APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

APMIS

DOI 10.1111/apm.13215

Study of humoral and cellular immunity in vaccinated with mRNA-1273

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Gutiérrez-Bautista JF, López-Nevot MÁ, Gómez-Vicente E, Quesada T, Marín EM, Rodríguez A, Rodríguez AI, Rodríguez-Granger J, Cobo F, Sampedro A. Study of humoral and cellular immunity in vaccinated with mRNA-1273. APMIS. 2022.

The new vaccines against SARS-CoV-2 have raised a lot of expectations about their ability to induce immunity and the duration of this. This is the case of mRNA vaccines such as Moderna's mRNA-1273. Therefore, it is necessary to study the humoral and cellular immunity generated by these vaccines. Our objectives are determining what is the normal response of antibody production, and what is the level of protective antibodies and monitoring patients in case of subsequent infection with COVID-19. We present the first results of a longitudinal study of the humoral response in 601 health workers vaccinated with Moderna. The results show a humoral immunity at 90 days after the second dose of 100%, with a strong decrease between the levels of circulating anti-S IgG antibodies between days 30 and 90 post-vaccination. Observing a steeper decline in those who had higher titles at the beginning. In addition, we present a cellular response of 86% at three months after the second dose, which is related to low humoral response.

Key words: Moderna vaccine; humoral response; SARS-CoV-2; mRNA vaccines; mRNA-1273 vaccine.

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The global pandemic caused by the SARS-CoV-2 betacoronavirus has produced 216 million infections and more than 4.5 million deaths worldwide [1]. Despite the numerous measures carried out, the spread of the virus has required the rapid development of vaccines with the objective of obtaining immunity against the virus and stopping the pandemic [2]. Various vaccines have been developed and used to deal with the pandemic. On the one hand, human adenovirus-based vaccines are used: ChAdOx1 nCoV-19 (AZD1222) from Oxford-AstraZeneca [3], Ad26.COV2.S from Janssen [4], and Sputnik V [5]. While on the other hand, two mRNA vaccines against SARS-CoV-2 have been approved and used in humans: BNT162b2 mRNA COVID-19 vaccine by BioNTech and Pfizer [6] and mRNA-1273 vaccine codeveloped by researchers at the NIAID Vaccine Research Center and Moderna in Cambridge [7]. The efficacy and safety of vaccines have already been demonstrated [8], observing an effectiveness of 90% in the prevention of COVID-19 in mRNA vaccines and about 70% in the Janssen or AstraZeneca vaccine [9]. However, due to the importance of its early use, it was not possible to carry out studies on the type, intensity, and duration of immune response of the vaccines. Furthermore, with the appearance of the new variants, it is necessary to verify the efficacy of the vaccines against them [10]. For this, it is necessary to study the humoral immunity (determination of antibodies, neutralization against the different variants, etc.) and the cellular immunity generated by all the

Received 5 October 2021. Accepted 19 February 2022

vaccines used. In addition, knowing the duration of protective immunity is vital when deciding whether or not future revaccination is necessary.

We present results for longitudinal monitoring of humoral response against SARS-CoV-2 in a group of 601 post-vaccination healthcare workers with the mRNA vaccine-1273. This vaccine encodes a stabilized version of the SARS-CoV-2 full-length spike glycoprotein trimer, S-2P, which has been modified to include two proline substitutions at the top of the central helix in the S2 subunit [7]. The mRNA is encapsulated in lipid nanoparticles at a concentration of 0.5 mg per milliliter [7]. Its administration requires two doses of 100 μg separated by 28 days. The follow-up of the studied population is carried out one month and three months after the administration of the second dose.

In addition, we have studied the cell immunity by the quantification of IFN-γ specific of SARS-CoV-2 in 56 patients at 3 months after vaccination.

With these results, we have the objective of determining what is the normal response of antibody production, determining what is the level of protective antibodies, and monitoring patients in case of subsequent infection with COVID-19.

