

Immunogenicity and Safety of the Spikevax® (Moderna) mRNA SARS-CoV-2 Vaccine in Patients with Primary Humoral Immunodeficiency

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Keywords

SARS-CoV-2 · Vaccination · Spikevax ·
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Abstract

Introduction: Reports on the immunogenicity and efficacy of the Spikevax® vaccine against SARS-CoV-2 in immunodeficient patients are still scarce. We aimed to evaluate the safety and immunogenicity of the vaccine in patients with primary humoral immunodeficiency. **Methods:** We enrolled 46 patients, including 34 patients with common variable immunodeficiency (CVID), 10 patients with unclassified hypogammaglobulinemia (Hypolg), and 2 patients with X-linked agammaglobulinemia. We collected the blood samples before vaccination (D 0), and 10 days (D +38) and 90 days (D +118) after the second vaccination. Further, we quantified SARS-CoV-2-specific T-cell response (QuantiFERON ELISA test), serum anti-RBD IgG, and anti-RBD IgA-specific antibodies (enzyme immunoassay). **Results:** We found that the vaccination elicited predominantly mild adverse events, com-

parable to healthy population. Vaccination response negatively correlated with a value of Immune Deficiency and Dysregulation Activity in all measured parameters. D +38, seroconversion for anti-RBD IgG and anti-RBD IgA was observed in 65% and 21% CVID patients, respectively. SARS-CoV-2-specific T-cell response was detected in less than 50% of CVID patients. Meanwhile, Hypolg patients had 100%, 90%, and 60% positivity rates for anti-RBD IgG, anti-RBD IgA, and T-cell response, respectively. Three months after the second vaccination, 82% of the responders remained positive for anti-RBD IgG, but only less than 50% remained positive for T-cell activity in CVIDs. Low immunogenicity was observed in patients with lung involvement and/or rituximab treatment history. No SARS-CoV-2 infection was reported within 6 months after the second vaccination. **Conclusion:** Spikevax® seems to be safe with satisfactory immunogenicity in patients with primary humoral immunodeficiency.

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Introduction

The increasing prevalence of the coronavirus disease (COVID-19), caused by the newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in over 264 million infections and 5.2 million deaths worldwide until the end of November 2021 [1]. Moreover, the burden of associated complications leading to possible long-term disability upon SARS-CoV-2 infection is striking.

Risk factors for SARS-CoV-2 infection include old age, male gender, underlying comorbidities such as hypertension, diabetes, obesity, chronic lung diseases, heart, liver, and kidney diseases, tumors, pregnancy, and immunodeficiencies [2]. A possible risk subgroup of individuals who may suffer from a severe manifestation of COVID-19 includes patients with primary hypogammaglobulinemia, which comprises individuals with organ impairment, lung disease, or B-cell lymphoproliferation [3]. Patients with common variable immunodeficiency (CVID) are present with heterogeneous group of diseases with variable impairment of specific T-cell immunity [4]. Although recurrent bacterial infections are the predominant clinical manifestation in these patients, opportunistic and severe viral infections including COVID-19 cannot be excluded [5].

Several studies have demonstrated that the mortality rate of inborn errors of immunity (IEI) patients infected with COVID-19 should be comparable to the general population with other comorbidities [3, 6, 7]. However, patients with interferonopathies, possibly with combined immunodeficiency, were an exception [8, 9]. On the other hand, Meyts et al. [3] reported the death of 9 out of 94 IEI patients with SARS-CoV-2 infection. Seven out of 9 deceased patients had specific humoral immunodeficiency and suffered from various complications, including lung, kidney, and heart diseases, lymphoproliferation, and diabetes [3].

In general, vaccination is an effective prophylaxis against several viral diseases, including severe COVID-19. Spikevax[®] mRNA SARS-CoV-2 vaccine elicits a specific humoral and cell-mediated immune response in young healthy volunteers and older adults [10–12]. However, data about the immunogenicity and efficacy of this vaccine in patients with immunodeficiency are still scarce [13–15]. Therefore, in this study, we aimed to evaluate the safety and immunogenicity of the Spikevax[®] vaccine in these patients.

Materials and Methods

Patients

This study was approved by the local Ethics Committee of the University Hospital Hradec Kralove, Czech Republic (reference number 201906S25P). Written informed consents were obtained from all the enrolled patients.

A total of 46 patients with primary hypogammaglobulinemia were enrolled in this study (28 females, 18 males, mean age 46 ± 13 years; mean \pm standard deviation; range 22–70 years). Of them, 34 patients were with CVID, 10 had unclassified hypogammaglobulinemia (HypoIg), and 2 had X-linked agammaglobulinemia (XLA). All CVID patients met the ESID/PAGID diagnostics criteria [16]. Patients with unclassified hypogammaglobulinemia were characterized by ESID Registry – Working Definitions for Clinical Diagnosis of Primary Immunodeficiency [17]. All patients required regular immunoglobulin substitution therapy. Secondary causes of hypogammaglobulinemia have been excluded in all patients (e.g., infection, protein loss, medication, malignancy).

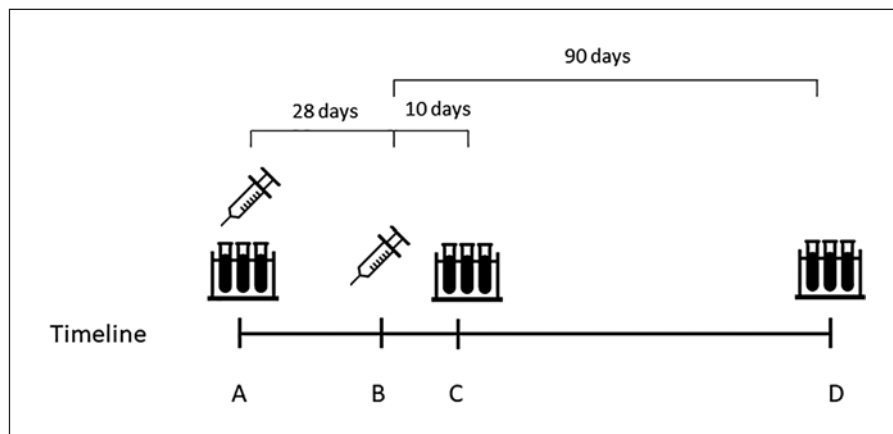
Next-generation sequencing was previously performed in 15/44 patients (excluding XLA). There were identified (per 1 patient) homozygous NF κ B2 NM_001077494.3:c.2296_2299dup; p.(Gly767Alafs*7), heterozygous NF κ B1 NM_003998.4: c.39+5G>C and heterozygous TNFRSF13B NM_012452.3:c.542C>A; p.Ala181Glu. Both XLA patients were genetically proved (NM_000061.3: c.1684C>T; p.(Arg562Trp) and NM_000061.3:c.1751G>A; p.Gly584Glu). Most patients were treated with a regular immunoglobulin substitution therapy (18 intravenous, 15 subcutaneous, and 10 hyaluronidase-facilitated subcutaneous therapy), but 3 patients had a low compliance. Information on the sex, age, noninfectious disease complications, Freiburg classification, serum immunoglobulin levels, and absolute number of CD3+, CD4+, CD8+, CD19+ cells close to the vaccination date was collected. Immune Deficiency and Dysregulation Activity (IDDA) score was obtained from all patients [18]. The IDDA for CVID and HypoIg group together was 20 ± 11 , with a range of 4.5–60. A total of 15 participants had a history of SARS-CoV-2 infection (12 CVID, 3 HypoIg), and 5 of them were clinically asymptomatic (data not shown).

