JASN® Journal of the American Society of Nephrology

# Antibody and T Cell Response to SARS-CoV-2 Messenger RNA BNT162b2 Vaccine in Kidney Transplant Recipients and Hemodialysis Patients



| | |
|---|---|
| Journal: | *Journal of the American Society of Nephrology* |
| Manuscript ID | JASN-2021-04-0480.R1 |
| Manuscript Type: | Original Article - Rapid Communications |
| Date Submitted by the Author: | 03-May-2021 |
| Keywords: | kidney transplantation, hemodialysis, clinical immunology, COVID-19, SARS-CoV-2 |



Complete List of Authors:
Bertrand, Dominique; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Hamzaoui, Mouad; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Lemée, Veronique; Rouen University Hospital, Department of Virology
Lamulle, Julie; Rouen University Hospital, Department Of Immunology and Biotherapies
Hanoy, Melanie; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Laurent, Charlotte; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Lebourg, Ludivine; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Etienne, Isabelle; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Lemoine, Mathilde; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Le Roy, Frank; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Nezam, Dorian; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Plantier, Jean-Christophe; Rouen University Hospital, Department of Virology
Boyer, Olivier; Rouen University Hospital, Department of Immunology and Biotherapies; University of Rouen Normandy, INSERM U1234
Guerrot, Dominique; Rouen University Hospital, Department of Nephrology, Transplantation and hemodialysis
Candon, Sophie; Rouen University Hospital, Department of Immunology and Biotherapies; University of Rouen Normandy, INSERM U1234

**Authors:** Bertrand, Dominique; Hamzaoui, Mouad; LemÃ©e, Veronique; Lamulle, Julie; Hanoy, Melanie; Laurent, Charlotte; Lebourg, Ludivine; Etienne, Isabelle; Lemoine, Mathilde; Le Roy, Frank; Nezam, Dorian; Plantier, Jean-Christophe; Boyer, Olivier; Guerrot, Dominique; Candon, Sophie

**Title:** Antibody and T Cell Response to SARS-CoV-2 Messenger RNA BNT162b2 Vaccine in Kidney Transplant Recipients and Hemodialysis Patients

**Running title:** SARS-CoV-2 vaccine in ESRD patients

**Manuscript Type:** Original Article - Rapid Communications

**Manuscript Category:** CUST_BASIC_COMMUNICATION_CATEGORY :No data available.

**Funders:** FUNDREF :No data available.

**Financial Disclosure:** No J. Plantier reports Research Funding from Abbott, Beckman, and Cepheid. O. Boyer reports Consultancy Agreements with BMS, ARGENX; Research Funding from CSL BEHRING, RA PHARMA, ARGENX, GRIFOLS; Honoraria from CSL BEHRING, ARGENX, BMS, ELSEVIER; and Scientific Advisor or Membership via FOCIS board of directors, and the IUIS education committee.

**Study Group/Organization Name:** CUST_STUDY_GROUP/ORGANIZATION_NAME :No data available.

**Study Group Members' Names:** CUST_STUDY_GROUP_MEMBERS :No data available.

**Total number of words:** 1954

**Abstract:** Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a high rate of mortality in patients with end stage renal disease and vaccination is hoped to prevent infection.
Methods. Between January 18, and February 24, 2021, 225 kidney transplant recipients (KTR) and 45 hemodialysis patients (HDP) received two injections of mRNA BNT162b2 vaccine. The post-vaccinal humoral and cellular response was explored in the first 45 KTR and 10 HDP.
Results. After the second dose, 8 HDP (88.9%) and 8 KTR (17.8%) developed anti-spike SARS-CoV-2 antibodies (p<0.0001). Median titer of antibodies in responders was 1052 AU/mL (IQR: 515-2689) in HDP and 671 AU/mL (IQR: 172-1523) in KTR (p=0.4). Nine HDP (100%) and 26 KTR (57.8%) showed a specific T cell response (p=0.06) after the second injection. In responders, median numbers of spikeâ€"reactive T cells were 305 SFC/106 CD3+ T cells (IQR: 95-947) in HDP and 212 SFC/106 CD3+ T cells (IQR: 61-330) in KTR (p=0.4). In KTR, the immune response to BNT162b2 seemed influenced by the immunosuppressive regimen, particularly tacrolimus or belatacept.
Conclusion. Immunization with BNT162b2 seems more efficient in HDP, indicating that vaccination should be highly recommended in these patients awaiting a transplant. However, the current vaccinal strategy for KTR may not provide effective protection against COVID-19 and will likely need to be improved.

**Significance Statement:**

Antibody and T cell responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines are poorly reported in kidney transplant recipients and hemodialysis patients. The authors investigated the response to BNT162b2 vaccine in 45 kidney transplants recipients (KTR) and 10 chronic hemodialysis patients (HDP). After the second dose, 88.9% of HDP and only 17.8% of KTR developed anti-SARS-CoV-2 antibodies. A specific T-cell response was induced in 100 % of HDP and 57.8% of KTR. The immune response seemed influenced by the immunosuppressive regimen in KTR, particularly tacrolimus and belatacept. These results could help to better define the strategy of vaccination in this immunocompromised population.