MATERIALS AND METHODS

Population studied

The study was carried out with a population of 601 workers made up of 399 women and 202 men, belonging to the Hospital Universitario Virgen de las Nieves complex, who were vaccinated with Moderna's mRNA-1273 vaccine. The mean general age was 48.1 years (21–68), with 48.8 (21–66) for women and 46.6 (23–68) for men.

Patients completed an informed consent where affirmed had not been exposed to the disease. In addition, we perform anti-N (nucleocapsid) IgG determination in those patients with a level of antibodies to protein S > 6000 BAU/mL, with the aim of detecting possible patients who had the disease in an asymptomatic way. Likewise, a review of the clinical history was carried out to verify that the participants did not have the disease, observing the results of the real-time polymerase chain reaction (RT-PCR) against SARS-CoV-2 and of serological screenings carried out by the institution for the control of personnel. Any participant who previously presented serology or PCR positive was excluded from the study.

In the second antibody determination (at 90 days), the study population decreased to 455 participants (307 women and 148 men). The mean general age was 49.3 years (22–68), with women being 50 (22–66) and 47.8 (23–68) for men.

For the determination of cellular immunity, we selected 60 patients according to the levels of antibodies in the first determination. Selecting 20 patients with a low response <1000 BAU/mL, 20 patients with a response between 1000 and 4000 BAU/mL, and 20 patients with a response > 4000 BAU/mL. In addition, the patients were adjusted for sex and age in each group and globally. Finally, the number of final patients was 56 (34 women). The mean general age was 49.2 years (24–68), with 49 (26–66) for women and 49.5 (24–68) for men.

All patient samples were collected according to the local medical ethics regulation, after informed consent was obtained by the subjects, their legal representatives, or both, according to the Declaration of Helsinki. The study was approved by the local ethics committee (CEIM/CEI Provincial de Granada).

Antibodies against SARS-CoV-2 quantification

Participants underwent blood extraction 1 month (30 days) and 3 months (90 days) after inoculation of the second dose. A quantitative determination of immunoglobulin G (IgG) was performed against protein S (Spike). The quantification of IgG was carried out by the chemiluminescent COVID-2 IgG assay (Alinity, Abbott) following the manufacturer's instructions. The results were expressed in BAU/mL (binding antibody units per milliliter). The cutoff for positivity was marked at >7.5 BAU/mL.

SARS-CoV-2-specific INF-γ quantification

The determination of cellular immunity was carried out by quantifying the specific IFN-γ of SARS-CoV-2, using the QuantiFERON SARS-CoV-2 kit (Qiagen). Quantification was carried out following the manufacturer's instructions. The determination was carried out together with the determination of antibodies 90 days after the second dose. It was performed in 56 patients (34 women), with a mean age of 49.2 years. The results were expressed in UI/mL (international unit per milliliter). The cutoff point for positivity was marked at >0.1 IU/mL for either of the two tubes (Ag1 tube and Ag2 tube) of the technique. The IU/mL value of each tube (Ag1 or Ag2) was calculated by subtracting the value obtained in that tube minus the Nil tube. The tubes contain an original combination of specific peptides from the spike antigen (S1, S2, and RBD subdomain) eliciting CD4 (Ag1) and CD4+CD8 (Ag2) T-cell immune responses.

Statistical analysis

SPSS statistical software (Windows version 26, IBM, Armonk, NY, USA) was used for statistical analysis. Independent-sample Student's t-test was used to compare the mean of antibodies between them. Moreover, paired-sample Student's t-test was used to compare the mean of antibodies between ears, within each group. p values < 0.05 were considered statistically significant.

