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Coronavirus Pandemic

Comparative humoral response of mRNA and inactivated vaccines against COVID-19 in healthy adults aged 60 years and older

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Abstract

Introduction: A vaccine against coronavirus disease 2019 (COVID-19) is critically needed for older adults because of the increased morbidity and mortality rates.

Methodology: In this prospective study, we analysed the titre magnitude of the IgG antibodies directed against the SARS-CoV-2 Spike Protein S1 (S1-RBD) antigen in both CoronaVac and Pfizer-BioNTech groups. The samples were tested to detect antibodies that bind to the receptor-binding domain of the spike protein of SARS-CoV-2 using the Enzyme-Linked Immunosorbent Assay (ELISA) technique with SARS-CoV-2 IgG II Quant. The cut-off value was > 50 AU/mL. GraphPad Prism software was used. Statistical significance was defined at $p < 0.05$.

Results: The CoronaVac group (12 females, 13 males) had a mean age of 69.64 ± 1.38 years. The Pfizer-BioNTech group (13 males, 12 females) had a mean age of 72.36 ± 1.44 years. The anti- S1-RBD titre decrease rate from the 1st to the 3rd month for CoronaVac and Pfizer-BioNTech groups was 74.31% and 86.48%, respectively. There was no statistically significant difference in the antibody titre between the 1st month and 3rd month for the CoronaVac group. However, there was a significant difference between the 1st and 3rd month in the Pfizer-BioNTech group. In addition, there was no statistically significant difference in the genders between the 1st and 3rd month of the antibody titres for both the CoronaVac Pfizer-BioNTech group.

Conclusions: The levels of anti-S1-RBD, the preliminary outcome data of our study, represents one piece of the puzzle of humoral response and duration of vaccination protection.

Key words: COVID-19; vaccine; humoral immunity; cellular immunity; Cyprus.

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Introduction

Several candidate vaccines including nucleic acid vaccines, inactivated virus vaccines, live attenuated vaccines, protein or peptide subunit vaccines, and viral-vectored vaccines are being developed and tested [1]. These candidates are currently in various stages of preclinical and clinical testing [2]. The efficacy of immune protection against possible coronavirus diseases 2019 (COVID-19) infection is still under investigation. The coronavirus (SARS-CoV-2) infection affects all age groups; however, patients over 60 years old are affected more severely, and therefore the safety/efficacy of vaccines in older people is important for their success. Even though older people (≥ 60 years of age) are prioritized for vaccination, this patient group is usually left out of clinical trials [3,4]. The primary goal of most vaccines is the induction of neutralizing antibodies due to their potential for reducing disease severity. Multiple studies have reported that antibodies to SARS-CoV-2 may be short-lived, or their effects are low in extent. Thus, long-lasting CD4+, CD8+ T cells with proper specificity and the rapid expansion of vaccine-induced memory lymphocytes may be necessary to boost immunity and reduce the transmission of the COVID-19 disease [2].

Vaccines against SARS-CoV-2 that elicit protective immune responses are crucial for the prevention as well as the reduction of the risk of morbidity and mortality caused by the SARS-CoV-2 infection. However, our knowledge about the extent and durability of vaccine

immunity and the breadth of vaccine coverage against SARS-CoV-2 variants is still evolving. Current understanding suggests that a balanced humoral and Th1-directed cellular immune response might be important for protection from COVID-19.

Generally, in human SARS-CoV-2 vaccine studies, binding antibody detection is confirmed by ELISA-IgG. The antigens used for IgG detection are the spike (S) glycoprotein, receptor binding domain (RBD), and trimeric spike glycoprotein [5]. In general, in older adults, the response to vaccines is decreased as a result of immunosenescence [1,6]. During the COVID-19 pandemic, the World Health Organization (WHO) had reported that the major risk group is the population aged ≥ 60 years [7]. Therefore, more study data is needed to understand the immunogenicity and duration of protection by COVID-19 vaccines for this population. We aimed to compare the humoral response and duration of protection of CoronaVac, inactivated SARS-CoV-2, BNT162b2, and Pfizer-BioNTech vaccines in individuals aged ≥ 60 years who met the inclusion and exclusion criteria.

Four different kinds of vaccines (CoronaVac, Pfizer-BioNTech, AstraZeneca, and Johnson & Johnson) are being used in the northern part of Cyprus. Both CoronaVac and Pfizer-BioNTech have been used for individuals ≥ 60 years since January 2021.

This prospective study aims to compare the humoral response and antibody titres specific to the spike protein of SARS-COV2 (anti-S1-RBD) at the first and third month to estimate the duration of protection after the second dose of immunization in individuals aged ≥ 60 years who met the inclusion and exclusion criteria.