# Antibody and T cell response to SARS-CoV-2 messenger RNA BNT162b2 vaccine in kidney transplant recipients and hemodialysis patients

Dominique Bertrand[1], Mouad Hamzaoui[1], Veronique Lemée[2], Julie Lamulle[3], Mélanie Hanoy[1], Charlotte Laurent[1], Ludivine Lebourg[1], Isabelle Etienne[1], Mathilde Lemoine[1], Frank Le Roy[1], Dorian Nezam[1], Jean-Christophe Plantier[2], Olivier Boyer[3,4], Dominique Guerrot [1], Sophie Candon[3, 4].

[1] Department of Nephrology, Transplantation and hemodialysis, Rouen University Hospital, Rouen, France

[2] Department of Virology, Rouen University Hospital, Rouen, France

[3] Department of Immunology and Biotherapies, Rouen University Hospital, Rouen, France

[4] INSERM U1234, University of Rouen Normandy, Rouen, France

**Running Title: SARS-CoV-2 vaccine in ESRD patients**

**Word count:**

Abstract: 217 words

Text: 1954 words

**Corresponding author:**

Dominique Bertrand

1 rue de Germont, Rouen University Hospital, 76000 Rouen

dominique.bertrand@chu-rouen.fr

**Keywords: hemodialysis, kidney transplantation, SARS-CoV-2, SARS-CoV-2 antibody, T cell immunity, COVID-19, tacrolimus, belatacept.**

**ABSTRACT**

**Background**. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a high rate of mortality in patients with end stage renal disease and vaccination is hoped to prevent infection.

**Methods.** Between January 18, and February 24, 2021, 225 kidney transplant recipients (KTR) and 45 hemodialysis patients (HDP) received two injections of mRNA BNT162b2 vaccine. The post-vaccinal humoral and cellular response was explored in the first 45 KTR and 10 HDP.

**Results.** After the second dose, 8 HDP (88.9%) and 8 KTR (17.8%) developed anti-spike SARS-CoV-2 antibodies ($p<0.0001$). Median titer of antibodies in responders was 1052 AU/mL (IQR: 515-2689) in HDP and 671 AU/mL (IQR: 172-1523) in KTR ($p=0.4$). Nine HDP (100%) and 26 KTR (57.8%) showed a specific T cell response ($p=0.06$) after the second injection. In responders, median numbers of spike–reactive T cells were 305 SFC/$10^6$ CD3+ T cells (IQR: 95-947) in HDP and 212 SFC/$10^6$ CD3+ T cells (IQR: 61-330) in KTR ($p=0.4$). In KTR, the immune response to BNT162b2 seemed influenced by the immunosuppressive regimen, particularly tacrolimus or belatacept.

**Conclusion**. Immunization with BNT162b2 seems more efficient in HDP, indicating that vaccination should be highly recommended in these patients awaiting a transplant. However, the current vaccinal strategy for KTR may not provide effective protection against COVID-19 and will likely need to be improved.

## INTRODUCTION

Pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been particularly deleterious in kidney transplant recipients (1) (2) (3) and in patients with end stage renal disease (ESRD) (4), because of the severity of the disease and the high rate of morbidity and mortality. Moreover, the kidney transplantation activity has been highly impacted by the pandemic (5) (6). In order to protect these populations, SARS-CoV-2 vaccination is recommended through international guidelines (7) (8). However, KTR and dialyzed patients are considered low responders to vaccines (9) and were not included in SARS-COV-2 pre-authorization vaccine clinical trials.

A low after a first of an mRNA COVID-19 vaccine in solid organ transplant recipients has recently been reported (10). Evaluation of the humoral response to a vaccine readily evaluates its efficacy. However, in a population known to have lower seroconversion rates than the general non immunosuppressed population, the measurement of the cellular immune response could be particularly helpful and relevant.

We thus aimed in this study to explore the immunogenicity of mRNA BNT162b2 vaccine, after the first and second doses, not only by measuring vaccine-induced antibodies but also evaluating anti-SARS-CoV-2 spike-specific T cell response.

## METHODS

Between January 18 and February 3, 2021, 225 KTR and 45 hemodialysis patients received a first injection of Pfizer SARS-CoV-2 mRNA BNT162b2 vaccine and three weeks later the second injection. Blood samples were collected from the first 45 KTR (20%) and 10 (22.2%) hemodialysis patients were explored for both humoral and cellular immune response on the day of the second injection and one month later. Data were retrospectively analyzed. This retrospective study was submitted to the approbation of Rouen Centre Institutional Review Board.

