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LETTER TO EDITOR

Safety of COVID-19 Vaccination in Immune-Deficient Patients Receiving Supplemental Immunoglobulin Therapies

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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 use of 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

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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		No	
2	AztraZeneca	XLA	IVIG	Allergic colitis, bronchiectasis	M	20	Yes	Moderate: injection site pain, fever, fatigue, headache	Yes	Moderate: injection site pain, fever, fatigue, myalgias, arthralgias
3	AstraZeneca	CVID	IVIG		F	49	No		No	
4	AstraZeneca	CVID	SCIG	GLILD, Hashimoto's, oral carcinoma	F	53	No		Yes	
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		No	
8	Pfizer-BioNTech	CVID	IVIG	Metastatic melanoma, CLL	F	39	Yes	Mild: injection site pain	Yes	Severe: fever, fatigue, chills, headache, elevated liver enzymes
9	Pfizer-BioNTech	CVID	SCIG	Lymphocytic colitis	F	70	No			
10	Pfizer-BioNTech	CVID	IVIG	IBD	F	52	No		Yes	Mild: injection site pain
11	Pfizer-BioNTech	CVID	SCIG	Asthma, breast cancer	F	80	No		Yes	Mild: injection site pain
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	Mild: injection site pain, fatigue, low-grade fever
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		Yes	Mild: rash (> 48 h after)
17	Moderna	CVID	SCIG	Enteropathy	F	25	Yes	Mild: injection site pain	Yes	Moderate: fever, fatigue, 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		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	
25	Moderna	CVID	SCIG	Enteropathy	F	29	No		Yes	Severe: fever, fatigue, headaches, cold sores

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 (#25). 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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