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ANTIBODIES IN SOLID ORGAN TRANSPLANT RECIPIENTS SIX MONTHS AFTER BNT162B2 VACCINATION

VACCIM
Vaccination Clinic for immunocompromised

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BACKGROUND

Previous studies have shown an inferior response to mRNA SARS-CoV-2 vaccination in solid organ transplant (SOT) recipients up six months after vaccination[1]. We examined the development in anti-receptor binding domain (RBD) IgG after two doses of BNT162b2 in SOT recipients six months after vaccination compared to immunocompetent controls.

WE AIMED TO:

- Investigate humoral responses six months after BNT162b2 SARS-CoV-2 mRNA vaccination in SOT recipients compared to immunocompetent controls.

Primary outcome:
- IgG antibody concentration

Secondary outcomes:
- Neutralizing capacity of antibodies.
- Risk factors for humoral non-response
- T-cell response

METHODS

In this prospective observational study including 200 SOT recipients and 200 age- and sex-matched controls, we measured immunogenicity of two doses of BNT162b2 vaccine up to six months after vaccination. An in-house enzyme-linked immunosorbent assay (ELISA) based system was used to measure concentrations of anti-receptor binding domain (RBD) IgG. Neutralizing capacity of antibodies was estimated using an in-house ELISA based pseudo-neutralization assay. Presence of anti-SARS-CoV-2 nucleocapsid (N) antibodies was assed using an electrochemiluminescence based kit from Roche diagnostics. Presence of N-antibodies was used as evidence of previous natural infection. In 99 SOT recipients and 37 controls an interferon-gamma (IFN-γ) releasing assay was used to assess T-cell responses. A positive humoral response was defined as having the combination of SARS-CoV-2 RBD IgG concentration ≥ 225 AU/mL and ≥25% inhibition in the neutralizing assay after vaccination. A positive T-cell response was defined as an IFN-γ concentration above 200 mIU/mL.

Statistics: IgG was reported as geometric mean concentrations (GMC) with 95% confidence intervals (CI). Changes in IgG levels were compared using a two-part linear mixed model and two-part natural cubic spline model. Poisson regression with robust standard errors was used to test associations between humoral response and independent variables in SOT recipients after adjusting for sex and age. P-values <0.05 were considered significant.

Baseline characteristics	SOT recipients	Controls	P-value
Participants, n	200	200	N/A
Median age, years (IQR)	56.0 (57-64)	56.5 (49-62)	0.172
Male sex, n (%)	110 (55 %)	114 (57%)	0.763
BMI, mean (SD)	26.1 (5.5)	25.8 (4.5)	0.656
GMC AU/mL [95% CI]			
- Baseline	1.14 [1.08; 1.24]	2.56 [2.03; 3.33]	
- Three weeks	11.97 [7.73; 18.77]	496.55 [373.44; 640.99]	
- Two months	249.29 [153.70 ; 385.19]	12650.49 [10252.80; 15465.30]	
- Six months	55.85 (36.95-83.33)	1447.94 (1131.82-1798.96)	

Table 1 – Baseline characteristics of the study population
GMC: Geometric mean concentration, missing data on BMI from 100 SOT recipients and 26 controls

RESULTS

Geometric mean concentration of anti-RBD IgG

In SOT recipients GMC of anti-RBD IgG increased from baseline (1.14 AU/mL, 95% CI 1.08-1.24**)** to three weeks after the first vaccine dose (11.97 AU/mL, 95% CI 7.73-18.77) and from three weeks to two months after the first vaccine dose and after receiving the second dose (249.29 AU/mL**,** 95% CI 153.70 – 385.19, figure 1+2). From two to six months after first vaccine there was a significant decline in GMC of anti-RBD IgG to 55.85 AU/mL (95% CI 36.95-83.33). The predicted GMC of anti-RBD IgG in SOT recipients was lower than in controls at all time points (figure 1+2).

T-cell reponses

More controls had a T-cell response six months after vaccination (13.1 % of SOT recipients vs. 59.4 % of controls p<0.001).