RESULTS

There has been an IgG response (IgG >7.5 BAU/mL) in the entire population studied 30 days after inoculation of the vaccine, with values ranging from 65 to >10000 BAU/mL. The mean of antibodies detected was 2700 BAU/mL (Figure 1), with 2617 BAU/mL for women and 2865 BAU/mL for

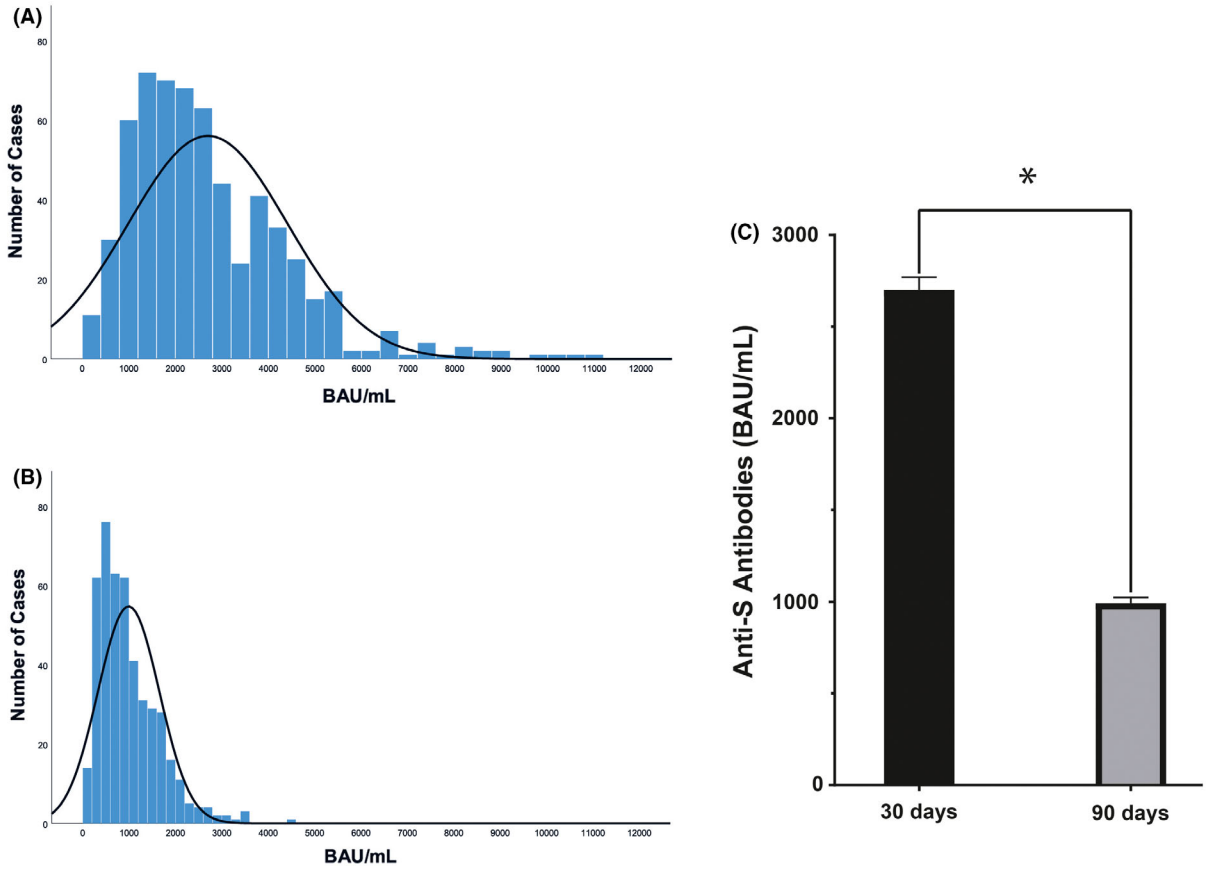

Fig. 1. (A) Distribution of the population according to the level of antibodies at 30 days post-vaccination. (B) Distribution of the population according to the level of antibodies at 90 days post-vaccination. (C) Anti-S antibodies mean at 30 and 90 days post-vaccination. * = significance, p-value <0.05.

men, not finding significant differences between them ($p > 0.05$) (Table 1).

More than 50% of patients have responses between 1000 and 3000 BAU/mL. We have classified these patients as normal responders. The rest of the patients were classified as low responders (7.5–500 BAU/mL), moderate responders (500–1000 BAU/mL), large responders (3000–5000 BAU/mL), and very large responders (> 5000 BAU/mL).