Study Design and Methods

The enrolled patients were encouraged to report all possible side effects of the vaccination within a week after the first and second doses of the Spikevax[®], Moderna mRNA-1273 vaccine (Biotech, Spain). Data about local (pain, erythema) and systemic (fever, headache, musculoskeletal problems, sickness, fatigue, chills) adverse reactions were included in our questionnaire. The use of rescue medications and possible allergic reactions were also monitored. The adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI 2017) [19].

Blood samples of the patients were collected before the first dose (D 0), and 10 (D +38) and 90 (D +118) days after the second vaccine dose. The interval between the first and the second doses was 28 days (Fig. 1). Minimum 1-week interval after the last application of intravenous/hyaluronidase-facilitated subcutaneous immunoglobulin substitution therapy was required due to reduction of possible negative influence of presenting anti-receptor-binding domain (RBD) IgG in commercial preparations. SARS-CoV-2-specific T-cell and humoral responses were measured. The

Fig. 1. Study design and schedule. A (day 0): 1st blood sampling and 1st dose of vaccine; B (day +28): 2nd dose of vaccine; C (day +38): 2nd blood samples; D (day +118): 3rd blood samples.



number of clinically symptomatic COVID-19 cases was recorded within 6 months after the second vaccine dose.

SARS-CoV-2-specific T-cell-mediated immune response was detected using the QuantiFERON SARS-CoV-2 diagnostic kit (Qiagen, Hilden, Germany) based on the Interferon-Gamma Release Immuno-Assay technology. Blood samples were collected directly into each of the four QuantiFERON[®] SARS-CoV-2 tubes. The tubes contained the spike protein antigenic peptides: tube Ag1 for CD4+ T cells (QTF-Ag1) and tube Ag2 for both CD4+ and CD8+ T-cell stimulation (QTF-Ag2), positive and negative controls. Testing tubes were incubated at 37°C for 16–24 h. After incubation, plasma was isolated by centrifugation for 15 min at 3,000 g with the subsequent detection of IFN- γ (IU/mL) using QuantiFERON ELISA (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The readings were obtained at 450 nm with a 620–650 nm reference filter on a microplate reader (MRX; Dynex Technologies, Inc., Chantilly, VA, USA). IFN- γ levels of more than 0.2 IU/mL were considered positive. Limit of detection for ELISA assay was 0.065 IU/mL. The data are displayed as difference between QTF-Ag1,2 and negative control.

Specific IgG and IgA antibodies against the RBD of the S1 subunit of the spike protein and the nucleocapsid protein of SARS-CoV-2 were measured by the EIA COVID-19 RBD and EIA COVID-19 nucleocapsid protein (TestLine Clinical Diagnostics Ltd., Brno, Czech Republic) according to the manufacturer's instructions. The reading was taken at 450 nm with a 620–650-nm reference filter on the microplate reader (MRX; Dynex Technologies, Inc., Chantilly, VA, USA). Seroconversion was defined when values more than 1.1 index of positivity (IP) were reached. Limit of detection for anti-RBD IgG was 0.05 and for anti-RBD IgA was not determined.

Data Analysis

All variables for each group were tested for normality using the Shapiro-Wilk test. Patients with XLA were evaluated separately. None of the variables exhibited the normal distribution, with a few exceptions. Therefore, nonparametric tests were used for statistical evaluation. Spearman's rank correlation coefficient was used where indicated. Continuous variables are presented as median and quartiles. Further, the Mann-Whitney U test and Kruskal-Wallis test were used for comparison between groups. Contingency tables and χ^2 test were used for the evaluation of adverse events. Further, the Bonferroni post hoc correction was performed. All

analyses were calculated using the JASP Software 0.14.1 version, Netherlands, and charts were plotted using the GraphPad Prism 8 for Windows OS (GraphPad Software, San Diego, CA, USA).

Results

Safety of Spikevax[®] (Moderna) SARS-CoV-2 Vaccine

Forty-two responders filled a questionnaire separately for the first and the second vaccine doses. In general, the Moderna vaccine was well tolerated among the patients. Local adverse events, specifically pain, were reported in 88% of the patients after the first dose and in 81% of patients after the second dose. Systemic adverse events, such as headache, fever, chills, musculoskeletal pain, fatigue, or sickness, were reported in 48% and 60% of patients after the first and second doses, respectively. Fever was more frequent after the second dose ($p = 0.043$). Adverse events were predominantly mild, with only 15% of the patients reporting moderate adverse side effects with the necessity of rescue medication (nonsteroidal anti-inflammatory drugs). No severe or life-threatening complications were recorded. Nearly all adverse events were resolved within 6 days. Only 1 patient reported protracted pain in her arm after the second dose, approximately for 6 weeks, without any other complication. No allergic reaction was noticed among patients.

Immunogenicity of Spikevax[®] (Moderna)

SARS-CoV-2 Vaccine

The descriptive statistics on the immunogenicity of the vaccine are shown in Tables 1 and 2. Characteristics and results of the whole cohort are shown in online Supplement 1 (see www.karger.com/doi/10.1159/000526375 for all online suppl. material).

Table 1. Descriptive statistics (comparison between patients with COVID and unclassified humoral immunodeficiency)

| | <i>n</i> | Day 0, median (Q1; Q3) |
|-------------------|----------|-------------------------------|
| QTF-Ag1, IU/mL | | |
| COVID | 31 | 0.000 (0.000; 0.020) |
| Hypolg | 9 | 0.010 (0.000; 0.030) |
| QTF-Ag2, IU/mL | | |
| COVID | 31 | 0.000 (0.000; 0.030) |
| Hypolg | 9 | 0.000 (0.000; 0.060) |
| Anti-RBD IgG (IP) | | |
| COVID | 31 | 0.400 (0.145; 0.650) |
| Hypolg | 9 | 0.230 (0.140; 0.400) |
| Anti-RBD IgA (IP) | | |
| COVID | 31 | 0.120 (0.105; 0.140) |
| Hypolg | 9 | 0.360 (0.240; 0.430) |
| | <i>n</i> | Day +38, median (Q1; Q3) |
| QTF-Ag1, IU/mL | | |
| COVID | 34 | 0.115 (0.040; 0.905) |
| Hypolg | 10 | 0.345 (0.063; 0.780) |
| QTF-Ag2, IU/mL | | |
| COVID | 34 | 0.185 (0.045; 1.813) |
| Hypolg | 10 | 0.700 (0.215; 1.340) |
| Anti-RBD IgG (IP) | | |
| COVID | 34 | 6.080 (0.210; 6.622) |
| Hypolg | 10 | 6.695 (6.407; 7.162) |
| Anti-RBD IgA (IP) | | |
| COVID | 34 | 0.140 (0.120; 0.240) |
| Hypolg | 10 | 7.945 (6.908; 8.205) |
| | <i>n</i> | Day +118*, median (Q1; Q3) |
| QTF-Ag1, IU/mL | | |
| COVID | 14 | 0.130 (0.040; 0.330) |
| Hypolg | 8 | 0.130 (0.040; 0.247) |
| QTF-Ag2, IU/mL | | |
| COVID | 17 | 0.030 (0.000; 0.380) |
| Hypolg | 8 | 0.050 (0.000; 0.175) |
| Anti-RBD IgG (IP) | | |
| COVID | 20 | 7.740 (3.195; 9.625) |
| Hypolg | 10 | 10.160 (7.315; 10.348) |
| Anti-RBD IgA (IP) | | |
| COVID | 7 | 0.560 (0.345; 1.310) |
| Hypolg | 9 | 4.480 (0.890; 9.410) |

QuantiFERON (QFT) assay contained two tubes with the spike protein antigenic peptides, positive and negative control. Tube Ag1 stimulated CD4+ T cells and tube Ag2 both CD4+ and CD8+ T cells. Detected IFN- γ levels of more than 0.2 IU/mL were considered positive. Anti-RBD IgG and IgA are displayed as index of positivity (IP), and values more than 1.1 were considered as positive.