Methodology

Study design and participants

In this prospective study, the first group consisted of volunteers ≥ 60 years of age who had not been infected with COVID-19 and had received two doses of the CoronaVac vaccine. The second group consisted of volunteers ≥ 60 years of age who had not been infected with COVID-19 and had received two doses of the Pfizer-BioNTech vaccine. Exclusion criteria included having a known allergy to components of the study vaccines, recent (within the past 6 months) or planned use of immunosuppressive therapy, the use of immunoglobulins, suspected immunodeficiency diseases and comorbidities (especially related to immunodeficiencies). Ethical approval for our study was obtained at the meeting of the Near East University (NEU) Institutional Review Board on 25/02/2021 with project number NEU-2021/88-1281. In addition, informed consent was obtained from all the volunteers.

Study procedure

The vaccine was administered by intramuscular injection in two doses: days 0 and 28 for CoronaVac, and day 0 and weeks 6-8 for Pfizer-BioNTech. The blood samples were collected after 28 days of the second dose (1st Month) and a further 28 days after the 1st Month (3rd Month).

Antibody testing assay for SARS-COV-2

Approximately 5 mL blood samples were taken from each of the volunteers and placed into jelled dry tubes between March to July 2021. The blood samples were delivered to the laboratory of Near East University (NEU) Hospital immediately after collection, and their serums were separated by centrifugation. The serum samples were stored at -80 °C until the time of use. The sera were tested for anti-S1-RBD IgG using fully automated ELISA (Abbott, Sligo, Ireland) with SARS-CoV-2 IgG II Quant (Abbott, Sligo, Ireland). A cut-off value of > 50 AU/mL was considered positive according to the manufacturer's instructions. The assay presented a sensitivity/positive predictive value (PPA) of 92.11% and specificity/negative predictive value (NPA) of 99.97%. Agreement with neutralization in microneutralization tests were PPA: 100%, NPA: 95.72.

Statistical analysis

Frequency and percentage for qualitative variables, and arithmetic mean and standard deviation for quantitative variables were calculated as descriptive statistics. The changes in antibody levels and affecting variables were analyzed using both two-way and three-way repeated-measures analysis of variance (ANOVA), where appropriate. In the case of statistical significance, Sidak's post hoc test was applied to investigate the pairwise differences between grouping factors. A Pearson correlation analysis was performed to understand the possible associations between age and antibody levels. GraphPad Prism (Version 9.0.0. (86) for Mac) and SPSS (Version 26.0 for Mac) software were used for calculations and analysis. Statistical significance was accepted to be 0.05.

Results

The CoronaVac group (n = 25; females = 12, males = 13) had a mean age of 69.64 ± 1.38 years and age range of 61-86 years. The Pfizer-BioNTech group consisted (n = 25, females = 12, males = 13) had a mean

age of 72.36 ± 1.44 years and age range of 60-92 years. Among the CoronaVac group, 13 volunteers had received the influenza vaccine and 17 had received the pneumococcal vaccine. Among the Pfizer-BioNTech group, 5 volunteers had received the influenza vaccine and 17 had received the pneumococcal vaccine.

When the correlation between age and the anti-S1-RBD IgG (according to groups) was calculated, it was shown that there was a statistically significant decrease in anti-S1-RBD IgG with increasing age in both the 1st and 3rd-month antibody titres. (r = -485; $p < 0.05$ and r = -630; $p < 0.05$) only in the Pfizer-BioNTech group. This correlation was not statistically significant in the CoronaVac group.

Among the females, the mean values of the 1st month for the anti-S1-RBD IgG were 1125.6 AU/mL and 9263.3 AU/mL for the CoronaVac and Pfizer-BioNTech groups, respectively, and the mean anti-S1-RBD IgG values for the 3rd month were 294.1 AU/mL and 1206.5 AU/mL for the CoronaVac and Pfizer-BioNTech groups, respectively. In the case of males, the mean anti-S1-RBD IgG for the 1st month were 525.1 AU/mL and 9154.3 AU/mL for the CoronaVac and Pfizer-BioNTech groups, respectively. The mean anti-S1-RBD IgG value in males for the 3rd month was 130.4 AU/mL and 1278.5 AU/mL for the CoronaVac and Pfizer-BioNTech groups, respectively (Table 1). There was no statistically significant difference between the 1st month and 3rd month of the anti-S1-RBD IgG for the groups divided by gender. ($p > 0.005$). In addition, no statistically significant difference was observed when the antibody level was compared with whether or not the volunteers had previously been vaccinated against influenza or pneumonia ($p > 0.05$).

