HUMORAL RESPONSE TO SARS-COV-2 mRNA VACCINE IN HEART TRANSPLANT RECIPIENTS

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BACKGROUND

- The clinical course of COVID-19 is aggressive in heart transplant recipients (HTR) with a case-fatality rate as high as 25% during the first pandemic wave prior to vaccines release[1]
- Recent studies reported poor to moderate humoral response after 2 vaccine doses in HTR.[2] Currently, French healthcare authorities recommend 2 and 3 vaccine injections for transplant recipients with and without prior SARS-CoV-2 infection, respectively. A 260 BAU/mL threshold of Anti-S IgG was defined as marker of vaccine efficacy by these authorities. A fourth dose is in discussion for immunocompromised patients.
- This study aimed to assess:
  - Whether third and fourth doses of vaccine improve SARS-CoV-2 antibody response
  - Durability of immunogenicity after three and four vaccine doses
  - Effect of maintenance immunosuppressive regimen on vaccine response

METHODS

- All HTR followed at Paris Bichat university hospital who received at least one dose of vaccine between January 2021 and January 2022 (n=197) were enrolled in this single-center prospective observational cohort study.
- Controls were obtained from HCWs vaccinated with BNT162b2 (Pfizer-BioNTech) from Bichat-Claude Bernard University Hospital Virology department sample collection.
- Analyses were performed using automated a chemiluminescent microparticle immunoassay (CMIA) (Alinity, Abbott). The SARS-CoV-2 IgG II Quant Alinity was used to quantify anti-spike SARS-CoV-2 IgG targeting the spike receptor binding domain (RBD). A calibration on the International Standard NIBSC OMS (20/136) allowed to express the results in BAU/ml (binding antibody units) with a positivity cut-off of ≥ 7.1 BAU/mL. The SARS-CoV-2 IgG assay Alinity was used to detect anti-nucleocapsid IgG (cut-off index > 0.49).
- Three immunosuppressive regimens were compared : calcineurin inhibitors (CNI)-based therapy, mammalian target of rapamycin (mTOR) inhibitor-based therapy and belatacept-based therapy
- Statistical analyses were performed using Graphpad Prism. Categorical variables were described as number (%) and continuous variables with median (IQR). Medians were compared using Mann-Whitney U test or Wilcoxon test when paired while categorical variables were compared using Chi-2 test.
- This study was approved by the Comité d'Evaluation de l'Ethique des projets de Recherche Biomedicale, OUEST III of the Centre Hospitalier et Universitaire, La Milètrie, POITIERS and Assistance Publique-Hôpitaux de Paris (AP-HP) upon the approval number APHP211456 / IDRCB 2021-A02517-34.

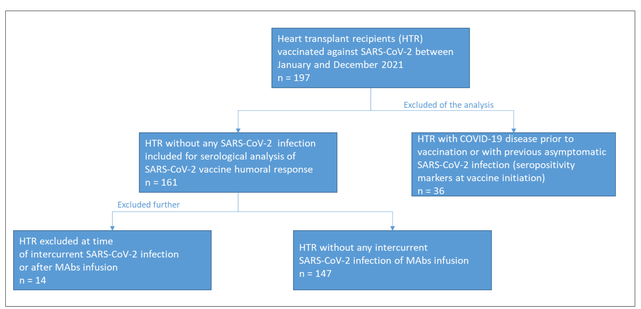


Figure 1 : Flowchart of the heart transplant recipients (HTR) included for analysis of humoral response to SARS-CoV-2 vaccination among all the HTR of the study.

RESULTS

- A total of 197 HTR were vaccinated during the period of the study. Only the 161 HTR without any COVID-19 disease or any hallmark of SARS-CoV-2 infection prior to vaccination were included in this analysis. Patients with undercurrent COVID-19 disease or serological marker of asymptomatic SARS-CoV-2 infection (anti-N antibodies) were further excluded since the time of infection for the analysis of humoral response to vaccination. **(Figure 1)**
- A total of 161 HTR were included in the analysis of humoral response to SARS-CoV-2 infection with the characteristics shown in **Table 1.** The group of HTR receiving Nulojix was significantly different from the CNI- and mTORi groups regarding age, sex and cardiac transplant indication.

