 kidney transplant recipients. Neutralizing antibodies were expressed as the concentration capable of inhibiting 50% of the virus inoculum (ID50; limit of detection: 7.5, dotted line). A neutralizing ID50 >30 was considered as positive (black line). The percentages of patients showing neutralizing activity against delta variant before and after the fourth dose are shown in the graph. Blue lines represent patients with a neutralizing ID50 >30 , whereas red lines denote patients with a neutralizing ID50 <30 .

Figure 1 C. Scattergram and regression line showing a significant positive correlation between anti-receptor binding domain (RBD) IgG antibody titers (log BAUs/mL) and neutralizing ID50 against the delta strain (log ID50) before and after the fourth dose of the mRNA-1273 (Moderna) vaccine in 67 kidney transplant recipients (Pearson's $r^2=0.54$, $p < 0.0001$). The dotted line parallel to the Y axis represents the cut-off for a positive neutralizing ID50 titer (30), whereas the dotted line parallel to the X axis represents the cut-off for a weak RBD IgG antibody titer (143 BAUs/mL).