The mean of the anti-S1-RBD IgG of the CoronaVac group for the 1st and 3rd months was 837 AU/mL (106.4 - 4153.0) and 215 (12.0 - 676.6) AU/mL, respectively. The anti-S1-RBD IgG decrease rate from the 1st month to the 3rd month was 74.31%. The mean of the anti-S1-RBD IgG of the Pfizer-BioNTech group for the 1st and 3rd months was 9206.6 AU/mL (minimum:763.0, maximum: 33679.9) and 1244.1 AU/mL (minimum: 177.5; maximum: 5479.5), respectively. There was no statistically significant difference in the anti-S1-RBD IgG between the 1st month and 3rd month for the CoronaVac group. The anti-S1-RBD IgG decrease rate from the 1st month to the 3rd month was 86.48%. There was a statistically significant difference between the 1st month and 3rd month of the Pfizer-BioNTech group ($p < 0.001$). The anti-S1-RBD IgG of both groups (CoronaVac and Pfizer-BioNTech) were compared to each other, and a significantly higher difference was observed in the 1st-month ($p < 0.001$). However, there was no statistically significant difference in the 3rd month.

Discussion

We found that the volunteers who received the CoronaVac vaccine had lower anti-S1-RBD IgG than volunteers who received the BNT162b2 vaccine. These results were similar to a study conducted by Lim *et al*., who demonstrated that individuals who were immunized with inactivated vaccine had lower geometric means of PRNT50, and PRNT90 titre than individuals who were immunized with the BNT162b2 vaccine [8].

A study demonstrated that women show a greater immune response to foreign antigens which can improve vaccine efficacy [9,10]. However. in our results, there was no gender difference in this regard which was also similar in the study by Tylicki *et al* [9].

We observed that although the anti-S1-RBD IgG decrease rate was 74.31% from the 1st month to the 3rd month, for the CoronaVac group, this difference was not statistically significant. However, the decrease rate for the Pfizer-BioNTech group (86.48%) was statistically significant.

According to our study, there was a statistically significant decrease in anti-S1-RBD IgG with increasing age in the 1st and 3rd month results in the Pfizer BioNTech group. However, this correlation was not statistically significant in the CoronaVac Group. When the anti-S1-RBD IgG of both groups was compared to each other, a statistically significant difference was observed in the 1st-month antibody titres as the antibody titres from the RNA vaccine elicited high titres. It was reported in published human studies that mRNA vaccines had higher antibody titres,

Table 1. Details of the anti- S1-RBD titer according to gender.

	Female		Male	
	CoronoVac Group	**Pfizer-BioNTech Group**	**CoronoVac Group**	**Pfizer-BioNTech Group**
1st month (min -max) AU/mL	114.0 - 4153.0	763.0 - 2461.8	106.4 – 1424.0	1875.3 - 33676.9
3rd month (min -max) AU/mL	84.5 - 676.6	177.5 - 3070.0	12.0 - 337.9	308.2 - 5479.5

whereas the inactivated virus vaccines achieved minimal boost or dose-dependent increases in antibody titres after the second dose of immunization [5].

According to the 3rd-month measurements, the mRNA vaccine elicited more antibody titres'; however, it was shown that there was no statistically significant difference in the antibody titres of both vaccination groups. This was probably due to the higher decrease rate of mRNA vaccine antibody titres. In addition, the anti-S1-RBD IgG level of the two groups was compared according to whether or not previous vaccinations had been applied against influenza or pneumonia and no statistically significant difference was found as a bystander effect produced by viruses may cause a cross-reaction against SARS-CoV-2 [11,12]. Therefore, we can conclude that the previous vaccinations did not affect the antibody levels of SARS-CoV-2. The level of SARS-CoV-2 antibody titres depends on the vaccine administered and has been proposed to correlate with the level of protection against SARS-CoV-2 infection [13]. In our study, none of the volunteers had been infected with SARS-CoV-2 during these 3 months.

Conclusions

Our study is one of the first to research the humoral response of two different types of the COVID-19 vaccine in individuals aged ≥ 60 years. One limitation is the number of volunteers which was relatively low for both groups. The antibody titres, which was the preliminary outcome data of our study, only represents one piece of the puzzle of immunogenicity and duration of vaccination protection. Further studies are needed to complete this puzzle and to analyse both the humoral and cellular immune responses (mainly CD4, CD8 T cells, and memory lymphocytes) of this group of volunteers who will be followed up prospectively for 1 year

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