Risk factors associated with humoral non-response

We found increasing age (RR 1.23 per 10 years, 95% CI: 1.11-1.35 p<0.001), use of mycophenolate (RR 1.53, 95% CI: 1.18-1.99, p = 0.001), use of corticosteroids (RR 1.45 95% CI: 1.10-1.90), p = 0.009), kidney transplantation compared to liver transplantation (RR 1.70, 95% CI 1.25-2.30, p = 0.001) lung transplantation compared to liver transplantation (RR 1.63, 95% CI: 1.16-2.29, p = 0.005, de novo non-skin cancer (RR = 1.52 95% CI: 1.26-1.82 p<0.001) and being within one year of transplantation (RR 1.55, 95% CI: 1.30-1.85, p<0.001) to be associated with increased risk of humoral non-response six months after first vaccine dose.

REFERENCES:
1. ALEJO JL, MITCHELL J, CHIANG TP-Y, ET AL. SIX-MONTH ANTIBODY KINETICS AND DURABILITY IN SARS-COV-2 MRNA VACCINATED SOLID ORGAN TRANSPLANT RECIPIENTS. *TRANSPLANTATION*. PUBLISHED ONLINE 2021. DOI:10.1097/TP.0000000000003975

CONCLUSIONS

We found humoral and cellular responses to two doses of BNT162b2 to be inferior in SOT recipients compared to immunocompetent controls. Furthermore, anti-RBD concentration declined from two months after first dose to six months after first dose. Further investigations of clinical significance of anti-RBD IgG concentration and vaccine non-response is warranted to optimize the timing and use of booster vaccines. Multiple risk factors for non-response were identified and might help identify SOT recipients at high risk of vaccine non-response.

ACKKNOWLEDGEMENTS:
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SOT-recipients characteristics	
Transplant type	
- Liver transplant recipients	61 (30.5%)
- Kidney transplant recipients	102 (51.0%)
- Lung transplant recipients	37 (18.5%)
Comorbidites n (%)	
- Cardiovascular disease	139 (69.5 %)
- Chronic pulmonary disease	20 (10.0%)
- Diabetes mellitus	45 (22.5%)
- De novo non-skin cancer	6 (3.0%)
Immunosuppresive treatment	
- Azathioprine	31 (15.5%)
- Mycophenolate	141 (70.5%)
- Calcineurin inhibitor	181 (90.5%)
- mTOR inhibitor	29 (14.5%)
- Corticosteroids	146 (73.0%)
High dose methyl-prednisone rejection treatment <90 days before vaccination % (n)	3 (1.5%)

Table 2 – SOT recipients characteristics

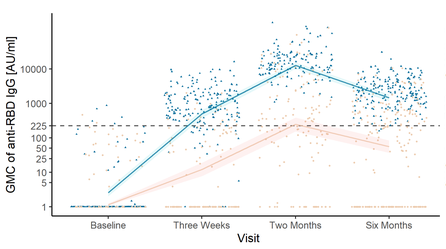

Figure 1. Observed anti-RBD IgG concentrations and predicted GMC of anti-RBD in SOT recipients and controls. Development in predicted geometric mean concentration of anti-RBD IgG represented in AU/mL plotted on top of observed individual concentration of anti-RBD IgG at each sample time from solid organ transplant recipients (yellow) and controls (blue). The dashed horizontal line indicates the minimum threshold for positive humoral response.

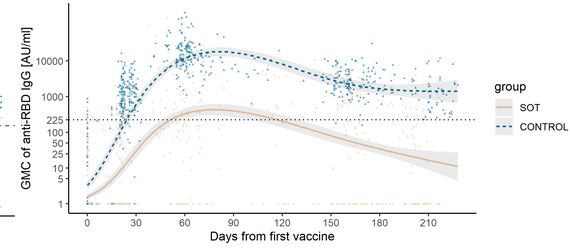

Figure 2. Observed anti-RBD IgG concentration and predicted GMC of anti-RBD IgG in SOT recipients and controls. Development in predicted anti-RBD IgG concentration represented in AU/mL plotted on top of observed individual concentration of anti-RBD IgG from day of first vaccination to 228 days after first vaccination from solid organ transplant recipients (yellow) and controls (blue). The dashed horizontal line indicates the minimum threshold for positive humoral response.