To the Editor:

Currently, available COVID-19 vaccines in the USA include both the Pfizer-BioNTech and Moderna 2-dose mRNA lipid nanoparticle vaccines given at 21-day and 28-day intervals, respectively, along with the Janssen (Johnson & Johnson) single-dose recombinant adenoviral vector vaccine. Outside of the USA, the AstraZeneca vaccine, a modified chimpanzee adenoviral vector 2-dose series given 28-days apart, and the CoronaVac (Sinovac), a 2-dose inactivated viral vaccine given 21-days apart, among others, are being utilized [1]. Local and systemic side effects are frequently reported by COVID-19 vaccine recipients, with reported reactions ranging between 70 and 75% following Pfizer-BioNTech and Moderna vaccines and 86–88% of AstraZeneca vaccine trial recipients with slightly lower rates reported in the Janssen (35–62%) and CoronaVac (29–38%) vaccine trials [2–5].

Despite the growing literature on the use of COVID-19 vaccines, many unknowns remain about the safety and tolerability of these vaccines in immune-deficient patients. While there are recent reports of diminished immunogenicity to COVID-19 vaccines in immunocompromised patients [6], there are also case series of patients with immunodeficiency mounting specific antibody and T-cell responses to an mRNA COVID-19 vaccine [7]. Therefore, it is generally recommended that patients with immunocompromised states or immune deficiency receive the COVID-19 vaccine. However, the lack of published data on the safety of the COVID-19 vaccines in patients with immunodeficiencies may deter some from receiving the vaccines as recommended. We sought to better understand the safety and tolerability of COVID-19 vaccination in patients with immunodeficiencies who were receiving supplemental immunoglobulins.

An online survey (full survey available in Supplemental Material) was sent to 562 members of the Clinical Immunology Society (CIS). The survey was open from February 3, 2021, to March 17, 2021. Survey respondents provided answers regarding patient diagnosis, related comorbidities, type and dose of immunoglobulin replacement, age at vaccination, which COVID-19 vaccine was received, and adverse events following vaccination. Respondents were asked to grade the perceived severity of the adverse event based on the patient’s reported symptoms. Deidentified patient information was provided for 37 patients from 24 CIS members from the USA, Canada, Spain, Brazil, and Egypt, primarily from academic medical centers. For the final analysis, 25 patients had complete survey information regarding reaction to an initial dose and 22 had complete information for both the first and second doses.

Patient characteristics demonstrated that 68.0% (17/25) of patients were female, 96.0% (24/25) were White and 20.0% (5/25) were identified as Hispanic or Latino. The most common diagnosis was common variable immunodeficiency (CVID) in 72.0% (18/25 patients), and 1 patient each was reported with secondary hypogammaglobulinemia due to rituximab, X-linked agammaglobulinemia (XLA), severe combined immune deficiency (SCID) due to adenosine deaminase deficiency following gene therapy, Hyper-IgE syndrome, ataxia telangiectasia with hypogammaglobulinemia, CD25 deficiency (compound heterozygote), and combined immunodeficiency (CID) with hypogammaglobulinemia (see Table 1).

Information regarding comorbidities was collected including diagnoses of lung disease, allergic, autoimmune, or malignant conditions (see Table 1). Allergic conditions included asthma in patient #11, allergic colitis in patient #2, and eczema in the patient Hyper-IgE syndrome (#13). There were 3 total patients with one or more cytopenia: one with a history of autoimmune cytopenias (#6), one with immune...
Table 1  Characteristics and reported adverse events following COVID-19 vaccination in patients with immunodeficiency