Table 2. Descriptive statistics (individuals with and without prior SARS-CoV-2 infection)

| | <i>n</i> | Day 0, median (Q1; Q3) |
|-------------------|----------|-------------------------------|
| QTF-Ag1, IU/mL | | |
| COVID- | 26 | 0.000 (0.000; 0.007) |
| COVID+ | 14 | 0.040 (0.020; 0.063) |
| QTF-Ag2, IU/mL | | |
| COVID- | 26 | 0.000 (0.000; 0.000) |
| COVID+ | 14 | 0.065 (0.030; 0.263) |
| Anti-RBD IgG (IP) | | |
| COVID- | 26 | 0.215 (0.130; 0.415) |
| COVID+ | 14 | 1.735 (0.453; 3.410) |
| | <i>n</i> | Day +38, median (Q1; Q3) |
| QTF-Ag1, IU/mL | | |
| COVID- | 29 | 0.070 (0.030; 0.600) |
| COVID+ | 15 | 0.310 (0.090; 0.945) |
| QTF-Ag2, IU/mL | | |
| COVID- | 29 | 0.130 (0.040; 0.860) |
| COVID+ | 15 | 0.970 (0.205; 2.125) |
| Anti-RBD IgG (IP) | | |
| COVID- | 29 | 6.090 (0.160; 6.750) |
| COVID+ | 15 | 6.460 (5.925; 6.865) |
| | <i>n</i> | Day +118*, median (Q1; Q3) |
| QTF-Ag1, IU/mL | | |
| COVID- | 13 | 0.080 (0.030; 0.420) |
| COVID+ | 12 | 0.190 (0.085; 0.330) |
| QTF-Ag2, IU/mL | | |
| COVID- | 13 | 0.010 (0.000; 0.310) |
| COVID+ | 12 | 0.115 (0.022-0.393) |
| Anti-RBD IgG (IP) | | |
| COVID- | 18 | 6.630 (2.805; 9.540) |
| COVID+ | 12 | 9.765 (8.735; 10.240) |

QuantiFERON (QFT) assay contained two tubes with the spike protein antigenic peptides, positive and negative control. Tube Ag1 stimulated CD4+ T cells and tube Ag2 both CD4+ and CD8+ T cells. Detected IFN- γ levels of more than 0.2 IU/mL were considered positive. Anti-RBD IgG and IgA are displayed as index of positivity (IP), and values more than 1.1 were considered as positive.

Response to Vaccination D +38

Serum levels of anti-RBD IgG- and IgA-specific antibodies were significantly higher after the second dose than the pre-vaccination serum levels ($p < 0.001$) for the enrolled cohort of patients enlisted in IEI. The serum levels of the antibodies did not correlate with age, total serum immunoglobulin IgG level, and the absolute number

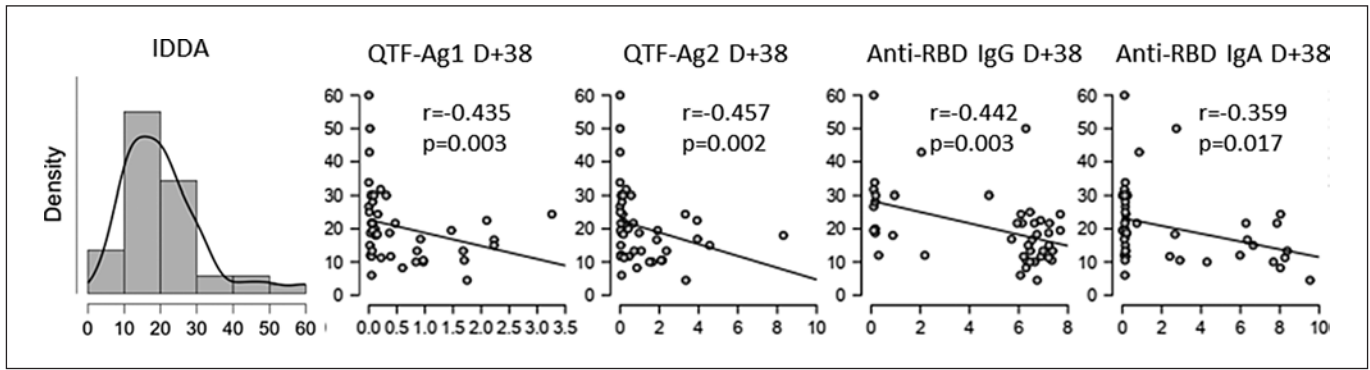


Fig. 2. IDDA severity score negatively correlated with QTF-Ag1, QTF-Ag2, anti-RBD-IgG, and anti-RBD IgA.