The anti-SARS-CoV-2 post-vaccinal antibody response against the spike protein was assessed using the ARCHITECT IgG II Quant test (Abbott, USA) with titers >50 arbitrary units per mL (AU/mL) being considered as positive. (Detection range: 6.8–40000 AU/mL; positive agreement, 99.4%; negative agreement, 99.6%).

Peripheral blood mononuclear cells were isolated by density gradient centrifugation of blood samples and used immediately. PBMCs (in concentrations adjusted to $2x10^5$ CD3+ T cells per well) were plated in anti-IFNγ–coated Elispot 96-well plate in presence of overlapping 15-mer peptide pools spanning the sequence of SARS-CoV-2 spike protein S (pool S1 spanning the N-terminal part of the protein including the S1-subunit, and pool S2 spanning the C-terminal part), as well as N, M, ORF3A and ORF7A in order to detect a potential exposition to SARS-CoV-2 (JPT, Strassberg, Germany). Negative and positive control stimulation, respectively medium only and CEFX, a pool of 176 known peptides from various infectious agents (JPT, Strassberg Germany), were included in the assay. After an overnight culture, cells were washed and captured IFNγ was revealed using a colorimetric assay (UCytech, Utrecht, The Netherlands). Spots were counted with an automated ELISPOT reader (AID, Strassberg, Germany). For each stimulation condition, the average spot number observed in wells without antigen was subtracted. Results were expressed as spot forming cells (SFC) per $10^6$ CD3+ T cells. For each assay, a specific response was

considered positive if SFC number was superior to 3 standard deviations of spot numbers observed in wells without antigens (ranging between 9 and 20 SFC/$10^6$ CD3+ T cells) (11).

Quantitative data were presented as mean (SD), or median (IQR: interquartile range). Qualitative data were presented as percentages. The non-parametric Wilcoxon and Mann Withney tests were used to compare characteristics between groups with StatView version 5.0 (SAS Institute, USA).

## RESULTS

### Baseline characteristics (Table 1)

Baseline characteristics of the 45 KTR are described in Table 1. No patient developed a SARS-CoV-2 infection for up to one month after the second injection.

Regarding HDP, mean age was 71.2 ± 16.4 years. Their median duration of chronic dialysis was 3.14 years (0.6-12.6). One HDP experienced a SARS-CoV-2 infection 3 days after the second injection of vaccine. She was maintained at home until recovery. She was excluded from the analysis after the second dose.

### Humoral response after the first and second injection of vaccine in KTR and hemodialysis patients (Figure 1 A).

Three weeks after the first injection, only one HDP (11.1%) and one KTR (2.2%) developed anti-SARS-CoV-2 antibodies (p=0.19). Antibody titers in responders were 178.9 AU/mL in HDP and 311 AU/mL in KTR. One month after the second injection, 8 HDP (88.9%) and 8 KTR (17.8%) developed anti-SARS-CoV-2 antibodies (p<0.0001). Median antibody titers in responders were 1052 AU/mL (IQR: 515-2689) in HDP and 671 AU/mL (IQR: 172-1523) in KTR (p=0.4).

The single patient who tested positive for SARS-CoV-2, developed after the first a significant antibody titer (titer: 161 UA/mL), that dramatically increased after the second injection and COVID-19 (titer: 53737.6 UA/mL).

### Cellular response after the first and second injection of vaccine in KTR and hemodialysis patients (Figure 1 B)

Three weeks after the first injection, 5 HDP (55.6%) and 11 KTR (24.4%) displayed a significant number of spike–reactive T cells (p=0.06). In responders, median numbers of specific T cells were 208 SFC/$10^6$ CD3+ T cells (IQR: 65-315) in HDP and 45 SFC/$10^6$ CD3+ T cells (IQR: 35-55) in KTR (p=0.02). No response to N, M, ORF3A and ORF7A was evidenced in KTR and HDP, excluding a potential exposition to SARS-CoV-2.

One month after the second injection, a specific T cell response was detected in 9 HDP (100%) and 26 KTR (57.8%) (p=0.06). In responders, median numbers of spike–reactive T cells were 305 SFC/$10^6$ CD3+ T cells (IQR: 95-947) in HDP and 212 SFC/$10^6$ CD3+ T cells (IQR: 61-330) in KTR (p=0.4).

In the patient who tested positive for SARS-CoV-2, spike-specific T cell numbers were 155 SFC/$10^6$ CD3+ three weeks after the first injection and 3245 SFC/$10^6$ CD3+ after the second injection and SARS-CoV-2 infection. In this case, T-cell responses to N, M, ORF3A and ORF7A were detected.

**Humoral and cellular responses to vaccine in KTR, according to the immunosuppressive regimen.**

Baseline characteristics of the 45 KTR according to the baseline immunosuppressive (IS) regimen are described in Table 2.

One month after the second injection, 2 KTR (8.3%) developed anti-SARS-CoV-2 antibodies in group 1, 0 in group 2 and 6 (54.5%) in group 3 (group 1 vs group 2, p=0.34; group 2 vs group 3, p=0.005; group 1 vs group 3, p=0.002) (Figure 2A).