Table 1 : Characteristics of heart transplant recipients included for the humoral response to vaccination analysis

	All patients (n=161)	CNI-based treatment (n=85)	mTORi-based treatment (n=55)	Belatacept-based treatment (n=13)	*p-value*
Age – *years, median [IQR]*	60 [50–67]	59 [45–68]	61 [51–65]	66 [60–74]	*0.04*
Sex – *female, n(%)*	38 (24%)	27 (32%)	6 (11%)	3 (23%)	*0.01*
Cardiac transplant indication – *no (%)*					
- Cardiomyopathy	71 (44%)	39 (46%)	19 (34%)	9 (69%)	*0.07*
- Coronary artery disease	64 (40%)	25 (29%)	31 (56%)	4 (31%)	*0.006*
- Valvular cardiomyopathy	17 (11%)	13 (15%)	4 (7%)	0 (%)	*0.8*
- Other transplant indications	9 (6%)	8 (9%)	1 (2%)	0 (%)	*0.7*
Vaccination – Transplantation delay – *no (%)*					
Vaccination before heart transplant	10 (16%)	3 (4%)	1 (2%)		
Delay between transplantation and vaccination initiation (year) - median, [IQR]	4 [2–7]	4 [1–7]	5 [3–7]	5 [3–6]	*0.09*

- Humoral response follow up was assessed in 161 patients at different points **(Figure 2)**
  - 10/66 (15%) of the HTR had positive anti-S IgG serology within the 2 months after second dose injection, with only 4 of them above the 260 BAU/mL threshold
  - Within 3 months after the third dose, a third of the HTR had positive IgG anti-S serology (36/96, 38%) and 10% had anti-S IgG titers above 260 BAU/mL
  - When comparing the 56 patients both tested within 3 months and more than 6 months after 3rd dose, humoral response was stable with 41% (23/56) of the HTR still seropositive but with low titers of anti-S IgG (9% above 260 BAU/mL) (p=0.3)

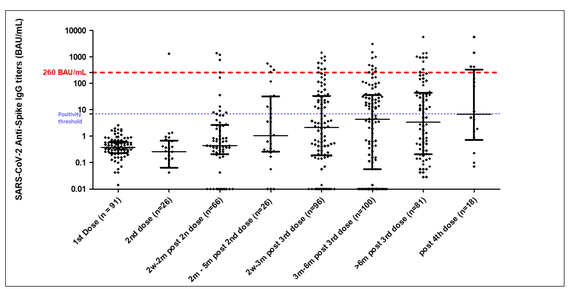


Figure 2 : Serological follow up of 161 heart transplant recipients after the first, second and third doses of SARS-CoV-2 vaccine

- Humoral response was compared between the different immunosuppressive treatments of HTR
  - Humoral response within two months after the second dose was lower for HTR than control groups whatever the immunosuppressive treatment they were receiving **(Figure 3)**
  - After the third dose, humoral response of HTR was still significantly lower than the control group and the HTR group receiving Belatacept immunosuppressive based treatment showed a lower response than the HTR receiving CNI or mTORi based regimen **(Figure 4)**

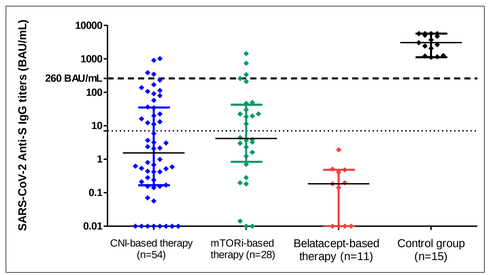


Figure 3: Comparison of humoral response to SARS-CoV-2 vaccination after 2 weeks and within 2 months after 2 doses of vaccine depending on immunosuppressive treatment

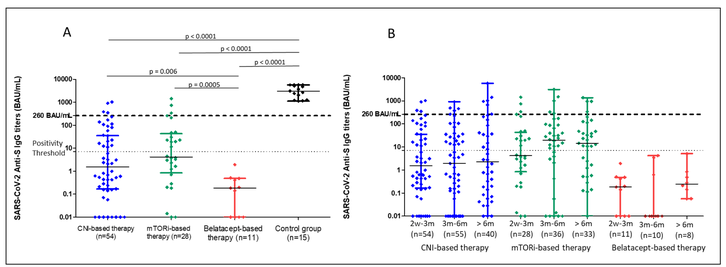


Figure 4: Comparison of humoral response to SARS-CoV-2 vaccination after 3 doses of vaccine depending on immunosuppressive treatment: A) within 3 months post 3rd dose, B) within 3 months, 3 to 6 months and more than 6 months after 3rd dose.

CONCLUSION

- This study gives new insights on the effect of the 3rd vaccine dose in HTR with low rate of seroconversion and low titers of anti-S IgG but sustained humoral response when seroconversion occurs.
- Immunosuppressive treatment seems to have different impact on humoral response to SARS-CoV-2 vaccination with not any HTR receiving a Belatacept based regimen seroconverting
- A fourth vaccine dose is now proposed to non responding HTR and its effect has to be studied even more in HTR receiving Belatacept.

1. Clinical manifestations and outcomes of coronavirus disease-19 in heart transplant recipients: a multicentre case series with a systematic review and meta-analysis. Granger et al, Transplant International, March 2021.
2. Cellular and humoral immune response after mRNA-1273 SARS-CoV-2 vaccine in liver and heart transplant recipients. Herrera S et al, Am J Transplant, Dec 2021