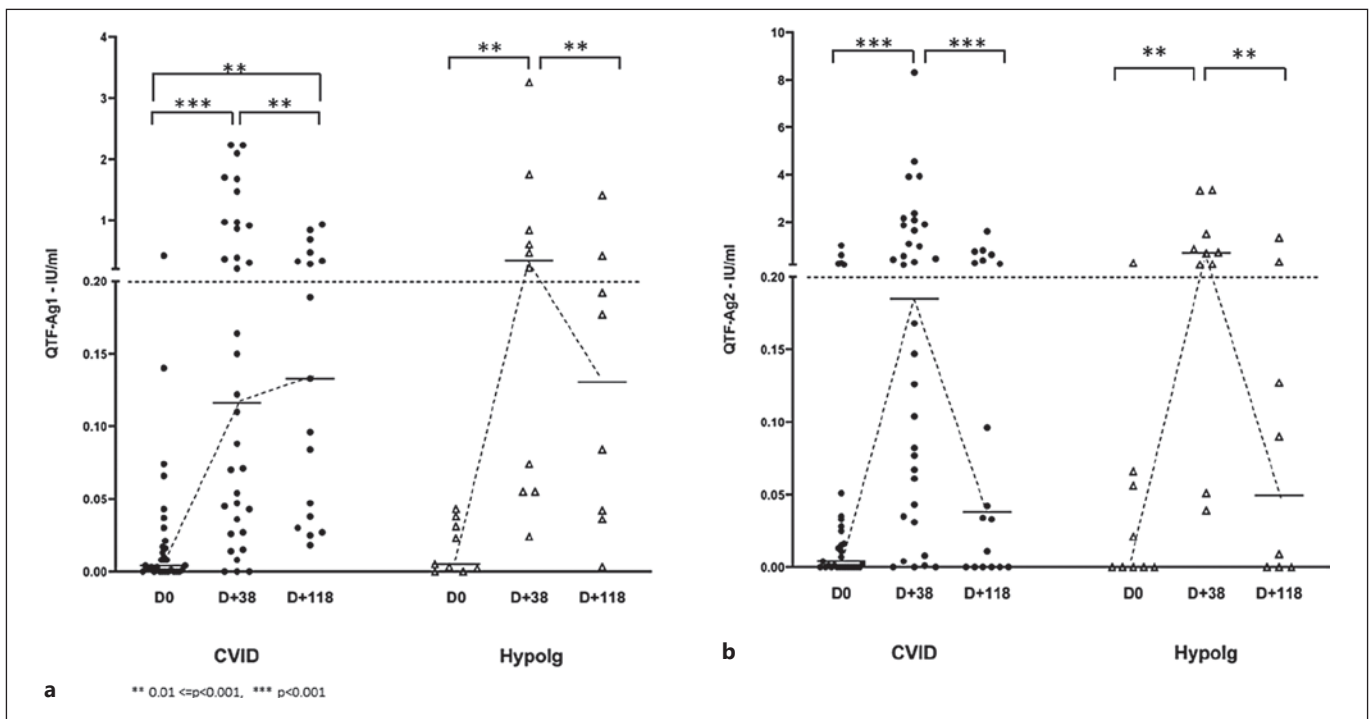


Fig. 3. T-cell-specific response QTF-Ag1 (a) and QTF-Ag2 (b) in CVID and HypoIg group. QuantiFERON assay contained two tubes with the spike protein antigenic peptides, positive and negative control. Tube Ag1 stimulated CD4+ T cells and tube Ag2 both CD4+ and CD8+ T cells. Detected IFN- γ levels of more than 0.2 IU/mL were considered positive. Limit of detection for ELISA assay was 0.065 IU/mL. The values are displayed as difference between QTF-Ag1,2 and negative control.

There was detected significant increase of IFN- γ D +38 after vaccination in both groups (CVID $p < 0.001$, HypoIg $p = 0.004$) for QTF-Ag1 and QTF-Ag2. QTF-Ag1 sustained at higher levels than before vaccination D +118 in CVIDs ($p = 0.002$). On the contrary, QTF-Ag2 significantly decreased to the pre-vaccination status at D +118 in both groups. * $0.01 < p \leq 0.05$, ** $0.001 < p \leq 0.01$, *** $p < 0.001$.

of CD3+ T cells, CD4+ helper, CD8+ cytotoxic T cells, and CD19+ B cells. Further, we did not observe any notable difference between female and male serum levels or the Freiburg classification in CVID patients (data not shown). The IDDA severity score negatively correlated

with the QTF-Ag1 ($r = -0.435$; $p = 0.003$), QTF-Ag2 ($r = -0.457$; $p = 0.002$), anti-RBD-IgG ($r = -0.442$; $p = 0.003$), and anti-RBD IgA ($r = -0.359$; $p = 0.017$) (Fig. 2). Anti-RBD IgA-specific antibodies positively correlated with serum IgA levels ($r = +0.595$; $p < 0.001$). HypoIg patients

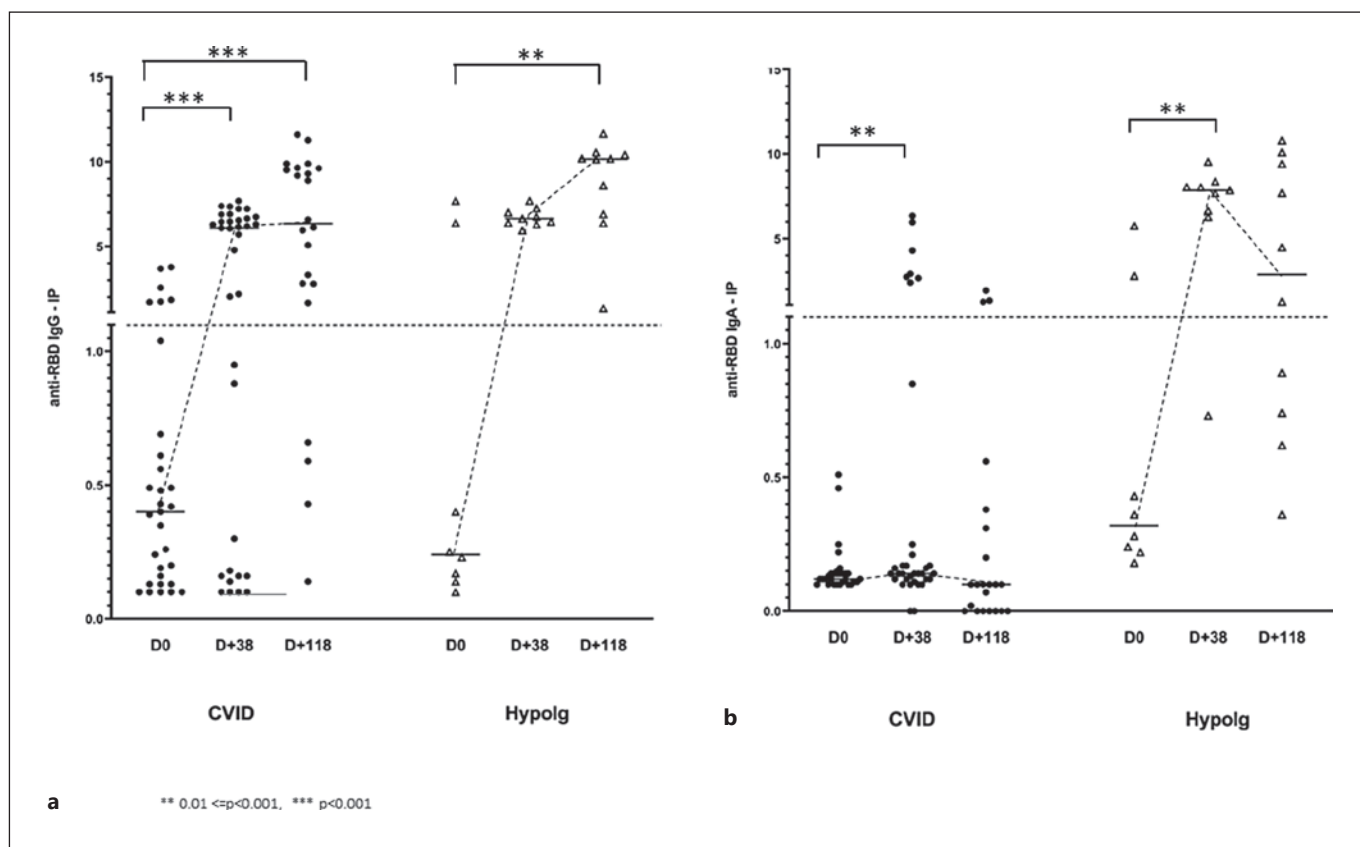


Fig. 4. Specific humoral response anti-RBD IgG (a) and anti-RBD IgA (b) in CVID and the HypoIg group. Data are shown as index of positivity, and values more than 1.1 were considered as positive. Anti-RBD IgG increased significantly D +38 after vaccination (CVID $p < 0.001$; HypoIg $p = 0.012$) and sustained positive D +118 in both groups (CVID $p < 0.001$; HypoIg $p = 0.004$) in comparison with pre-vaccination status. Only a few seroconversions in CVID

group in anti-RBD IgA were detected in D +38 with subsequent decrease in D +118. Patients in HypoIg group respond satisfactory D +38 in anti-RGB IgA ($p = 0.004$). No significant difference between CVID and HypoIg groups for anti-RBD IgG was noticed. Anti-RBD IgA in HypoIg group was significantly higher before vaccination and D +38 ($p < 0.001$) than in the CVID group.

