


LETTERS



Evaluation of the QuantiFERON SARS-CoV-2 assay to assess cellular immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in individuals with low and high humoral response

Areti Tychala^a, Georgios Meletis ^a, Eugenia Katsimpourlia^b, Ioanna Gkeka^a, Rodoula Dimitriadou^a, Eleni Sidiropoulou^a, and Lemonia Skoura^a

^aDepartment of Microbiology, Ahepa University Hospital, Thessaloniki, Greece; ^bDepartment of Immunology, General Hospital G. Papanikolaou, Exohi Thessaloniki, Greece

ABSTRACT

Vaccines against SARS-CoV-2 are known to be less immunogenic for some individuals, whereas others present notably high levels of antibody production. We assessed the cellular response to BNT162b2 among individuals with low post-vaccination antibody levels as well as in a small group of individuals with high titers. Antibody levels were assessed by the Abbott SARS-CoV-2 IgG II Quant assay. The interferon- γ production of T-cells in response to SARS-CoV-2 antigens was determined using Qiagen's QuantiFERON SARS-CoV-2 ELISA test. Our results showed that participants with high antibody levels presented adequate cellular response in all studied cases, whereas those with low antibody levels generally showed limited to almost absent cellular response five months post vaccination.

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Dear Editor,

Massive vaccination against the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is of utmost importance to tackle the spread of the coronavirus disease 19 (COVID-19) pandemic. The BNT162b2 mRNA COVID-19 vaccine has proved to be strongly immunogenic^{1,2} and impaired immune response was reported mainly for specific groups of individuals.^{3–6} Recent studies showed that the assessment of the humoral immune response as determined by the measurement of antibodies against the receptor-binding domain of the spike protein after vaccination underestimates the immunogenicity of COVID-19 vaccines and the combined analysis of humoral and cellular immunity was proposed for the identification of vaccine responders.⁷

Even though the serology assays are routinely performed in several laboratories worldwide, the methods to determine the cellular response to COVID-19 vaccines are still under evaluation.⁸ For this purpose, we recruited 17 health care workers (HCWs) (participants 1–17) that presented low antibody levels using the Abbott SARS-CoV-2 IgG II Quant assay and 5 HCWs (participants 18–22) with high antibody levels, 2 weeks after the second dose of the BNT162b2 mRNA Covid-19 vaccine. Antibody titers were converted to WHO international units following the equation: 1 BAU/mL = 0.142 AU/mL as suggested by the manufacturer. Low levels were determined to 4,000 AU/mL (converted to 568 BAU/mL) because the probability of high neutralizing antibody titers was 0.95 (95% CI: 0.78–0.99) according to the manufacturer's evaluation. High levels were set to >40,000 AU/mL (converted to >5680 BAU/mL) which is the upper limit of detection of the assay without dilution.

Five months after the second dose, we assessed the interferon- γ production of T-cells in response to SARS-CoV-2 antigens using Qiagen's QuantiFERON SARS-CoV-2 ELISA test and performed a second measurement of their anti-S antibodies. The median age was 57 y (range: 28–67). Interestingly, one of them (participant 13) was infected by SARS-CoV-2, 55 d after the administration of the second dose.

Using a cutoff of 0.15 IU/mL, as suggested by Van Praet et al.,⁹ only 5/17 specimens were tested positive for interferon- γ production by the CD4 T-cells (range: 0–0.59 IU/mL) and 8/17 for interferon- γ production by CD4 and/or CD8 T-cells (range: 0–3.13 IU/mL). The rate of positive samples decreases further for interferon- γ production by CD4 and/or CD8 T-cells (6/17) if a cutoff of 0.20 IU/mL is used as suggested by Jaganathan et al.¹⁰ Notably, participant 13 exhibited no CD4 T-cell response [Ag1(CD4)-Nil: 0.06 IU/mL and Ag2(CD4/CD8)-Nil: 0.4 IU/mL] even though the antibody levels 5 months after vaccination were 2011.44 BAU/mL (Table 1). The median values of the antibody levels 2 weeks post-vaccination, 5 months post-vaccination, the Ag1(CD4)-Nil and the Ag2(CD4/CD8)-Nil were 7984.96 BAU/mL, 520.29 BAU/mL, 0.28 IU/mL and 0.90 IU/mL, respectively, for the group of the five HCWs who had high anti-S antibody titers after the second vaccine dose. The Ag1 testing of participant 15 was considered invalid because of inadequate sample volume.

