International Journal of Infectious Diseases 114 (2022) 85–87

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Negative effect of the second dose of the BNT162b2 vaccine in a significant percentage of individuals with previous COVID infection

Elvira Baos [1], Alberto Delgado-Iribarren [1,2], Silvia OĆonnor [3], Ignacio Bardón [3], Mar Alvaréz [1], Iciar Rodríguez-Avial [1,2], Esther Culebras [1,2,*]

[1] Department of Clinical Microbiology, IML and IdISSC, Hospital Clínico San Carlos, Madrid, Spain
[2] Department of Medicine, Facultad de Medicina, Universidad Complutense, Madrid, Spain
[3] Occupational Health and Safety Service. Hospital Clínico San Carlos, Madrid, Spain

ARTICLE INFO

Article history:
Received 16 May 2021
Revised 13 October 2021
Accepted 1 November 2021

Introduction

Despite the efforts made since the beginning of the pandemic, the infection caused by SARS-CoV-2 is far from being under control. In the current situation, vaccines can be a turning point in the fight against the virus, and all countries attempt to encourage vaccination in their inhabitants, mainly in those groups with the highest risk.

To advance in pandemic control, some governments have decided to delay administering the second vaccine dose. They assume that the first dose would be enough to protect the population for a longer period than the pharmaceutical company recommended (Prendecki et al., 2021). Some previous studies support this supposition (Gobbi et al., 2021; Saadat et al., 2021), but high variability in vaccination response has been observed, and it is not clear what the situation will be with infection-naive people (Saadat et al., 2021; Prendecki et al., 2021; Thompson et al., 2021).

Material and methods

In January 2021, the Pfizer – BioNTech BNT162b2 began to be administered to health care workers in Spain. The main objective of this study was to analyze the response to the first and second doses of this vaccine in health care workers from Hospital Clinico San Carlos. Humoral immune responses were evaluated in 197 individuals, 98 with a previous COVID-19 infection (PI) and 99 who were infection-naïve (NI). All healthcare workers in this study received two identical doses, one 21 days after the other.

Vaccine response was evaluated 15-20 days after each dose by assays of total immunoglobulins IgG anti-RBD (receptor binding domain). Antibody titers were measured using the SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics) in the ARCHITECT i2000 equipment. The results were expressed as arbitrary units (AU) per milliliter. The positive threshold was 50 AU/mL per the manufacturer's recommendation. According to the EP34 Guide of CLSI (Budd, 2018), the ranges of result values that can be reported are 21.0-40,000 AU/mL (analytical measurement range) and 40,000-80,000 AU/mL (extended measurement range). In order to simplify calculations, any value > 80,000 AU/mL was considered equal to 81,000 AU/mL.

Qualitative detection of IgG antibodies to the nucleocapsid protein was also carried out with a SARS-CoV-IgG assay from Abbott Diagnostics. Samples were considered positive when the test yield results >1.4

Results and discussion

Data were presented as the mean ± s.e.m. Significance between the two groups was evaluated using unpaired Student's two-tailed t-test. Multi-group comparisons were made using a two-way analysis of variance (ANOVA) followed by Bonferroni's Multiple Comparison Test. Significance was accepted at $p<0.05$

PI individuals showed significantly higher titers of S-protein IgG than the NI after one vaccine dose (median 31,376.7±2,021 AU / mL [range 245.2 to > 80,000 AU/mL] vs 774,4±72.7 AU/mL [range 0,0-3,912 AU/mL])(Figure 1A and figure 1B).

After the second dose vaccine administration, a large increase in antibody levels were observed in all NI subjects. Average value reaches 18,121±1,113 (range 779.5-76,158 AU/mL). Differences between the first and the second dose were statistically significant.

* Corresponding author: Esther Culebras. Microbiology Department, Hospital Clinico San Carlos, C/ Martin Lagos s/n. 28040-Madrid, Spain.
E-mail address: esther.culebras@salud.madrid.org (E. Culebras).

https://doi.org/10.1016/j.ijid.2021.11.002

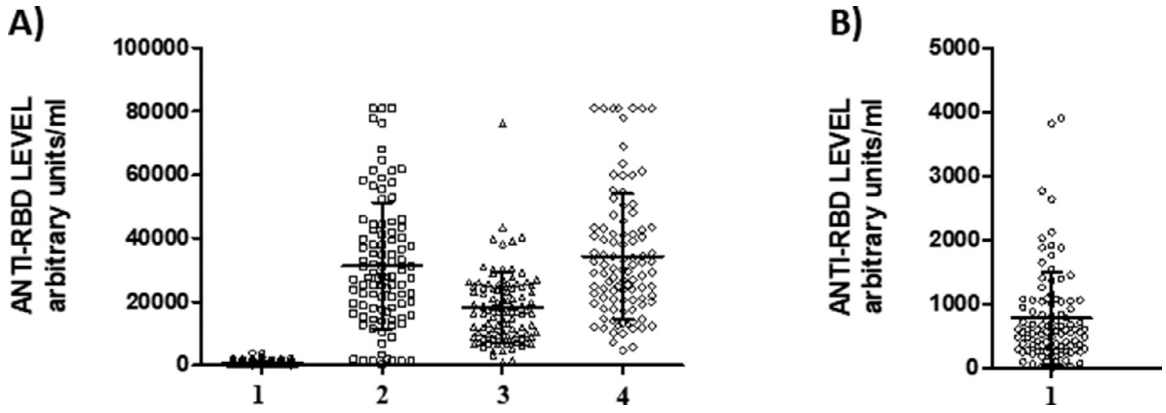

Figure 1. Anti-RBD levels after each dose of Pfizer – BioNTech BNT162b2 vaccine by COVID-19 history. A) Anti-RBD IgG antibodies in naïve (NI) and in previously infected individuals (PI) after first vaccine dose (1: NI 2: PI) and second vaccine dose (3: NI; 4: PI). B) Magnification of antibodies titers in naïve individuals after the first dose of vaccine. Mean ± SD is represented for each group.