had a higher production of anti-RBD IgA than that of CVID patients ($p < 0.001$). Seroconversion of specific anti-RBD IgG was detected in 22/34 (65%) CVID patients in general; in 10/12 (83%) of previously infected; and in 12/22 (55%) previously noninfected CVIDs, respectively. Seroconversion was detected in all HypoIg patients in anti-RBD IgG. Further, seroconversion of specific anti-RBD IgA was detected in 7/34 (21%) CVID patients in general and 9/10 (90%) HypoIg patients (Fig. 3). 26/34 (76%) CVID patients had total serum IgA 0.07 mg/L and less, and we observed seroconversion of anti-RBD IgA in only two of them (No. 17 and 29). A positive SARS-CoV-2-specific T-cell response was detected in 14/34 (41%) CVID and 6/10 (60%) HypoIg patients for QTF-Ag1, and 17/34 (50%) CVID and 7/10 (70%) HypoIg patients for QTF-Ag2 (Fig. 4). Unresponsiveness to both specific hu-

moral and T-cell-mediated immunity was found in 10/34 (29%) CVID patients. Positive response to mitogen was detected in all patients in QuantiFERON assay with median 16.5 IU/mL.

In specific subgroups of CVID patients, we observed that patients with a history of rituximab (RTX) treatment (finished more than 6 months before enrollment) manifested a very low response rate to the vaccine. We detected a positive response for both humoral and cellular parameters in only 1 patient with a previous history of SARS-CoV-2 infection among the 7 patients treated with RTX (No. 6). Patient No. 2 responded only to QTF-Ag2. In an overlapping group with granulomatous/lymphocytic interstitial lung disease (GLILD), we found one responder with a humoral seroconversion (No. 9) and 2 patients positive for QTF-Ag2 (No. 2, 7). Both XLA pa-

Table 3. Specific subgroups of patients – main characteristics including noninfectious complications, their treatment, and current immunosuppressive therapy (a) and their results (b)

a

| No. | Age, years | Sex | Diagnosis | Complications | Medical history/ ongoing treatment |
|-----|------------|-----|-------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | 46 | M | CVID | NHL | R-CHOP (aged 35)/ x |
| 2 | 24 | F | CVID (TACI) | GLILD, ITP | RTX (aged 10, 19), prednisone ¹ , ciclosporin A ¹ / Prednisone 5 mg/day, ciclosporin A (200 mg/ day) ² |
| 3 | 40 | M | CVID | GLILD, AIHA | RTX (aged 38), prednisone ¹ / x |
| 4 | 50 | M | CVID | NHL, GLILD, gastric cancer, enteropathy | R-CHOP (aged 45)/ x |
| 5 | 23 | M | CVID | NHL, GLILD | R-CHOP (6 months earlier)/ x |
| 6 | 42 | M | CVID | HL, Evans syndrome | R-CHOP (aged 38)/ x |
| 7 | 40 | F | NFkappaB1 | GLILD | Prednisone ¹ / Prednisone 5 mg/day ² |
| 8 | 26 | F | CVID | GLILD | RTX (aged 20), prednisone ¹ / Prednisone 5 mg/day ² |
| 9 | 31 | F | Hypoglg | GLILD | Prednisone (last 3 months)/ Prednisone 5 mg/day ² |
| 10 | 61 | F | CTLA4 | Psoriasis, enteropathy | x |
| 11 | 32 | M | NFkappaB2 | Bronchiectasis, epidermolysis bullosa | x |
| 12 | 39 | M | XLA | Lung lobectomy | x |
| 13 | 33 | M | XLA | | x |

(Table continued on next page.)

tients reached the highest levels in the QuantiFERON test among all our patients. However, patient 10 (NFκB2 deficient) had only slight specific T-cell response without the specific humoral response (shown in Table 3a, b).

IEI patients with a history of SARS-CoV-2 infection had higher values of QTF-Ag1, QTF-Ag2, and anti-RBD IgG before vaccination than the patients without prior infection ($p < 0.001$). These groups did not differ in all parameters D +38 (Fig. 5, 6).

Response to Vaccination D +118

Responders to vaccination were tested 3 months after the second vaccine dose. From 22 anti-RBD IgG positive CVID patients on D +38, 18 CVID patients remained positive on D +118, which represents 82%. From 10 anti-RBD IgG positive HypoIg patients on D +38, 9 HypoIg patients remained positive on D +118, which represents 90%. From 7 anti-RBD IgA positive CVID patients on D +38, 3 CVID patients were positive on D +118 (43%), and 6 from 9 (67%) in HypoIg group. Whereas 7/14 (50%),

resp. 7/17 (41%) CVID patients were positive for QTF-Ag1, resp. QTF-Ag2 on D +118. In addition, in only 2/6 (33%), resp. 2/7 (29%) HypoIg patients positive values were detected for QTF-Ag1, resp. QTF-Ag2 on D +118 in comparison with D +38.

These data indicate overall seropositivity for anti-RBD IgG in 18/34 (53%), and for QTF-Ag1,2 in 7/34 (21%) CVID patients 3 months after the second vaccine dose. There was not observed any difference between patients with or without COVID-19 history in all parameters. No patient with clinical symptomatic SARS-CoV-2 infection was noticed within 6 months after the second dose of vaccine.

Discussion/Conclusion

Impairment of specific antibody response is a characteristic of a large number of IEI patients. Patients with primary hypogammaglobulinemia are generally diag-