Ninety days after the inoculation of the second dose, the determination of IgG against protein S continues to show general positivity, with values ranging from 21 to 4535 BAU/mL. The mean of antibodies was 992 BAU/mL (Figure 1), with 953 BAU/mL for women and 1073 BAU/mL for men, not finding significant differences between them ($p > 0.05$) (Table 1).

A clear general decrease in antibodies was observed in all cases (Figure 1). The mean decrease in percentage was 64% (60–66%) (Table 1). The decrease in percentage was similar in all groups. The mean variation in absolute number was 1765 BAU/mL, with higher decreases being observed in those groups that presented a higher antibody titer in the first determination (large responders and very large responders) (Figure 2).

The means of antibodies in the first and second determination by age range and sex, and the means of variation in absolute data and in percentage both by age range and sex did not show significant differences (Table 1).

Only two patients presented an increase in the level of antibodies in the second determination compared to the first. They presented an increase of about 200% with respect to the first determination. Both presented positive SARS-CoV-2 PCR prior to the second determination. Both were excluded from the study.

The cellular response showed positivity in 86% of the 56 individuals studied (Table 2). Discrepancies were detected in two patients who produced IFN-γ in tube 1 but not in tube 2. These patients

Table 1. Mean antibody values in BAU/mL by age range and sex at 30 (n = 601) and 90 (n = 455) days post-vaccination. Variation of mean antibody values in percentage

		Male			Female		
Age range (years)	Days post-vaccination	30	90	Variation (%)	30	90	Variation (%)
20–30		3171	1329	−62	2352	869	−59
31–40		2953	940	−57	2196	813	−63
41–50		2776	1067	−63	2603	916	−66
51–60		3162	1194	−63	2689	1008	−63
61–68		2542	737	−70	3067	1027	−64

Negative signs express descent. Comparisons were made between sexes and age ranges at 30 and 90 days, not finding differences in any of them.

are considered positive. Patients with negative IFN-γ quantification had a lower mean circulating antibodies in the same determination than patients with positive cellular response, and this difference is significant (Table 2).

DISCUSSION

Our results show a 100% response in the production of anti-S IgG antibodies up to 3 months after vaccination with the vaccine developed by Moderna. These results are in line with those obtained by Doria-Rose et al. that show a level of antibodies maintained up to 6 months post-vaccination in 33 patients [11]. Similarly, Richards et al. reported an antibody response in 99.9% of those vaccinated with Moderna [12]. In fact, these studies show better results at the humoral level than those reported in cases of infection where seroconversion did not reach 100% [13]. Compared to other vaccines, a 92% response has been observed in vaccinated with the first dose of Pfizer [14]. In vaccinated with Ad26.COV.2.S, antibodies were observed up to 8 months later [15]. So there seems to be a good response with all vaccines.

The evolution of circulating antibodies in our population has led to an average decrease of 64% between the first and third months after vaccination. The mean antibody drops to 992 BAU/mL at 90 days, which is closer to the normal responders (1000–3000 BAU/mL). The decline is more pronounced in the large responder and very large responder groups. Approaching more moderate circulating antibodies may indicate that such high circulating antibodies are not necessary to provide protection. The high levels of antibodies found in the first determination may be due to the recent antigenic stimulation with the second dose of the vaccine and the high concentration of mRNA that is inoculated with Moderna's vaccine (100 μg). In addition, higher levels of antibodies have been detected in vaccinated with Moderna than by Pfizer [16]. This first value of circulating antibodies may correspond to the peak of antibody production detected between 5 and 7 weeks post-infection [17, 18]. Likewise, the decrease detected at 3 months would correspond to a contraction stage that would comprise between six- and 14-week post-infection [17]. This antibody dynamic follows that described for individuals who experienced the disease with a pattern of peak, plateau, and subsequent persistence at low levels of antibodies, with an initial rapid decline followed by a slower decline [19, 20].