One month after the second injection, 12 KTR (50%) in group 1, 4 KTR (40%) in group 2 and 10 KTR (90.9%) in group 3 displayed a specific T cell response (group 1 vs group 2, p=0.4; group 2 vs group 3, p=0.01; group 1 vs group 3, p=0.02). (Figure 2B). Median numbers of SARS-CoV-2–reactive T cells, after the second dose, were 160 SFC/$10^6$ CD3+ T cells (IQR: 46-303) in group 1, 42.5 SFC/$10^6$ CD3+ T cells

(IQR: 35-69) in group 2 and 298 SFC/$10^6$ CD3+ T cells (IQR: 240-475) in group 3 (group 1 vs group 2, p=0.05; group 2 vs group 3, p=0.005; group 1 vs group 3, p=0.01).

In univariate analysis, predictive factors for a positive antibody response were the duration of kidney transplantation (p=0.003) and a cyclosporine-based immunosuppressive regimen (p=0.0003). No factor predictive of a significant T cell response was identified. T cell counts were not associated with the detection or the magnitude of the antibody but was associated with T cell response to the vaccine in univariate analysis (p=0.01 for CD3, p=0.05 for CD4, p=0.03for CD8).

## DISCUSSION

We report here the anti-SARS-CoV-2 antibody and T-cell responses after 2 doses of mRNA vaccine BNT162b2 in a cohort of KTR and hemodialysis patients. We demonstrate that an antibody response is scarcely induced in immunocompromised KTR after a first vaccine dose and in only 17.8% of them after the second dose. Induction of an anti-spike T cell specific response occurs more frequently in 51.1 % of KTR after the second injection. By contrast, in HDP, a specific humoral and cellular response is observed in respectively 88.9% and 100% of patients after the second dose. These results contrast with the robust and early induced immunity observed during mRNA vaccine trials, showing 100% anti-spike seroconversion after vaccination with mRNA-1273 (12) or BNT162b2 (13). Narasimhan et al. observed after the first vaccine dose in a naïve population, using the same serological assay (14), median IgG titers of 2217 AU/mL (95% CI, 0-44182), that, following the booster dose, dramatically increased 8.2 fold to 18 272 AU/mL (at 98% CI, 11724-21750) ($p<0.001$). Specific IgG titers found in our HDP and KTR were significantly lower. Using a similar IFNγ Elispot assay, Angyal et al (15) recently reported in SARS-CoV-2-naïve healthcare workers, median numbers of spike-specific T cells of 58 SFU/$10^6$ PBMCs (IQR 29-146) after a single dose of BNT162b2 and 165 SFU/$10^6$ PBMCs (IQR 101-277) after two doses. These values are in the same range than those observed in our study in KTR and HDP, especially after the second dose. Thus, post-vaccinal T cell immunity in KTR and HDP seems comparable to that of healthy naïve subjects.

Data regarding vaccination in dialysis are very scarce. Seroconversion rates after influenza vaccine administration in such patients vary in the literature, ranging from 33% to 80% (16) (17) (18).. Regarding the protection from SARS-CoV-2 in dialysis patients, among 31 waitlisted ESRD patients, 87% of them mounted an antibody response after a first vaccine dose ($p < 0.05$) (19). Grupper et al (20) reported very recently that most of 56 hemodialyzed patients (96%) developed specific antibodies following full BNT162b2 vaccination, but with significantly lower titers than controls. Our data are in line with these

results and extend them by showing effective induction of both humoral and T cell responses after two doses of the BNT162b2 vaccine.

In KTR, vaccinal responses are expected to be impaired, particularly early post-transplantation, after treatment for rejection or rituximab therapy (21) (22) (23). KTR of 65 years and older on ≥ 2 g of daily mycophenolate mofetil generally have reduced humoral responses to influenza vaccines (24). Regarding the efficacy of SARS-CoV-2 mRNA vaccine in KTR, Boyarsky et al (10) reported that 82.6% of transplant recipients (n=436) did not mount significant anti-spike antibody titers after a first dose of mRNA vaccine. In the same vein, Benotmane et al. (25) showed that only 10.8% of KTR had a positive serology 28 days after a first injection of mRNA-1273 vaccine. The median IgG titer was 224 AU/mL (IQR: 76−496 AU/mL). Similarly, Yi et al (19) reported a seroconversion rate of only 6.2% of KTR, after a first mRNA vaccine dose. Our results are thus in line with these studies, showing in addition that after a second vaccine dose, the seroconversion rate is only modestly increased (17.8%). Furthermore, they show that despite a low seroconversion rate, an anti-spike-specific T cell response is triggered in half of the patients after 2 vaccine doses. Presence of anti-spike T cells in absence of specific antibodies could provide some level of protection from SARS-CoV-2 infection, by limiting the extent of viral replication, as reported in the context of CMV infection in KTR (26) (27).