Table 3 (continued)**b**

| No. | QTF-Ag1, IU/mL | QTF-Ag2, IU/mL | anti-RBD IgG (IP) |
|-----------------|----------------|----------------|---------------------------|
| <i>Day 0</i> | | | |
| 1 | x | x | x |
| 2 | 0.003 | 0.001 | 0.490 |
| 3 | 0.000 | 0.000 | 0.100 |
| 4 | 0.004 | 0.016 | 0.430 |
| 5 | 0.000 | 0.000 | 0.260 |
| 6 | 0.017 | 0.033 | 1.720 ³ |
| 7 | 0.030 | 0.607 | 1.750 |
| 8 | 0.066 | 0.208 | 0.130 |
| 9 | 0.005 | 0.000 | 0.230 |
| 10 | 0.000 | 0.000 | 0.490 |
| 11 | x | x | x |
| 12 | 0.030 | 0.000 | x |
| No. | QTF-Ag1, IU/mL | QTF-Ag2, IU/mL | anti-RBD IgG (IP) |
| <i>Day +38</i> | | | |
| 1 | 0.027 | 0.077 | 0.160 |
| 2 | 0.110 | 0.418 | 0,16 |
| 3 | 0.000 | 0.000 | 0.100 |
| 4 | 0.000 | 0.001 | 0.140 |
| 5 | 0.070 | 0.031 | 0.100 |
| 6 | 0.306 | 0.563 | 4.790 |
| 7 | 0.122 | 8.305 | 0.880 |
| 8 | 0.043 | 0.061 | 0.950 |
| 9 | 0.055 | 0.051 | 7.250 |
| 10 | 0.207 | 0.311 | 0.100 |
| 11 | 7.062 | 8.613 | x |
| 12 | 4.877 | 8.080 | x |
| No. | QTF-Ag1, IU/mL | QTF-Ag2, IU/mL | anti-RBD IgG (IP) |
| <i>Day +118</i> | | | |
| 1 | x | x | x |
| 2 | 0.027 | 0.000 | |
| 3 | x | x | x |
| 4 | x | x | x |
| 5 | x | x | x |
| 6 | x | x | x |
| 7 | 0.096 | 0.033 | 0.430 |
| 8 | x | x | x |
| 9 | x | x | 8.590 |
| 10 | 0.047 | 0.000 | x |
| 11 | 4.410 | 4.318 | x |
| 12 | 0.725 | 0.599 | x |

Patients No. 6, 7, 8 had history of SARS-CoV-2 positivity. XLA patients (No. 12, 13) showed a good specific T-cell response to the vaccination persisting 3 months after the second dose. CVID patients No. 1–6 and 8 with a history of RTX treatment elicited low responsiveness to vaccination. Anti-RBD IgG positivity reached only patient No. 6 with a history of SARS-CoV-2 infection. Almost all presented CVIDs had low absolute number of B cells. A transient-specific T-cell response was noticed in patients No. 2 and 6. CVID, common variable immunodeficiency; Hypog, unclassified hypogammaglobulinemia; XLA, X-linked agammaglobulinaemia; NHL, non-Hodgkin lymphoma; GLILD, granulomatous/lymphocytic interstitial lung disease; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; HL, Hodgkin lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RTX, rituximab; x, not performed. ¹ More than 5 years. ² Current treatment. ³ Bold type indicates positive values in performed assays.

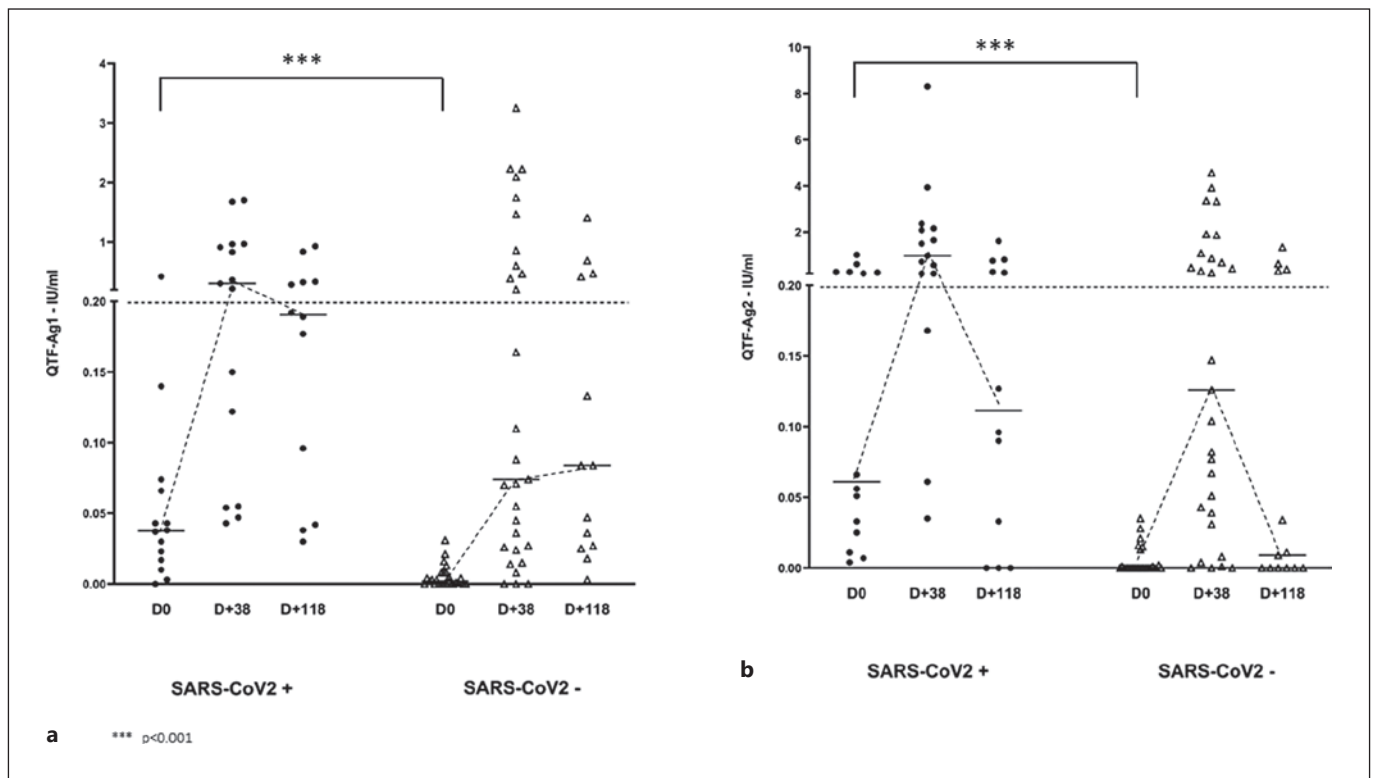


Fig. 5. T-cell-specific response QTF-Ag1 (a) and QTF-Ag2 (b) in patients with or without a history of SARS-CoV-2 infection. QuantiFERON assay contained two tubes with the spike protein antigenic peptides, positive and negative control. Tube Ag1 stimulated CD4+ T cells and tube Ag2 both CD4+ and CD8+ T cells. Detected IFN- γ levels of more than 0.2 IU/mL were considered positive. Limit of detection for ELISA assay was 0.065 IU/mL. The values

are displayed as difference between QTF-Ag1,2 and negative control. However, patients with a history of SARS-CoV-2 infection had a significantly higher response for Ag2 ($p = 0.035$), Ag1 ($p = 0.038$), and anti-RBD IgG before vaccination in comparison with previously noninfected people; no difference was noticed in D +38 or D +118 in all measured parameters.

nosed with a low responsiveness to polysaccharide challenge by *Streptococcus pneumoniae* or *Salmonella typhi* Vi polysaccharide vaccines and show diminished specific T-cell response against protein antigens such as tetanus toxoid [20, 21]. The immunogenicity and efficacy of antiviral vaccines are not well understood in IEI patients. Although there are studies on this topic, the majority of them are on influenza virus vaccines and there are several limitations in these studies. Even though the humoral response seems to be decreased in a majority of IEI patients, specific cellular immune responses may be effective [22–25].