| Patient number | Vaccine received | Diagnosis | IVIG or SCIG | Associated conditions | Sex | Age at vaccination (years) | Adverse event after 1st vaccine | Severity and symptoms | Adverse event after 2nd vaccine | Severity and symptoms |
|----------------|------------------|-----------|--------------|-----------------------|-----|---------------------------|-------------------------------|------------------------|---------------------------|------------------------|
| 1              | Coronavac        | CVID      | SCIG         |                       | M   | 40                        | No                            |                        |                           |                        |
| 2              | AztraZeneca      | XLA       | IVIG         | Allergic colitis, bronchiectasis | M   | 20                        | Yes                           | Moderate: injection site pain, fever, fatigue, headache |                           |                        |
| 3              | AstraZeneca      | CVID      | IVIG         |                       | F   | 49                        | No                            |                        |                           |                        |
| 4              | AstraZeneca      | CVID      | SCIG         | GLILD, Hashimoto’s, oral carcinoma | F   | 53                        | No                            |                        |                           |                        |
| 5              | Janssen          | Ataxia-elangiectasia | SCIG | Cognitive impairment | F   | 18                        | Yes                           | Moderate: fever, nausea, myalgias, cough |                           | No                      |
| 6              | Pfizer-BioNTech  | CD25 Deficiency | SCIG | Autoimmune cytopenias | F   | 17                        | Yes                           | Mild: injection site pain |                           | No                      |
| 7              | Pfizer-BioNTech  | CID       | IVIG         | Evan’s syndrome       | M   | 52                        | No                            |                        |                           |                        |
| 8              | Pfizer-BioNTech  | CVID      | IVIG         | Metastatic melanoma, CLL | F   | 39                        | Yes                           | Mild: injection site pain |                           | Yes                    |
| 9              | Pfizer-BioNTech  | CVID      | SCIG         | Lymphocytic colitis IBD | F   | 70                        | No                            |                        |                           |                        |
| 10             | Pfizer-BioNTech  | CVID      | IVIG         | Asthma, breast cancer | F   | 52                        | No                            |                        |                           |                        |
| 11             | Pfizer-BioNTech  | CVID      | SCIG         | Asthma, breast cancer | F   | 80                        | No                            |                        |                           |                        |
| 12             | Pfizer-BioNTech  | CVID      | IVIG         | IBD, COPD, prostate and thyroid cancer | M   | 71                        | Yes                           | Mild: fatigue |                           |                        |
| 13             | Moderna          | Hyper-IgE syndrome | IVIG | Eczema, restrictive lung disease, pneumatocele | F   | 46                        | Yes                           | Mild: injection site pain |                           | Yes                    |
| 14             | Moderna          | Rituximab-induced hypogammaglobulinemia | IVIG | History of Hodgkin's lymphoma | M   | 17                        | No                            |                        |                           |                        |
| 15             | Moderna          | ADA-SCID (post gene therapy) | IVIG | Interstitial lung disease | F   | 22                        | No                            |                        |                           | No                      |
| 16             | Moderna          | CVID      | IVIG         | Sarcoidosis           | F   | 67                        | No                            |                        |                           | No                      |
| 17             | Moderna          | CVID      | SCIG         | Enteropathy           | F   | 25                        | Yes                           | Mild: injection site pain |                           | Yes                    |

Notes: IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin; M = male; F = female; Yes/No indicates presence/absence of adverse effect; Severity and symptoms provided for severe and moderate events; Mild events not mentioned unless specified; Other symptoms not listed could include injection site pain, fatigue, myalgias, arthralgias, fever, chills, headache, nausea.
# Table 1 (continued)

| Patient number | Vaccine received | Diagnosis | IVIG or SCIG | Associated conditions | Sex | Age at vaccination (years) | Adverse event after 1st vaccine | Severity and symptoms | Adverse event after 2nd vaccine | Severity and symptoms |
|----------------|------------------|-----------|--------------|-----------------------|-----|---------------------------|-------------------------------|----------------------|---------------------------|----------------------|
| 18             | Moderna          | CVID      | IVIG         | Myopathy, GLILD, papillary thyroid cancer | F   | 55                        | Yes                           | Mild: injection site pain, fatigue, headache | Yes                       | Mild: injection site pain, fatigue, headache |
| 19             | Moderna          | CVID      | IVIG         | Rheumatoid arthritis   | F   | 77                        | Yes                           | Mild: injection site pain      | Yes                       | Moderate: fever, fatigue, chills, myalgias |
| 20             | Moderna          | CVID      | IVIG         | IBD, prostate and thyroid papillary microcarcinoma | M   | 71                        | Yes                           | Mild: injection site pain, myalgias | No                        |                       |
| 21             | Moderna          | CVID      | SCIG         | ITP, benign parotid gland lymphoepithelial neoplasm | F   | 38                        | No                            |                           | Yes                       | Mild: injection site pain, chills, myalgias |
| 22             | Moderna          | CVID      | IVIG         | Enteropathy            | M   | 67                        | Yes                           | Mild: injection site pain      | Yes                       | Mild: injection site pain |
| 23             | Moderna          | CVID      | SCIG         | Enteropathy            | F   | 39                        | Yes                           | Mild: injection site pain      | Yes                       | Moderate: injection site pain, fatigue, chills, arm & wrist pain/weakness |
| 24             | Moderna          | CVID      | IVIG         | Type 1 diabetes       | M   | 32                        | No                            |                           | No                        | Severe: fever, fatigue, headaches, cold sores |
| 25             | Moderna          | CVID      | SCIG         | Enteropathy            | F   | 29                        | No                            |                           | Yes                       |                       |