Our results suggest that the immune response to BNT262b2 vaccine is essentially influenced by the intensity of the immunosuppressive regimen. Belatacept-treated patients were indeed the worst responders, developing no antibodies and no or only few specific T cells, Belatacept is in fact suspected to be associated with an increased in the incidence of opportunistic infections (28) (29) and CMV disease (30). Tacrolimus-treated patients also responded weakly to vaccination, although significant T cell numbers were induced in some of them. It should be noted that the majority of our patients were on MMF, which may have contributed to impairing post-vaccine antibody responses (31).

In conclusion, the mRNA BNT162b2 vaccine seems efficient in HDP, indicating that vaccination should be highly recommended in these patients. By contrast, the low seroconversion rate observed in KTR is

worrying. In seronegative patients displaying significant numbers of anti-spike T cells a third dose of vaccine might trigger a humoral response. However, in patients failing to generate any response, should we prefer standard adjuvanted vaccines or adenovirus-based vaccines? Alternatively, should immunizing household members and close contacts be the priority? Post-vaccination COVID-19 incidence data in KTR should provide answers to these questions.

**Authors Contributions:**

Sophie Candon, Veronique Lemee and Dominique Bertrand designed the study; Julie Lamulle performed Elispot assays; Sophie Candon, Veronique Lemee and Dominique Bertrand collected data; Mouad Hamzaoui, Sophie Candon and Dominique Bertrand analyzed the data; Sophie Candon and Dominique Bertrand wrote the paper; and all authors provided feedback and critical review.

**Acknowledgements:**

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 unit.

**Disclosures:**

J. Plantier reports Research Funding from Abbott, Beckman, and Cepheid. O. Boyer reports Consultancy Agreements with BMS, ARGENX; Research Funding from CSL BEHRING, RA PHARMA, ARGENX, GRIFOLS; Honoraria from CSL BEHRING, ARGENX, BMS, ELSEVIER; and Scientific Advisor or Membership via FOCIS board of directors, and the IUIS education committee. The remaining authors have no conflict of interest to disclose related to the work reported here.

**Funding.** The authors declare no funding received for this work

## REFERENCES


1. Caillard S, Anglicheau D, Matignon M, Durrbach A, Greze C, Frimat L, et al. An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants. Kidney Int. déc 2020;98(6):1549‑58.

2. Thaunat O, Legeai C, Anglicheau D, Couzi L, Blancho G, Hazzan M, et al. IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT). Kidney Int. déc 2020;98(6):1568‑77.

3. Caillard S, Chavarot N, Francois H, Matignon M, Greze C, Kamar N, et al. Is COVID-19 infection more severe in kidney transplant recipients? Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. mars 2021;21(3):1295‑303.

4. Jager KJ, Kramer A, Chesnaye NC, Couchoud C, Sánchez-Álvarez JE, Garneata L, et al. Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. Kidney Int. déc 2020;98(6):1540‑8.

5. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E. COVID-19 and Solid Organ Transplantation: A Review Article. Transplantation. 1 janv 2021;105(1):37‑55.

6. Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. mars 2021;21(3):925‑37.

7. COVID-19 Vaccination Program Operational Guidance | CDC [Internet]. 2021 [cité 2 avr 2021]. Disponible sur: https://www.cdc.gov/vaccines/covid-19/covid19-vaccination-guidance.html

8. Page not found [Internet]. European Centre for Disease Prevention and Control. [cité 2 avr 2021]. Disponible sur: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-vaccination-and-prioritisation-strategies.pdf.

9. Krueger KM, Ison MG, Ghossein C. Practical Guide to Vaccination in All Stages of CKD, Including Patients Treated by Dialysis or Kidney Transplantation. Am J Kidney Dis Off J Natl Kidney Found. mars 2020;75(3):417‑25.

10. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients. JAMA. 15 mars 2021;

11. Candon S, Guerrot D, Drouot L, Lemoine M, Lebourg L, Hanoy M, et al. T cell and antibody responses to SARS-CoV-2: Experience from a French transplantation and hemodialysis center during the COVID-19 pandemic. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. févr 2021;21(2):854‑63.

12. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. N Engl J Med. 12 nov 2020;383(20):1920‑31.

13. Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 17 déc 2020;383(25):2439‑50.

