
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

**Table 1**
Skin Testing Results

| Steps[a] | PEG 3350 MiraLAX (170 mg/mL) | Methylprednisolone acetate (40 mg/mL) | Control Methylprednisolone sodium (40 mg/mL) | Polysorbate 20 Polysorbate 20 (0.5 mg/mL) | Polysorbate 80 Triamcinolone acetonide (40 mg/mL) | Refresh eye drops | Prevnar 13 vaccine | mRNA COVID-19 vaccine Pfizer-BioNTech (lot number ER8731) |
|---|---|---|---|---|---|---|---|---|
| Step 1 | 1:100 SP (0) | 1:1 SP (0) | 1:1 SP (0) | 1:1 SP (0) | 1:1 SP (0) | 1:1 SP (0) | 1:10 SP (0) | 1:1 SP (0) |
| Step 2 | 1:10 SP (0) | 1:100 ID (0) | 1:100 ID (0) | | 1:100 ID (0) | 1:10 ID (3 × 3 wheal, 7 × 7 flare) | 1:100 ID (0) | |
| Step 3 | 1:1 SP (0) | 1:10 ID (0) | 1:10 ID (0) | | 1:10 ID (0 wheal, 4 × 4 flare) | | | |
| Step 4 | | | | | 1:1 ID (3 × 3 wheal, 8 × 8 flare) | | | |

Abbreviations: COVID-19, coronavirus disease 2019; ID, intradermal; PEG, polyethylene glycol; mRNA, messenger RNA; SP, skin prick.
[a]Controls done before testing include control prick (0), histamine 6 mg/mL SP (3 × 3 flare).

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# Detection of neutralizing anti–severe acute respiratory syndrome coronavirus 2 antibodies in patients with common variable immunodeficiency after immunization with messenger RNA vaccines

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Common variable immunodeficiency (CVID) is a rare disorder, occurring in approximately 2 to 4 per 100,000 individuals in the general population. Nevertheless, it is the most common symptomatic primary immunodeficiency disorder in adults and may account for a substantial proportion of patients in specialized immunology clinics. The cause is unknown; diagnosis relies on multiple criteria because no single clinical manifestation or laboratory test can aid in recognizing this entity.[1] Specifically, CVID may be diagnosed in case of a marked decrease of immunoglobulin G (IgG) (at least 2 SD below the mean for age) and a marked decrease in IgM or IgA, in addition to the following criteria: (1) onset of immunodeficiency at greater than 2 years of age; (2) absent isohemagglutinins and poor response to vaccines; and (3) exclusion of other possible causes of hypogammaglobulinemia.[1] Antibody production is always impaired in CVID, as a result of primary B-cell dysfunction or from lack of T cell help for antibody production.[1]

The current pandemic of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents an unprecedented challenge for health care systems across the world,[2] but the ongoing global mass vaccination against SARS-CoV-2 may help reduce the hospital burden worldwide. Patients with CVID, however, may not be included into the vaccination programs because of the common perception that they are not responsive to vaccination.[1] In countries such as Italy, where general practitioners are in charge of the recruitment of "fragile" patients into vaccination programs, it is paramount to address the issue of the effectiveness of COVID-19 vaccines in patients with primary immunodeficiency, also considering the low awareness on this peculiar group of diseases among physicians not specializing in clinical immunology.[3]

Therefore, to establish whether SARS-CoV-2 vaccination may be meaningful in individuals with CVID, we investigated whether these patients could generate protective antibodies against SARS-CoV-2 after administration of messenger RNA (mRNA) vaccines[4] and compared the outcome in healthy subjects from hospital staff undergoing COVID-19 vaccination.

A total of 5 patients (4 females, 1 male; median age, 54 years) with CVID (median age at diagnosis, 35 years) on monthly intravenous immunoglobulin replacement therapy agreed to receive an mRNA vaccine.[4] Serum SARS-CoV-2 antibodies were measured in all

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**Table 1**
Summary of Clinical and Laboratory Features of Patients With Common Variable Immunodeficiency and Outcome of Vaccination