*ADA-SCID*, adenosine deaminase severe combined immunodeficiency; *CLL*, chronic lymphocytic leukemia; *CVID*, common variable immunodeficiency; *GLILD*, granulomatous-lymphocytic interstitial lung disease; *IBD*, inflammatory bowel disease; *ITP*, immune thrombocytopenia; *IVIG*, intravenous immunoglobulin; *SCIG*, subcutaneous immunoglobulin; *XLA*, X-linked agammaglobulinemia
thrombocytopenia (#21), and one with Evan’s syndrome (#7). The patients with cytopenias received either the Pfizer-BioNTech or Moderna COVID-19 vaccines.

Of the patients reported, 60% were receiving intravenous immunoglobulin (IVIG) while 40% were receiving subcutaneous immunoglobulin (SCIG). Information on prior COVID infection was not obtained. The median age at vaccination was 45.8 years (range: 17–80 years). For vaccine type, 28.0% (7/25) received Pfizer, 52.0% (13/25) received Moderna, and 20.0% received another COVID-19 vaccine (1 CoronaVac, 3 AstraZeneca, and 1 Janssen). After the first dose of a COVID-19 vaccine, only 48.0% of patients reported a reaction/adverse event, with the majority (83.3%) being considered mild severity. No anaphylaxis or severe adverse events were reported after a first dose. Symptoms started >1 h but on the same day for most patients (75.0%) with the remaining 25.0% developing symptoms within 24–48 h. The most common symptom was injection site pain in 83.3% patients, followed by fatigue in 25.0% (Supplementary Fig. 1).

63.6% (14/22) of patients reported a reaction after the 2nd dose of a COVID-19 vaccine. Both injection site pain and fatigue were the most frequently reported symptoms in 57.1% of patients (Supplementary Fig. 1). Adverse events were considered mild in 53.9% of patients and moderate in 30.8%, but 15.4% (2/13) were considered severe. Additional information provided for the severe reactions included cold sores along with fever, fatigue, and headache in one patient (#2). The second patient (#8) developed elevated liver enzymes of unclear etiology, question of adverse effect from the vaccine versus concurrent terbinafine or pembrolizumab-induced hepatitis. This was ultimately treated with prednisone. There were no cases of anaphylaxis reported after a second dose. No patients reported new adverse events after subsequent SCIG or IVIG infusions following COVID-19 vaccination.

**Discussion**

There is presently limited information regarding the safety and tolerability of COVID-19 vaccines in patients with immunodeficiency or in those receiving supplemental immunoglobulin therapies. The survey responses indicate that the rates and severity of adverse reactions to COVID-19 vaccination in patients with immunocompromised states receiving supplemental immunoglobulin therapies are similar to the general population and those reported in the COVID-19 vaccine trials [2–5]. Reactions and adverse events were more common after the 2nd dose of a COVID-19 vaccine (63.6% of patients) versus the 1st dose (48.0%) but majority of the reactions were considered mild in severity. Injection site pain and fatigue were the most frequently reported symptoms after both doses.

While robust conclusions from the survey results are limited due to the small sample size, this report demonstrates that COVID-19 vaccines appear safe and well tolerated in patients with immunodeficiency who are receiving supplemental immunoglobulin therapy. These results may help physicians and other healthcare providers to encourage COVID-19 vaccination in patients with immunodeficiency.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10875-021-01101-8.

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**Data Availability** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Conflict of Interest** The authors declare no competing interests.

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