mRNA vaccines are generally safe for healthy and immunocompromised people with cancer, autoimmune diseases, or organ transplant patients [14, 15, 26, 27]. Moreover, currently used anti-SARS-CoV-2 vaccines seem to be safe in IEI patients [28–32]. Delmonte et al. [31] did not report any adverse event in 81 IEI patients vaccinated with the mRNA and Johnson & Johnson's vec-

tor vaccines. Hagin et al. [32] reported only local adverse events in 26 IEI patients after the first dose of the Pfizer-BioNTech COVID-19 vaccine. The second dose was accompanied by fever in 3 out of 26 cases, and 1 patient suffered from unilateral lymphadenopathy resolving within 5 days [32]. The safety of the Moderna vaccine against the SARS-CoV-2 was investigated by a US study, which enrolled more than 15,000 healthy participants [10]. Local adverse events were reported in 84% and 89% of participants, and systemic reactions were reported in 55% and 79% of participants after the first and second doses, respectively. The severity of these systemic events increased after the second dose, with a prolonged duration of these episodes. All adverse events were evaluated to be satisfactory for wide use of the vaccine. Our study, which focused on patients with humoral immunodeficiency, revealed a safety profile similar to the US study. However, the second dose was tolerated better in our pa-

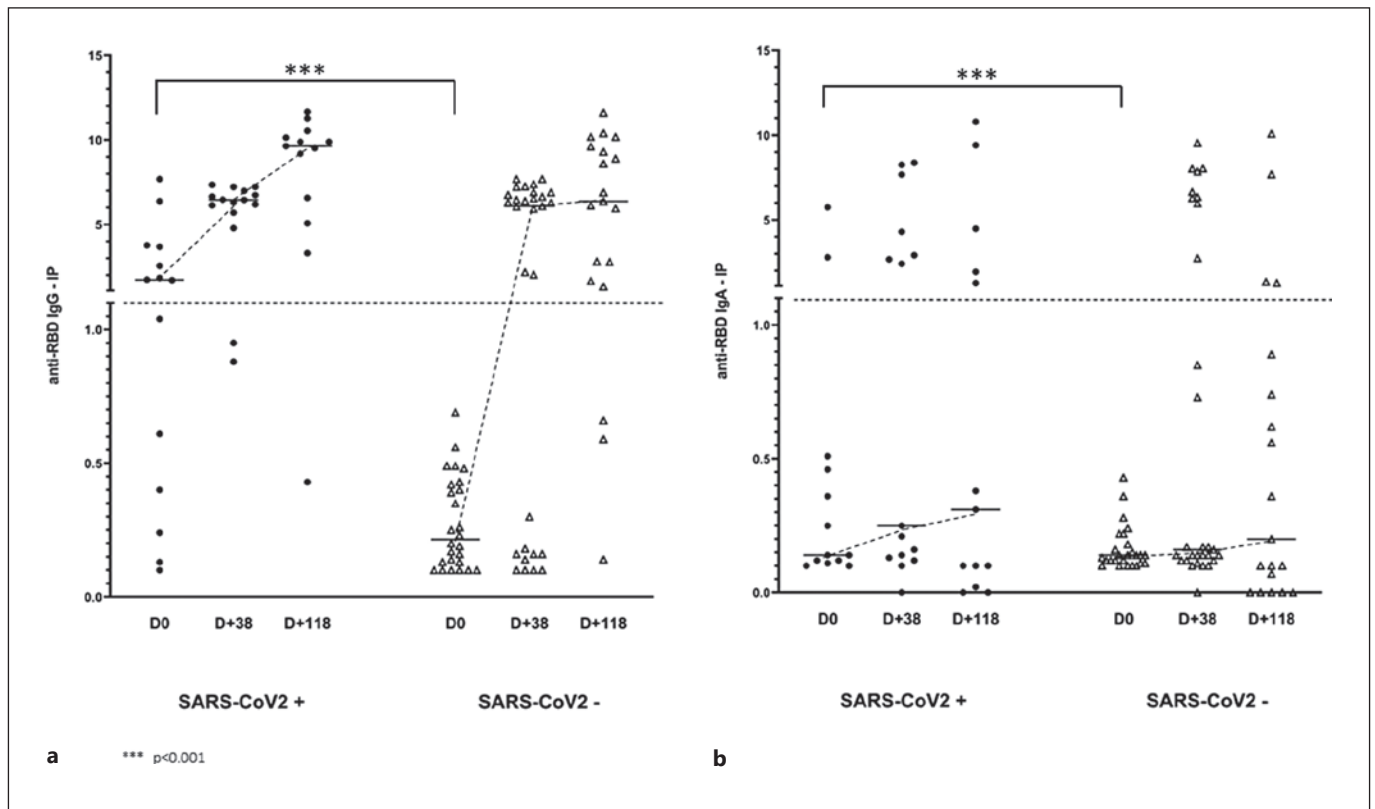


Fig. 6. Specific anti-RBD IgG (a) and anti-RBD IgA (b) in patients with or without a history of SARS-CoV-2 infection. Data are shown as index of positivity, and values more than 1.1 were considered as positive. Patients with a history of SARS-CoV-2 infection indicated a high level of anti-RBD IgG before vaccination ($p < 0.001$). No significant difference was observed in D +38 and D +118. No significant difference was noticed in anti-RBD IgA.

tients than the healthy volunteers in the US study, with less frequent systemic reactions ($p = 0.005$) [10].

Vaccination response to SARS-CoV-2 seems to be atypical and poorer in IEI patients than in healthy controls [30, 33–35]. Seroconversion rate has been reported variable across studies ranging between 20 and 86% [29–36]. Individual studies differ from number of participants, types of IEI, or used vaccines. Binding antibody titers correlates with the presence of neutralizing antibodies in IEI [36]. Further studies showed generation of atypical memory B cells with low binding capacity to spike protein in CVIDs after two doses of mRNA vaccine. Spike-specific T-cell response is also induced with a variable frequency in these patients [34, 37]. Delmonte et al. [31] reported 85% positivity of anti-spike antibodies in 74 IEI patients receiving different vaccines. However, only 16% of patients in this cohort had humoral immunodeficiency. A lower rate of seroconversion was observed in autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy patients, patients treated with RTX, and

patients with baseline counts of $<1,000$ CD3+ T cells/ μ L and <100 CD19+ B cells/ μ L [31]. Further, Hagin et al. [32] enrolled 26 adult IEI patients (4 XLA, 17 non-XLA, and patients suffering from immune dysregulation and antibody deficiency). He revealed 82% seroconversion in the IEI group (excluding XLA patients) and 73% of favorable specific cellular responses (all patients) using Comirnaty[®] [32].

Immunogenicity of Spikevax[®] in healthy volunteers is very high. Several studies reported anti-RBD IgG seroconversion in all participants 1 month after the second vaccine dose with sustainable positivity for further 2 months (day 119) [36–39]. Seroconversion rates in patients with clinically only mild antibody deficiencies and phagocytic defect seem to be comparable with healthy people after two doses of Spikevax[®] [36]. In agreement, we show seroconversion of anti-RBD IgG in all patients with unclassified hypogammaglobulinemia. Seroconversion of specific anti-RBD IgG was detected in 67% CVID patients in general and in 57% of previously noninfected

people. Nearly 82% of CVID responders sustained positive for specific anti-RBD IgG after 3 months of the second vaccine dose.