| CVID patient number | Sex | Age | Years since diagnosis | Lymphocyte counts | Lymphocyte subsets | Comorbidities | Latest serum immunoglobulin assessment[a] | Type of vaccine | Preimmunization anti–SARS-CoV-2 (antispike) antibodies | Postimmunization anti–SARS-CoV-2 (antispike) antibodies | Adverse effects after first vaccine dose | Adverse effects after second vaccine dose |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 58 | 9 | Normal | Normal | Obesity, hypertension, thyroid nodule | IgG, 832 mg/dL<br>IgA, 6 mg/dL<br>IgM, 9 mg/dL | Pfizer-BioNTech | Absent | 8.68 BAU/mL | Pain at injection site, diffuse myalgias, headache, fatigue | Pain at injection site |
| 2 | F | 54 | 19 | Normal | Normal | None | IgG, 777 mg/dL<br>IgA, 2 mg/dL<br>IgM, 2 mg/dL | Moderna | Absent | 812.90 BAU/mL | Pain at injection site | Low-grade fever, myalgias, headache, fatigue |
| 3 | F | 63 | 1 | Mild lymphopenia (1060/μL) | Normal | Celiac disease, osteoporosis with vertebral fractures | IgG, 665 mg/dL<br>IgA, 14 mg/dL<br>IgM, 6 mg/dL | Pfizer-BioNTech | Absent | 212.7 BAU/mL | Pain at injection site | Pain at injection site |
| 4 | M | 45 | 12 | Normal | Normal | None | IgG, 721 mg/dL<br>IgA, 3 mg/dL<br>IgM, 2 mg/dL | Pfizer-BioNTech | 160 BAU/mL | 10185 BAU/mL | Headache | Pain at injection site |
| 5 | F | 37 | 6 | Normal | CD19 B cells <1%[b] | Bronchiectasis, liver nodular lymphoid hyperplasia | IgG, 515 mg/dL<br>IgA, 2 mg/dL<br>IgM, 1 mg/dL | Pfizer-BioNTech | Absent | Absent | Pain at injection site, headache, myalgias, chills | Pain at injection site |

Abbreviations: BAU, binding arbitrary unit, according to the World Health Organization international standard (<1, negative; >1, positive); CVID, common variable immunodeficiency; ECLIA, electrochemiluminescence immunoassay; F, female; Ig, immunoglobulin; M, male.
NOTE. Antibodies were detected by ECLIA.
[a]Normal values for serum immunoglobulin isotypes were as follows: IgG, 700 to 1600 mg/dL; IgA, 70 to 400 mg/dL; IgM, 40 to 230 mg/dL.
[b]Normal B-cell frequencies: 6% to 20%.

patients immediately before vaccination and the next IgG infusion (because of the possibility of antibodies against SARS-CoV-2 in commercial intravenous immunoglobulin preparations[5]) and 30 days after the second vaccine jab, again just before the next IgG infusion. Adverse effects were recorded for all patient after each vaccine dose administration. Comorbidities and immunologic features were also registered. Patient #4 (Table 1) had a mild form of the natural infection with SARS-CoV-2 4 months before the vaccination. At that time, this patient only complained of fever (38°C) for 2 days and cough but it took nearly 4 weeks for his nasopharyngeal swab to turn negative on molecular recognition of SARS-CoV-2. Among the 5 patients subjected to vaccination, he was also the only one to have naturally occurring virus-specific neutralizing antibodies, which greatly increased after completion of the vaccination schedule (Table 1). The remaining 4 patients had no detectable anti–SARS-CoV-2 antibodies before vaccination. Postvaccination, all patients but 1 developed neutralizing antibodies against SARS-CoV-2, with varying degrees of positivity. Of note, the only patient who failed to have a substantial rise in postvaccination titers of anti–SARS-CoV-2 antibodies also had a marked decrease in the frequency of circulating B cells on flow cytometry assessment. Adverse effects were mild and transient and did not differ from those reported in other series.[6] Mild pain at injection site was reported by nearly all patients. Clinical and laboratory features of all patients are summarized in Table 1. Control subjects (3 males, 7 females; age range, 41-62 years) had variable titers of neutralizing antibodies as well (range, 256-9060 binding arbitrary units per milliliter), with median values close to 1200 binding arbitrary units per milliliter. They had been all vaccinated with the Pfizer-BioNTech mRNA vaccine (COMIRNATY, Pfizer Manufacturing Belgium NV, Puurs, Belgium, and BioNTech Manufacturing GmbH, Mainz, Germany).