This kinetics is very similar to antibody responses against other viruses, with maximum activity a few weeks after infection, which is followed by a contraction phase for several weeks [17]. The plateau and maintenance phase of antibody levels in convalescents patients were maintained up to 26 weeks after infection [17]. We will have to wait for the results of the determination at six and twelve months to see whether this trend is also maintained in those vaccinated. It is still early to know whether these mRNA vaccines are capable of inducing long-lasting immunity, but the first results show persistent and functional antibodies up to 6 months after the second dose of the mRNA-1273 vaccine [21]. The presence of neutralizing antibodies against SARS-CoV has been reported up to 17 years after

Fig. 2. (A) Evolution of circulating antibodies in patients with levels between 0 and 500 BAU/mL at 30 days. (B) Evolution of circulating antibodies in patients with levels between 500 and 1000 BAU/mL at 30 days. (C) Evolution of circulating antibodies in patients with levels between 1000 and 3000 BAU/mL at 30 days. (D) Evolution of circulating antibodies in patients with levels between 3000 and 4000 BAU/mL at 30 days. (E) Evolution of circulating antibodies in patients with levels between 4000 and 5000 BAU/mL at 30 days. (F) Evolution of circulating antibodies in patients with levels >5000 BAU/mL at 30 days. Patients with a higher antibody level on the first antibody determination show a more pronounced decline.