14. Narasimhan M, Mahimainathan L, Araj E, Clark AE, Markantonis J, Green A, et al. Clinical evaluation of the Abbott Alinity SARS-CoV-2 spike-specific quantitative IgG and IgM assays among infected, recovered, and vaccinated groups. J Clin Microbiol. 7 avr 2021;

15. T-Cell and Antibody Responses to First BNT162b2 Vaccine Dose in Previously SARS-CoV-2-Infected and Infection-Naive UK Healthcare Workers: A Multicentre, Prospective, Observational Cohort Study by Adrienn Angyal, Stephanie Longet, Shona Moore, Rebecca P. Payne, Adam Harding, Tom Tipton, Patpong Rongkard, Mohammad Ali, Luisa M. Hering, Naomi Meardon, James Austin, Rebecca Brown, Donal Skelly, Natalie Gillson, Sue L. Dobson, Andrew Cross, Gurjinder Sandhar, Jonathan A. Kilby, Jessica K. Tyerman, Alexander R. Nicols, Jarmila S. Spegarova, Hema Mehta, Hailey Hornsby, Rachel Whitham, Christopher P. Conlon, Katie Jeffery, Philip Goulder, John Frater, Christina Dold, Matthew Pace, Ane Ogbe, Helen Brown, Azim M. Ansari, Emily Adland, Anthony Brown, Meera A. Chand, Adrian Shields, Philippa Matthews, Susan Hopkins, Victoria Jane Hall, William James, Sarah L. Rowland-Jones, Paul Klenerman, Susanna Dunachie, Alex G. Richter, Christopher J. A. Duncan, Eleanor Barnes, Miles W. Carroll, Lance Turtle, Thushan I. de Silva, PITCH Consortium :: SSRN [Internet]. [cité 28 avr 2021]. Disponible sur: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3812375

16. Chang Y-T, Wang J-R, Lin M-T, Wu C-J, Tsai M-S, Wen-Chi CL, et al. Changes of immunogenic profiles between a single dose and one booster influenza vaccination in hemodialysis patients - an 18-week, open-label trial. Sci Rep. 12 févr 2016;6:20725.

17. Crespo M, Collado S, Mir M, Cao H, Barbosa F, Serra C, et al. Efficacy of influenza A H1N1/2009 vaccine in hemodialysis and kidney transplant patients. Clin J Am Soc Nephrol CJASN. sept 2011;6(9):2208‑14.

18. Lertdumrongluk P, Changsirikulchai S, Limkunakul C, Prachukthum P, Punpiput P, Buppanharun R, et al. Safety and immunogenicity of a 2009 influenza A (H1N1) vaccine in hemodialysis patients. Vaccine. 1 févr 2012;30(6):1108‑14.

19. Yi SG, Knight RJ, Graviss EA, Nguyen DT, Ghobrial RM, Gaber AO, et al. Kidney Transplant Recipients Rarely Show an Early Antibody Response Following the First COVID-19 Vaccine Administration. Transplantation. 19 mars 2021;

20. Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol CJASN. 6 avr 2021;

21. Danziger-Isakov L, Kumar D, AST Infectious Diseases Community of Practice. Vaccination in solid organ transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. mars 2013;13 Suppl 4:311‑7.

22. Pérez-Romero P, Bulnes-Ramos A, Torre-Cisneros J, Gavaldá J, Aydillo TA, Moreno A, et al. Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. nov 2015;21(11):1040.e11-18.

23. Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PloS One. 2013;8(2):e56974.

24. Hirzel C, Kumar D. Influenza vaccine strategies for solid organ transplant recipients. Curr Opin Infect Dis. août 2018;31(4):309‑15.

25. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, et al. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int. 25 mars 2021;

26. Litjens NHR, Huang L, Dedeoglu B, Meijers RWJ, Kwekkeboom J, Betjes MGH. Protective Cytomegalovirus (CMV)-Specific T-Cell Immunity Is Frequent in Kidney Transplant Patients without Serum Anti-CMV Antibodies. Front Immunol. 2017;8:1137.

27. Lúcia M, Crespo E, Melilli E, Cruzado JM, Luque S, Llaudó I, et al. Preformed frequencies of cytomegalovirus (CMV)-specific memory T and B cells identify protected CMV-sensitized individuals among seronegative kidney transplant recipients. Clin Infect Dis Off Publ Infect Dis Soc Am. 1 déc 2014;59(11):1537‑45.

28. Bertrand D, Chavarot N, Gatault P, Garrouste C, Bouvier N, Grall-Jezequel A, et al. Opportunistic infections after conversion to belatacept in kidney transplantation. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 1 févr 2020;35(2):336‑45.

29. Bertrand D, Terrec F, Etienne I, Chavarot N, Sberro R, Gatault P, et al. Opportunistic Infections and Efficacy Following Conversion to Belatacept-Based Therapy after Kidney Transplantation: A French Multicenter Cohort. J Clin Med. 28 oct 2020;9(11).

30. Chavarot N, Divard G, Scemla A, Amrouche L, Aubert O, Leruez-Ville M, et al. Increased incidence and unusual presentations of CMV disease in kidney transplant recipients after conversion to belatacept. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 6 déc 2020;

31. Struijk GH, Minnee RC, Koch SD, Zwinderman AH, van Donselaar-van der Pant KAMI, Idu MM, et al. Maintenance immunosuppressive therapy with everolimus preserves humoral immune responses. Kidney Int. nov 2010;78(9):934‑40.