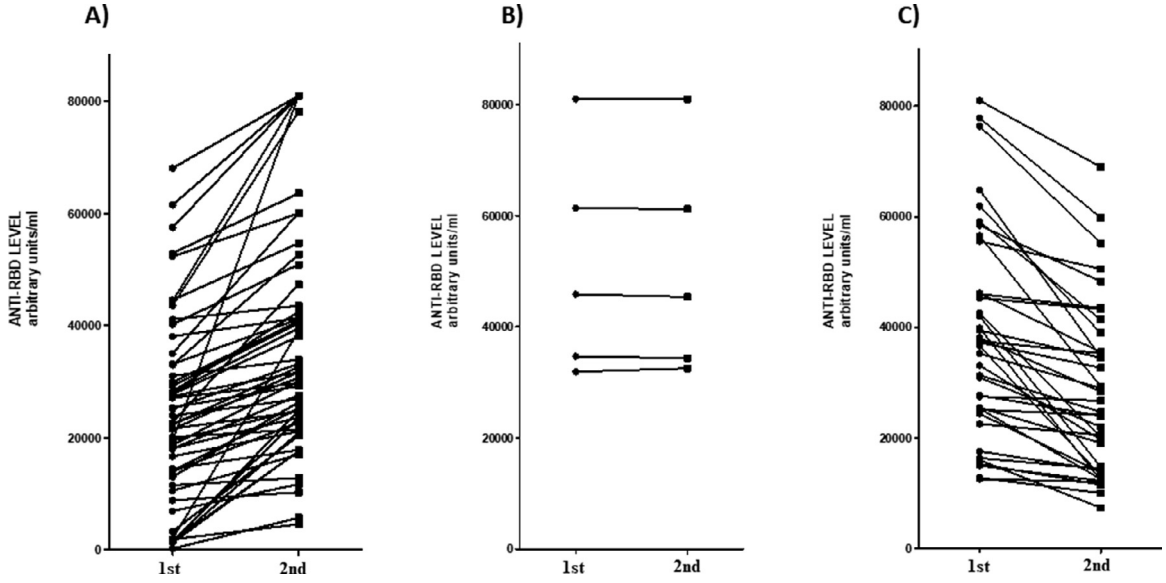

Figure 2. Antibodies titers variations in patients who had recovered from COVID among first and second vaccine doses. Connected lines represent measurements of the same patient. A) Individuals who increased IgG anti-RBD level with the second dose. B) Individuals who maintain IgG level. C) Individuals who decreased IgG level with second vaccine dose.

PI individuals had a mean antibodies level of 34,328±2,003 AU/mL (range 4,568 AU/mL - > 80,000 AU/mL). Responses in this cohort can be divided into three different groups: the first one include those who achieve higher titers with second vaccine dose (n = 54; 55,1 %), the second one those whose level remains similar to that of the previous dose (n= 6; 6,1 %) and the last group (n=38; 38.8%) who showed a lower level of IgG anti-RBD after the administration of the second dose of BNT162b2 (Figure 2).

It has not been possible to find any characteristics that explain the differences observed between the first and the third group in response to the second dose of the vaccine. Neither age, sex, nor antibodies to the nucleocapsid protein are different between the two groups.

Previous studies (Cassaniti et al., 2021; Parry et al., 2021; Salvaggio et al., 2021) reported that the majority of individuals earlier infected do not increase the antibody level between the first and second vaccine dose but, to our knowledge, this is the first time that an adverse effect of the second dose is described. The influence of the SARS-CoV-2 variant that infected participants as well as the individuals' haplotypes, could play an important role in the observed differences.

The participants in the study were age-stratified. Ranges were established according to the population recruited so that each group included the number of individuals that would yield statistically significant data. Three different age groups were considered: <35, 35-50, and >50 years old. If participants were divided into NI and PI, the younger group generates a significantly stronger serological response than the older group with the first dose (median 1059±173.5 AU/mL vs. 515.8±65.8 AU/mL) but not with the second one (median 21,653±1,993 AU/mL vs. 16,871±1,989 AU/mL). The differences observed were not significant with any doses, neither in the group with previous natural infection nor in the entire group.

As in previous studies (Krammer et al., 2021), our data indicate the differences in response to vaccination between naïve individuals and those with previous natural infections. In the last group, it is possible to distinguish a significant percentage of individuals in whom the IgG anti-RBD decreased with the second vaccine dose. To the best of our knowledge, this is the first description of a decrease in antibody IgG anti-RBD titers in individuals with previous COVID infection after administration of the second dose of the Pfizer – BioNTech BNT162b2 vaccine.

Although we have not been able to find an explanation for this behavior, our data suggest the importance of determining the serological response just before the second vaccine dose. In some of these subjects, it would probably not be necessary (it may even be adverse) to administer the second dose of the vaccine.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics and approval protocol

Ethics approval was obtained from the Ethics Committee of the Hospital Clinico San Carlos with ethical approved number 21/071E

Funding

This work did not receive any specific funding.

Acknowledgments

The authors are grateful to Hospital Clinico San Carlos workers for their contribution to the study. Also, they would like to thank the infrastructure support provided by the Microbiology Department of Hospital.

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