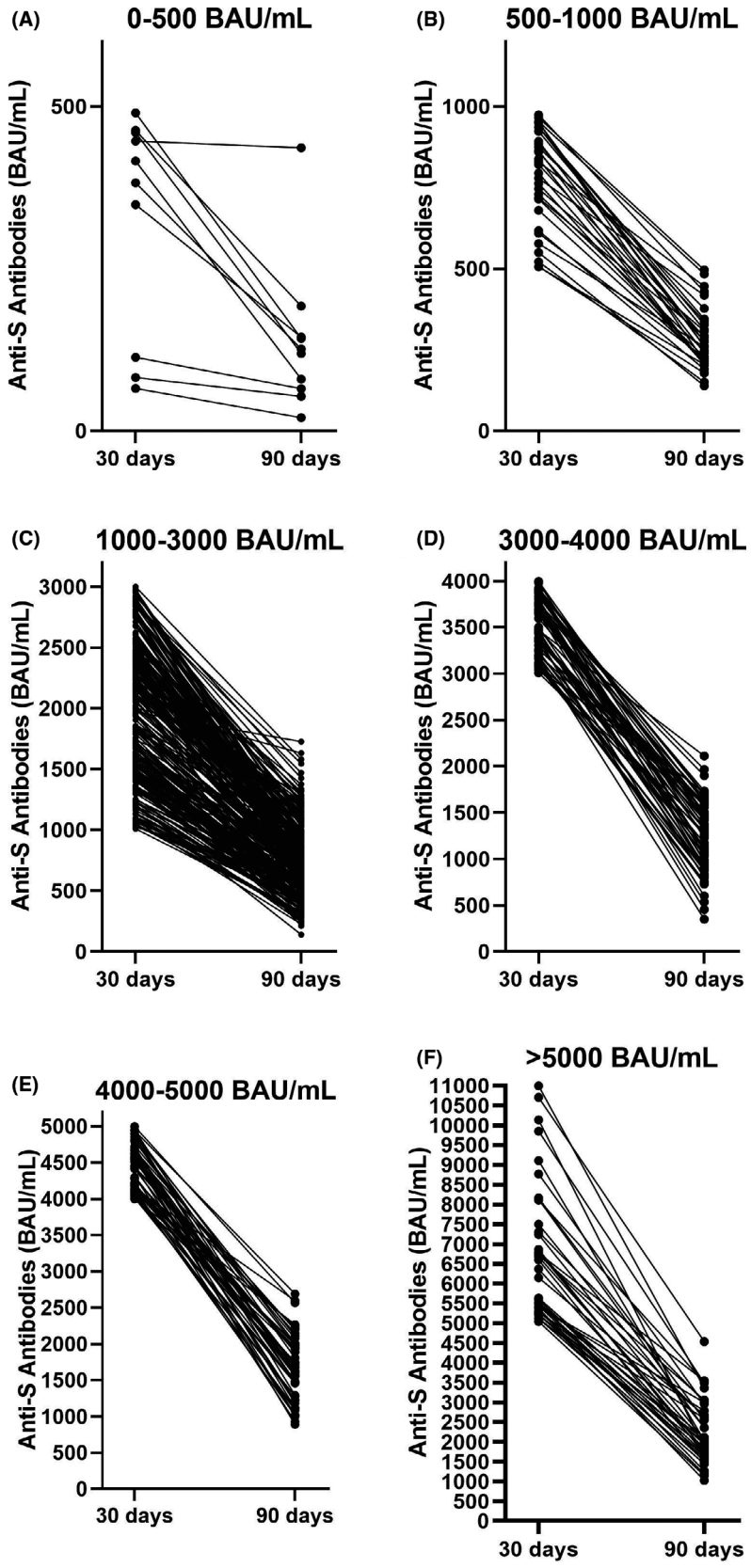

Table 2. SARS-CoV-2-specific IFN-γ test results

Results	Positive	Antibodies range in positive cases (BAU/mL)	Negative	Antibodies range in negative cases (BAU/mL)	Total	p
Number of cases (%)	48 (86%)		8 (14%)		56	
QuantiFERON SARS-CoV-2 Ag1 tube (%)	48 (86%)	220–4503	8 (14%)	53–652	56	
QuantiFERON SARS-CoV-2 Ag2 tube (%)	46 (82%)[1]	289–4503	10 (18%)	53–3325	56	
Mean antibodies (BAU/mL)	1265		253			5.7×10^{-8}

[1]There are discrepancies in two individuals with a positive response who did not respond in the Ag2 tube. The mean of antibodies is 90 days post-vaccination, as is the performance of the IFN-γ test. P = p-value. p-value was considered significant only when it was smaller than 0.05.

infection, which would demonstrate the ability of the immune system to generate long-term immunity against coronavirus species [19].

The decrease in antibodies detected between the first and second determination may be due to the decrease in plasmablasts [22]. It is known that the half-life of IgG is 3 weeks. Therefore, its continuous production by plasma cells is necessary, and this being what allows detectable circulating antibodies to be detected for decades against different pathogens [23]. Recently, the presence of long-lived bone marrow plasma cells (BMPCs) has been reported in patients convalescing from SARS-CoV-2. These cells can play a fundamental role in the rapid response to a new contact with the virus and in maintaining circulating antibody levels [22]. Probably, this type of plasma cell is also present in vaccinated people but will require studies to prove their existence. It has been observed that mRNA vaccines induce strong CD4 + T responses, germinal center B cells, and long-lasting plasma cells with neutralizing antibody responses in mice [24, 25].

On the other hand, although it is not possible to detect circulating antibodies, the immunological memory formed by specific T and B lymphocytes would be able to respond quickly to a new antigenic contact [26]. It is to be expected that this immunological memory is also present in vaccinated patients. The first results indicate that the frequency of memory B cells generated by vaccination is approximately the same as those produced in severely COVID-19 patients [27]. This may explain the increase in the production of antibodies in the two participants of the study, who after a new exposure to the virus (positive PCR), have presented an increase of about 200% in the levels of circulating antibodies. The new antigenic stimulation would have led to an activation of memory B lymphocytes, which will have differentiated into plasmablasts and antibody-producing plasma cells, producing an increase in these [22]. The presence of memory B lymphocytes against protein S in convalescent people from COVID-19, up to 8 months after infection has been informed [28]. It remains to be shown that this occurs in vaccinated individuals.