However, patients with CVID had less favorable results for the seroconversion of anti-RBD IgA. Less than 25% of patients with CVID had detectable anti-RBD IgA response to anti-SARS-CoV-2 vaccination which corresponds to the very low level of total IgA (equal or less than 0.07 g/L) in 88% of patients. Anti-RBD IgA seropositivity sustained only in 3 out of 7 responders in 3 months. COVID-19 mRNA vaccination in other studies also elicited a spike in antigen-specific IgA with similar kinetics of induction and time to peak levels followed by a more rapid decline in serum levels [40]. The clinical importance of specific anti-RBD IgA is still not well understood, but it may indicate high neutralizing potential [41, 42]. Further, it may be an important point in breast-fed newborns of vaccinated mothers [43].

mRNA vaccines induce spike-specific T cells, which recognize different regions of spike proteins and preferentially produce IL-2 and IFN γ [44]. These cells play a critical role from the day +10 after the second vaccine dose and contribute substantially to early protection against the virus [45]. Specific T cells were observed even at 3 months after vaccination. The average number of Spike-specific T cells induced by vaccination was equivalent to what has been detected in convalescent patients at a similar time after natural SARS-CoV-2 infection [46]. High variability between individuals has been observed [44, 46]. B-cell depletions may modify the response with CD4+ follicular T-cell deficit and preferential CD8+ T-cell induction [47]. Our results support variable T-cell functionality in CVID patients with only 50% of positive T-cell-specific response 10 days after the second vaccine dose. Noninfectious complications might lead to a significantly decreased T-cell response [36]. Patients who recovered from COVID-19 might show more effective T-cell-specific response. Only about one-third of responders stayed positive after 3 months.

However, lower immunogenicity was reported in the general population older than 65 years and any negative correlation was not found [27, 48]. We suppose that the main reason was significantly lower mean age in our cohort. Decreased immunogenicity of SARS-CoV-2 vaccines in patients with humoral immunodeficiency possibly correlates with a higher value of IDDA severity score, noninfectious complications in general, mainly GLILD, autoimmune cytopenia, or lymphoproliferative diseases with or without concomitant immunosuppression therapy [36]. History of RTX treatment represents major neg-

ative prognostic factor [49]. Learning from the other autoimmune diseases, we can presume that mycophenolate, especially in combination with corticosteroids, can be related to lower predicted relative risk for seroconversion 0.86 (0.52–1.32), 0.61 (0.40–0.90), respectively [49]. Multiple immunosuppressive therapy intensifies probability of vaccination failure [50]. Response to vaccine in patients treated with corticosteroids depends on its dosage. We may know the dose less than 10 mg/day may lead to comparable response like in the healthy controls [51]. Calcineurin inhibitors, primarily ciclosporin, seem to be less important factor in vaccination failure, as well [49, 50, 52].

XLA patients may be at a minor risk of life-threatening COVID-19. It seems that despite the disability to produce antibodies, they are capable of specific cellular response during disease or after vaccination [32, 53, 54], although it is still unclear if this is enough to protect against reinfection [55, 56]. Favorable effector T-cell response sustainable for 3 months after mRNA vaccine was found in both XLA patients in our study. NF κ B pathway activation in plasmacytoid dendritic cells is essential to produce large amounts of type I IFNs. All 4 patients with NF κ B1 or NF κ B2 mutations, mentioned in Meyts et al. [3] study, required hospitalization after SARS-CoV-2 infection, and both NF κ B2-deficient individuals were admitted to the intensive care unit. Moreover, our data together with previous findings support possible lower immunogenicity of anti-SARS-CoV-2 vaccines in these patients [32].

Individuals with previous SARS-CoV-2 infection elicit stronger antibody responses after the first dose than the antibody response in individuals without prior infection [57]. These observations indicate that an additional second dose has only a mild booster effect on the serum level of anti-spike antibodies in these patients [58]. Despite no difference between SARS-CoV-2 positive and negative subgroups in the context of specific humoral response, our cohort of immunodeficient patients with a history of SARS-CoV-2 infection showed a better outcome in T-cell-specific response after the second dose. The difference between SARS-CoV-2-positive and SARS-CoV-2-negative individuals may occur 3 months after the vaccination with a higher level of specific anti-RBD IgG in SARS-CoV-2-positive individuals in our cohort.

Vaccination of the third dose has been discussed. Available data indicate less symptomatic course of COVID-19 in comparison with unvaccinated patients or patients vaccinated with 2 doses against both the Omicron and

Delta variants, although the higher odds ratios for Omicron suggest less protection for Omicron than for Delta in general population [59, 60]. The third vaccination in patients with immune-mediated inflammatory disorders on immunosuppressants may provide significant benefit in patients treated by mycophenolate alone or in combination with weak responders to two doses. The seroconversion after the third vaccine dose in nonresponders is not exactly defined with variable, predominantly low response rate [61].

We can summarize that the vaccination against SARS-CoV-2 using Spikevax[®] led to seroconversion in two-thirds of COVID patients and to detectable T-cell response in more than half of the cases in our study. Low immunogenicity was observed in patients with lung involvement and/or RTX treatment history. In agreement with other experts, we support vaccination after natural infection and application of the third booster dose of vaccine in ICI patients to ameliorate the severity of potential disease [37, 62]. We can recommend checking the vaccination response. Nonresponders should be eligible for monoclonal antibody or early antiviral treatment in case of infection.

However, our study has certain limitations, including a low number of enrolled patients and impossibility to use control healthy group due to governmental (general/hospital) vaccination strategy at the time of study. Laboratory kit producers unfortunately have not identified intermediate values or protective values for antibodies and T-cell response yet. In addition, we think that definition of protective values is complicated to changing SARS-CoV-2 variants during the last 2 years. Further, the evaluation of favorable incidence of SARS-CoV-2 infection after vaccination could be influenced by the fact that patients with an inborn immune system error adhere to preventive measures rather strictly and a part of the observation comprised a period with lower infection incidence during summer in our country. Therefore, the result should be interpreted carefully in the context of other studies. On the contrary, the strengths of the study include a homogeneous group of patients with predominantly humoral immunodeficiency, the use of a single mRNA vaccine, and 6-month follow-up of monitoring number of breakthrough infections.

Further studies are needed to verify the duration of vaccination response in immunocompromised individuals. Spikevax[®] seems to be safe with rather satisfactory immunogenicity and efficacy in patients with primary humoral immunodeficiency. However, our data suggest an individualized schedule for revaccination.

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Statement of Ethics

This study was approved by the local Ethics Committee of the University Hospital Hradec Kralove, Czech Republic (reference number 201906S25P). Written informed consents were obtained from all the enrolled patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pavlina Kralickova created the study design, acquired, analyzed, and interpreted the data, and wrote the article. Jan Krejsek, Karolina Jankovicova, Ilona Sejkorova, Ondrej Soucek, Kanterina Koprivova, Marcela Drahosova, and Ctirad Andrys helped with the study design and analyzed the specimens. Ondrej Soucek interpreted the data and made figures. Jan Krejsek supervised the project. All authors edited, reviewed, and approved the final version of the manuscript.

Data Availability Statement

The basic data that support the findings of this study are included in online Supplement 1. Further data are not publicly available since they contain information that could compromise the privacy of research participants. However, the data are available on request from Pavlina Kralickova.

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