Overall, our experience reveals that SARS-CoV-2 vaccination is safe and effective even in patients with primary antibody deficiencies. Nevertheless, as inferred by the only patient who did not have an antibody response to vaccination, production of neutralizing immunoglobulins may at least require preservation of the B lymphocyte population. Whether the serum levels measured in patients with CVID are able to fully protect these subjects from mild or severe manifestations of COVID-19 is currently unknown, because there are not yet ad hoc studies. Further complicating things, patients with CVID are known to be able to even produce antibodies at normal titers, but these antibodies may have poor avidity with impaired opsonophagocytic function.[7] Likewise, comparing serum levels of anti–SARS-CoV-2 antibodies between patients with CVID and immunocompetent subjects to evaluate the magnitude of vaccination efficacy may as well be meaningless, because the level of neutralizing antibodies required to confer protection has not been definitively established.[8] Indeed, serum levels of anti–SARS-CoV-2 antibodies seemed to be overall more elevated in healthy hospital personnel than in patients with CVID, but, again, the clinical significance of this difference is currently unknown.[8] Interestingly, the only patient (#4) with previous, naturally acquired immunization against SARS-CoV-2 had an impressive rise in the titers of neutralizing antibodies after vaccination; thus, if previous immunization is a prerequisite for remarkable antibody responses after vaccination, it may theoretically be anticipated that a further vaccine jab would probably substantially enhance the protective antibody response in the remaining patients as well. Our data are fully consistent with those recently reported by 2 other studies of mRNA COVID-19 vaccine immunogenicity in patients with primary immunodeficiency.[9,10] In both reports, all patients with CVID but 2 (19 total, 6 and 13 in the 2 studies,[9,10] respectively) were able to mount specific antibody responses after vaccination. Accordingly, patients with absence of B cells (ie, patients with X-linked agammaglobulinemia) failed to have production of neutralizing antibodies against SARS-CoV-2.[9,10] Nevertheless, these patients did produce robust antiviral cellular responses,[10] which still may justify

vaccination. Likewise, adverse effects to vaccination were mild in both studies. Taken together, the results of our and these 2 other studies strongly support the notion that patients with CVID must be included in COVID-19 vaccination programs because of the ability of mRNA vaccines to safely induce production of neutralizing antibodies in this category of patients.

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# Specific antibody response of patients with common variable immunodeficiency to BNT162b2 coronavirus disease 2019 vaccination



On March 11, 2020, the World Health Organization declared that the coronavirus disease 2019 (COVID-19) was a pandemic.[1] Since then, the disease has reached a 1% to 3% estimated overall mortality rate.[2] COVID-19 severity ranges from asymptomatic to acute respiratory distress syndrome and possible death owing to multiorgan failure.[2] Therefore, to ameliorate the resultant poor health and social and economic consequences, prophylactic vaccines were developed. On December 11, 2020, the US Food and Drug Administration issued the first emergency use authorization of Pfizer-BioNTech (Pfizer Inc, New York City, New York) messenger RNA (mRNA) vaccine (BNT162b2) for COVID-19 prevention.[1] The vaccine was approved after a large randomized, placebo-controlled trial in approximately 44,000 participants aged 16 years or older and revealed that a 2-dose regimen of BNT162b2 conferred 95% protection against symptomatic COVID-19.[1] This novel lipid nanoparticle-formulated nucleoside-modified RNA vaccine encodes the full-length spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which contains the receptor binding domain (RBD) within the S1 subunit.[3] The RBD is a key functional component within the S1 subunit responsible for binding SARS-CoV-2 to angiotensin-converting enzyme 2 receptor, a critical initial step enabling SARS-CoV-2 to penetrate target cells.[4]

Among healthy adults, two 30 μg doses of BNT162b2 elicited robust antigen-specific CD8+ and $T_H1$-type CD4+ T-cell responses and strong specific antibody responses directed against RBD.[5] Nevertheless, it is unknown whether patients having primary immunodeficiency disorders of humoral immunity affecting B-cell differentiation and antibody production are able to produce effective specific antibody levels after the 2-dose BNT162b2 regimen. Common variable immunodeficiency (CVID) is an antibody deficiency with variable clinical manifestations; although patients mostly experience recurrent infections, there is an increased prevalence of autoimmune diseases and malignancy secondary to immune dysregulation.[6] A CVID diagnosis established after the fourth year of life requires a suggestive clinical history, a marked reduced total immunoglobulin G (IgG) serum concentration with low IgA or IgM, poor responses to vaccines (or absent isohemagglutinins), or low $IgD^-/CD27^+/CD19^+$ switched memory B (smB) cells, and no evidence of profound T-cell deficiency; in addition, other causes of secondary hypogammaglobulinemia must be excluded.[6]

We observed retrospectively the ability of patients with CVID to produce SARS-CoV-2 spike-specific IgG in response to the 2-dose BNT162b2 regimen as part of the national vaccination program of Israel. Furthermore, we looked for a correlation with CVID subgroups based on flow cytometry B-cell immunophenotyping.[7] All patients diagnosed as having CVID (n = 17) were treated with intravenous immunoglobulin (IVIG) every 4 weeks at Lin, Zvulun, and Carmel Medical Centers belonging to Clalit Health Services in Haifa, Israel. Revised European Society for Immunodeficiencies registry criteria[6] were used for CVID diagnosis. Between December 23, 2020, and

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