The presence of IgG against protein S is correlated with neutralizing activity of these [17]. However, the effector functions mediated by the Fc fraction of immunoglobulins may play an important role [29]. This is the case of the results of Tauzin et al., which showed a strong ADCC (Antibody-dependent cellular cytotoxicity) but a weak neutralization at 3 weeks after vaccination [30]. Therefore, despite the studies that speak of the neutralizing role of antibodies, we must value the effector functions of antibodies and cellular immunity. In fact, we should assess the potential of the vaccine not only for its neutralizing potential but also for its ability to avoid hospital admission, serious illness, and death [31].

Finally, we did not find differences between ages in the levels of circulating antibodies, coinciding with that reported by Pegu et al. [21], nor in the kinetics of decrease of these. However, it has been suggested that numerous factors can influence the production of immunity by vaccines, such as gender, nutrition, microbiome, genetics, and environment [32]. Women have been reported to have a higher antibody response to Dengue, Hepatitis A and B, Smallpox, etc. vaccines, while men have a better response to diphtheria and tetanus among others [33]. In general terms, it is said that women present higher antibody responses and that this makes them more resistant to infectious diseases [32]. We did not observe differences between sex, which could be due to the type of technology (mRNA) used in this vaccine.

In order to control an infection, a robust immune response is required that depends both on the function of antibodies as well as the effector function of T cells [34]. The role of cellular immunity in viral infections is very important [35]. We show a cellular response at 90 days post-vaccination of 86%. Interestingly, in the individuals

without cellular response, we found a much lower mean of antibodies than among the responders. This may be due to various factors such as the affinity of the peptide to HLA (Human Leukocyte Antigen) class II alleles, which could induce differentiation to follicular T cells but not to IFN-producing Th1 lymphocytes. However, a preferential production of Th1 cytokines (IFN-γ, IL-2, TNF-α) has been observed over Th2 in vaccinated with Moderna [7]. Low levels of IgG antibodies can be related to the lack of IFN-γ production which induces the isotype change to IgG [36]. Perhaps in these individuals, we can find another type of predominant immunoglobulin isotype. Recent studies have shown that both doses are necessary to detect 95% cellular immunity [37]. This may indicate that a possible revaccination is needed over time. Nevertheless, the literature reports cases of memory T lymphocytes that last up to 11 years in convalescent SARS-CoV patients [38]. Likewise, memory T lymphocytes have been detected in vaccinated with yellow fever and smallpox [39, 40].

In conclusion, there is a general humoral response in individuals vaccinated with Moderna's mRNA-1273 vaccine, which is similar in kinetics to convalescent patients from COVID-19. It will be necessary to continue studying the circulating levels of antibodies during the following months. Likewise, it will be important to closely monitor these patients to observe the response to a hypothetical COVID-19 infection. On the other hand, individuals with a low response could be the target of study to see whether they have any defect in the immune system that prevents them from producing a high level of antibodies or is due to the presence of certain HLA alleles that would induce a worse response, while those with very high responses will be studied for whether they have a possible association with autoimmune diseases or some failure in the regulation of the immune system.

This study presents a limitation in the population used since we only included individuals in the range of 18–65 years. This is because the chosen population of health workers is not older than 65 years. It will be interesting to study the population over 65 years of age and patients with various immunodeficiencies.

This study is part of the doctoral thesis of Juan Francisco Gutiérrez-Bautista. Programa de doctorado en Biomedicina, University of Granada, Granada, Spain.

FUNDING

This work was supported by "Investigación y Desarrollo (I + D) del Sistema Andaluz de Salud (SAS)" and Instituto de Salud Carlos III (Proyecto FIS PI21/01708).

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

MA and AS contributed to the design of the study. MA, AS, JG, EG, and JF coordinated the collection of samples and the signing of the informed consent. TQ, EM, AR, and AIR carried out the extraction of the samples, their custody and organization. MA, AS, and JF wrote the manuscript. AS, FC, and EG participated in checking the clinical history of the participants. JF performed the statistical analysis of the data. AS and JF build the database. JF, MA, and AS performed the analysis of the data. All authors contributed to manuscript revision, read, and approved the submitted version.

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