**Table 1 . Baseline characteristics of KTR explored.** KTR : kidney transplant recipients, M: male, F: female, BMI : body mass index, eGFR: estimated glomerular filtration rate, ATG: antithymoglobulines, R-IL2: interleukin 2 receptor, MMF: mycophenolate mofetil, AZA: azathioprine

| | KTR n=45 |
|---|---|
| Age - years | 63.5 ± 16.3 |
| Sex (M/F) - n | 23/22 |
| Diabetes mellitus - n (%) | 10 (22.2) |
| Hypertension - n (%) | 36 (80) |
| BMI - kg/m² | 26.2 ± 4.7 |
| Time from transplantation – years | |
| median (range) | 6.9 (0.22-30.2) |
| Immunized KTR – n (%) | 12 (26.7) |
| median PRA class I | 6 |
| median PRA class II | 14.5 |
| Previous history of rejection - n (%) | 1 (2.2) |
| eGFR - mL/min/1,73 m² | 43.3 ± 15.7 |
| P / C ratio - g/g | 0.26 ± 0.06 |
| Lymphocytes count - /mm³ | |
| CD3+ | 892 ± 476 |
| CD4+ | 447 ±263 |
| CD8+ | 397 ± 297 |
| Induction therapy for KT - n (%) | |
| ATG | 18 (40) |
| Anti R-IL2 | 27 (60) |
| IS regimen - n (%) | |
| Tacrolimus | 24 (53.3) |
| Ciclosporine | 8 (17.8) |
| MMF | 37 (82.2) |
| AZA | 4 (8.9) |
| everolimus | 3 (6.7) |
| Belatacept | 10 (22.2) |
| Steroids | 21 (46.7) |

**Table 2 . Baseline characteristics of KTR explored according to the immunosuppressive regimen**

Tac: tacrolimus, bela: belatacept, IS : immunosuppressive, KTR : kidney transplant recipients, M: male, F: female, BMI : body mass index, eGFR: estimated glomerular filtration rate, ATG: antithymoglobulines, R-IL2: interleukin 2 receptor, MMF: mycophenolate mofetil, AZA: azathioprine, C0: through level. p*: comparison between group 1 and 2; p**: comparaison between group 2 and 3; p***: comparison between group 1 and 3.

| | G1: Tac based IS regimen (n=24) | p* | G2: Bela based IS regimen (n=10) | p** | G3: Non-tac and non-bela based IS regimen (n=11) | p*** |
|---|---|---|---|---|---|---|
| **Age - years** | **60,2 ± 17,4** | **0,21** | **68,1 ± 13,7** | **0,82** | **66,6 ± 15,5** | **0,29** |
| **Sex (M/F) - n** | **12/12** | **0,59** | **6/4** | **0,51** | **5/6** | |
| **Time from transplantation – years** | **6,1 ± 4,9** | **0,92** | **6,3 ± 4,7** | **0,001** | **17,1 ± 7,9** | **< 0,0001** |
| **eGFR - mL/min/1,73 m²** | **45,6 ± 13,7** | **0,005** | **30,4 ± 11,6** | **0,007** | **50,1 ± 17,4** | **0,41** |
| **Induction therapy for KT - n (%)** | **11 (45,8)** | **0,16** | **2 (20)** | **0,21** | **5 (45,5)** | |
| **ATG** | **13 (54,2)** | | **8 (80)** | | **6 (54,5)** | |
| **Anti R-IL2** | | | | | | |
| **IS regimen - n (%)** | | | | | | |
| **Tacrolimus** | **24 (100)** | **< 0,0001** | **0** | **< 0,0001** | **0** | **< 0,0001** |
| **C0 tac** | **6,1 ± 1,8** | **0,007** | **-** | **0,54** | **-** | **< 0,0001** |
| **Ciclosporine** | **0** | **0,78** | **0** | **0,69** | **8 (72,7)** | **0,05** |
| **C0 ciclo** | **-** | **0,14** | **-** | **0,48** | **67,2 ± 15,3** | **0,26** |
| **MMF** | **23 (95,8)** | **0,12** | **6 (60)** | **0,60** | **8 (72,7)** | **0,56** |
| **MMF median of dosage mg** | **1000** | **< 0,0001** | **625** | **< 0,0001** | **1000** | **0,03** |
| **AZA** | **1 (4,2)** | **0,13** | **2 (20)** | **0,12** | **1 (9,1)** | **0,77** |
| **everolimus** | **0** | | **1 10)** | | **2 (18,2)** | |

| | | | |
|---|---|---|---|
| **Belatacept** | **0** | **10 (100)** | **0** |
| **Steroids** | **10 (41,7)** | **7 (70)** | **4 (36,4)** |