Our results showed that participants with high antibody levels presented adequate cellular response in all studied cases, whereas those with low antibody levels generally showed limited to almost absent cellular response five months post vaccination. Interestingly, two participants with delayed

Table 1. Participants' anti-S antibodies 2 weeks and 5 months after vaccination and CD4 and CD4/CD8 cellular response 5 months after vaccination.

| Participant | Age | Gender | Anti-S antibodies-2 weeks (BAU/mL) | Anti-S antibodies-5 months (BAU/mL) | Ag1 (CD4)-Nil (IU/mL) | Ag2 (CD4/CD8)-Nil (IU/mL) |
|-------------|-----|--------|------------------------------------|-------------------------------------|-----------------------|---------------------------|
| 1 | 53 | F | 420.70 | 29.21 | 0.01 | 0 |
| 2 | 48 | F | 229.66 | 95.21 | 0.02 | 0 |
| 3 | 50 | M | 128.08 | 6.70 | 0.01 | 0.04 |
| 4 | 56 | M | 64.08 | 9.57 | 0.02 | 0.06 |
| 5 | 51 | M | 276.00 | 197.92 | 0 | 0.09 |
| 6 | 48 | F | 159.34 | 12.01 | 0.14 | 0.1 |
| 7 | 63 | M | 74.75 | 6.49 | 0.2 | 0.1 |
| 8 | 67 | M | 55.14 | 7.80 | 0.23 | 0.1 |
| 9 | 40 | F | 27.36 | 1.82 | 0.2 | 0.11 |
| 10 | 59 | F | 47.56 | 88.81 | 0.1 | 0.15 |
| 11 | 52 | F | 126.55 | 15.25 | 0.14 | 0.17 |
| 12 | 28 | F | 545.78 | 35.07 | 0.59 | 0.38 |
| 13 | 36 | F | 100.82 | 2011.44 | 0.06 | 0.4 |
| 14 | 57 | M | 283.77 | 74.56 | 0.11 | 0.67 |
| 15 | 59 | F | 29.42 | 81.21 | Invalid | 0.86 |
| 16 | 63 | M | 212.65 | 12.81 | 0.08 | 1.11 |
| 17 | 49 | F | 145.49 | 41.68 | 0.27 | 3.13 |
| 18 | 57 | M | 6706.57 | 520.29 | 0.28 | 0.22 |
| 19 | 42 | F | 7102.70 | 627.91 | 0.26 | 0.32 |
| 20 | 30 | F | 7984.96 | 329.81 | 0.26 | 0.9 |
| 21 | 54 | M | 10643.16 | 536.87 | 0.68 | 1.36 |
| 22 | 52 | F | 8401.67 | 244.34 | 0.6 | 1.73 |

antibody production (10 and 15) that were under treatment with the immunosuppressive drug mycophenolate mofetil because of lupus erythematosus and anti-cancer treatment had sufficient cellular responses.

Identifying individuals presenting reduced T cell response to vaccination, especially when accompanied by inadequate antibody production, may be useful to predict which patients are more at risk of severe disease. Moreover, it could help to personalize the respective vaccination schemes in selected populations. To this end, further investigation should focus to improve the laboratory methods to assess T cell response and to determine the most appropriate thresholds for these assays. Overall, much remains to be elucidated regarding vaccine-induced cellular immunity to SARS-CoV-2 as well as the clinical usefulness of assays measuring T cell responses to COVID-19 vaccine candidates.

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ORCID

Georgios Meletis  <http://orcid.org/0000-0001-8750-513X>

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