**Figure 1**

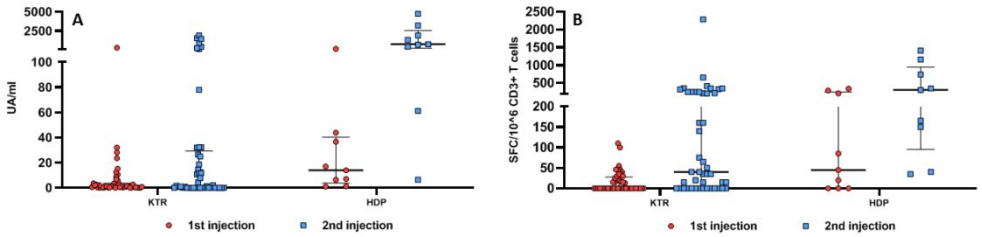



**Figure 1. SARS-CoV-2 anti-spike antibody** response (A) and SARS-CoV**-2–reactive IFNγ-producing T cells (B) in KTR and HDP following first and second injection of SARS-CoV-2 mRNA BNT162b2 vaccine**. Titers of S IgG are shown in the samplings of 45 KTR and 9 HDP. Median and IQR are shown. Numbers of T cells (expressed as SFC/$10^6$ CD3+ T cells) reactive to overlapping peptide pools spanning SARS-CoV-2 structural protein S (pools S1 and S2) in 45 KTR and 9 HDP. Median and IQR are shown.

**Figure 2**

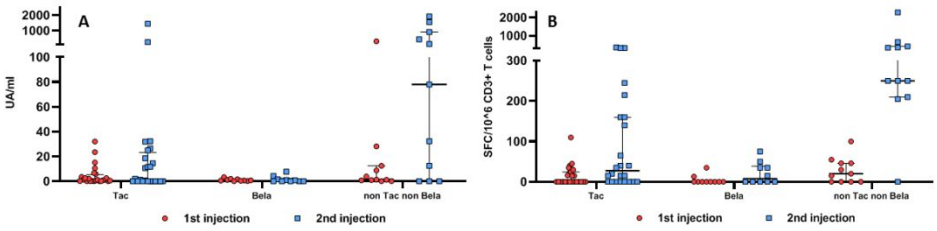
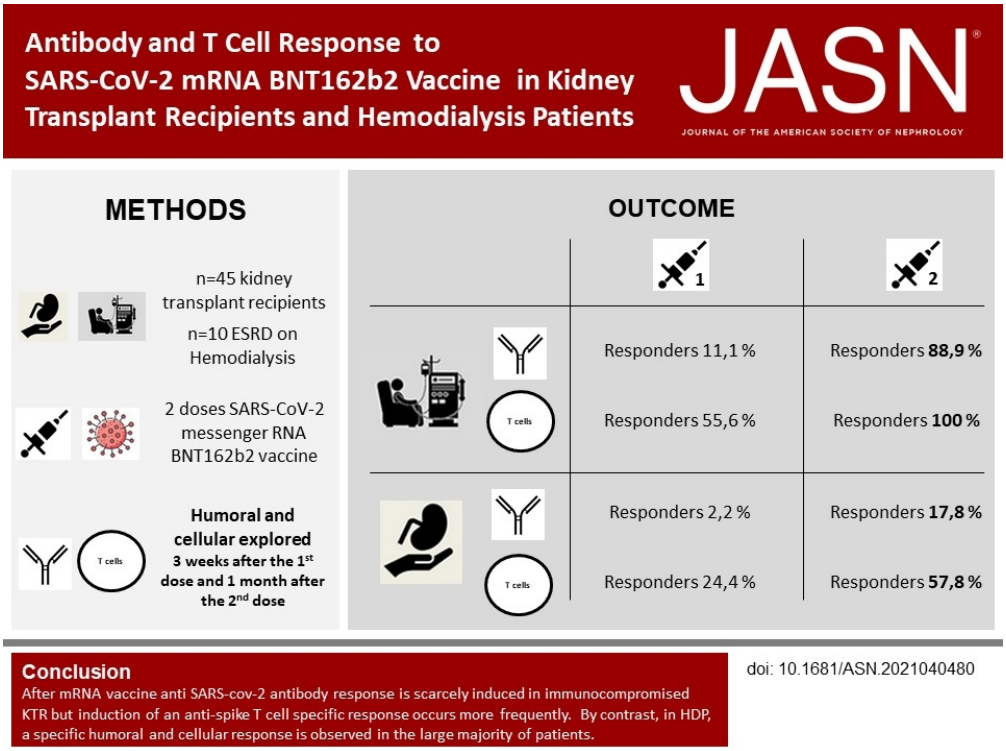



**Figure 2. SARS-CoV-2 anti spike antibody response (A) and SARS-CoV-2–reactive IFNγ-producing T cells (B) in KTR following first and second injection of SARS-CoV-2 mRNA BNT162b2 vaccine, according to immunosuppressive regimen**. Numbers of T cells (expressed as SFC/$10^6$ CD3+ T cells) reactive to overlapping peptide pools spanning SARS-CoV-2 structural protein S (pools S1and S2) in the samplings of 45 KTR. Median and IQR are shown.




254x190mm (96 x 96 DPI)