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.

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Review

Immunizing the imperfect immune system

Coronavirus disease 2019 vaccination in patients with inborn errors of immunity

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Key Messages

- Multiple international cohort studies have revealed the safety of coronavirus disease 2019 vaccines in patients with inborn errors of immunity (IEI) despite a high rate of reactogenicity.
- Reviewed studies published to date have revealed antibody responses in approximately 73% of patients with IEI who received coronavirus disease 2019 vaccination and spike-directed T cell immunity in most patients after vaccination.
- Risks for poor antibody response included diagnosis of common variable immunodeficiency, IEI with presence of autoimmune complications, agammaglobulinemia, and other causes of B cell aplasia, including recent treatment with rituximab.
- Further studies are ongoing to evaluate the duration of immunity after vaccination in those with IEI.

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ABSTRACT

Objective: To update clinicians on current evidence regarding the immunogenicity and safety of coronavirus disease 2019 (COVID-19) vaccines in patients with inborn errors of immunity (IEI).
Data Sources: Peer-reviewed, published studies in PubMed, clinical trials listed on ClinicalTrials.gov, and professional organization and governmental guidelines.
Study Selections: Literature searches on PubMed and ClinicalTrials.gov were performed using a combination of the following keywords: primary immunodeficiency, COVID-19, SARS-CoV-2, and vaccination.
Results: A total of 26 studies met the criteria and were included in this review. Overall, antibody responses to COVID-19 vaccination were found in 72% of study subjects, with stronger responses observed after messenger RNA vaccination. Neutralizing antibodies were detected in patients with IEI, though consistently at lower levels than healthy controls. Risk factors for poor antibody responses included diagnosis of common variable immunodeficiency, presence of autoimmune comorbidities, and use of rituximab. T cell responses were detectable in most patients with IEI, with poorer responses often found in patients with common variable immunodeficiency. Safety of COVID-19 vaccines in patients with IEI was acceptable with high rates of reactogenicity but very few serious adverse events, including in patients with immune dysregulation.
Conclusion: COVID-19 vaccines are safe in patients with IEI and seem to be immunogenic in most individuals, with stronger responses found after messenger RNA vaccinations.

Introduction

Since its emergence, coronavirus disease 2019 (COVID-19) has been a considerable threat to immunocompromised patients. From the earliest days of the ongoing COVID-19 pandemic, patients with underlying comorbidities or those with immunosuppression seemed to be at increased risk of severe disease.[1,2] The subsequent development of effective vaccines targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a critical tool in combating the pandemic. However, vaccine immunogenicity and

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safety in patients with inborn errors of immunity (IEI), in whom vaccine responses are often abnormal, have been an important topic of research. With the introduction of effective monoclonal antibodies and antiviral medications targeting SARS-CoV-2, including descriptions of increasing antibody titers against SARS-CoV-2 in immunoglobulin preparations, the question of appropriate prophylactic management of this population is an area of ongoing interest.

Here, we review the impact of the COVID-19 epidemic on patients with IEI and the current data regarding the use of COVID-19 vaccines in this patient population. Immunogenicity, efficacy, and safety in patients on immunosuppressive medications will also be briefly summarized given the frequent use of immunomodulatory therapy in patients with IEI, including passive immunity for patients unlikely to respond to vaccination. Finally, current recommendations for vaccinations in patient populations with IEI will be discussed.

Coronavirus Disease 2019 in Patients With Inborn Errors of Immunity

Multiple case series have addressed the elevated morbidity and mortality of COVID-19 in patients with IEI. Meyts et al[3] published an international case series of 94 patients with IEI representing a broad spectrum of immune defects. From this cohort, the clinical presentation and risk factors for severe COVID-19, including chronic lung disease and increased age, were similar to the general population. Intensive care unit admissions and mortality were elevated compared with the general population and trended toward increased severity at a younger age.On the basis of 100 patients, Shields et al revealed that patients with IEI and secondary immunodeficiency were at increased risk of morbidity and mortality from COVID-19, including at younger ages, with risk factors for hospitalization including prophylactic antibiotics, chronic liver disease, and chronic lung disease. Many additional small case series have been published with similar observations, including a meta-analysis which revealed a 1.3-fold increased mortality in IEI.[4-8] Certain IEIs have also been associated with particularly severe COVID-19, including patients who produce type I interferon autoantibodies or those with primary interferon pathway defects.[9,10] Unfortunately, the pandemic has had a substantialimpact on psychosocial functioning and mental health in patients with IEI and caregivers.[8,11,12]

The immunologic response to natural SARS-CoV-2 infection has been investigated in patients with IEI. Kinoshita et al published the first report of detectable serologic and cellular immunity to COVID-19 in patients with IEI.[13] Hanitsch et al reported 5 patients with IEI and severe or fatal COVID-19 who had prolonged viral shedding for up to 4 months and viremia in 3 of the 5 cases. All patients had observable $CD4^+$ T cell responses, but no humoral response to SARS-CoV-2.[14] Furthermore, persistent viral shedding and increased viral replication have been found in multiple immunocompromised populations, leading to concern about immunocompromised persons serving as a viral reservoir, with intrahost viral evolution leading to novel variants.[15-17]

Coronavirus Disease 2019 Vaccination in Healthy Individuals

To date, 3 vaccines (Moderna mRNA-1273, Pfizer BNT162B2, and Johnson and Johnson Ad26.COV2.S) are available in the United States after phase III clinical trials revealed robust prevention of COVID-19 disease.[18-20] Although reactogenicity was common, all 3 vaccines were immunogenic and effective. There were 2 vaccines that used a 2-primary dose messenger RNA (mRNA) platform for healthy individuals (mRNA-1273 and BNT162B2), whereas the Ad26.COV2.S involves a single dose of a replication-incompetent human adenovirus type 26 vector. Thus far, in the setting of an excellent safety profile, BNT162B2 and mRNA-1273 have received full approval from the US Food and Drug Administration (FDA). Owing to ongoing concerns regarding increased risk of thrombosis with thrombocytopenia syndrome, emergency authorization of Ad26.COV2.S is now limited to individuals for whom other COVID-19 vaccines are not accessible or clinically appropriate, or in individuals who would not otherwise receive COVID-19 vaccination.[21] In addition to serologic response, both $CD4^+$ and $CD8^+$ T cell responses have been detected in healthy individuals after vaccinations with each vaccine although $CD4^+$ T cell responses are more robust than $CD8^+$ T cell response (Fig 1).[22-24]

Although safe and effective, immunogenicity of vaccines in the United States wanes in several months.[25-27] T cell responses, however, seem to be more durable in healthy individuals than serologic response.[25] Thus, booster vaccinations are now recommended for all COVID-19 vaccines per the US Centers for Disease Control as of March 2022.[28] Emerging variants to SARS-CoV-2, most prominently Delta and Omicron, have also challenged vaccine efficacy.[29] Recipients of BNT162B2 had detectable neutralizing antibodies to the Omicron variant, but with reduced titers compared with the ancestral virus, Beta or Delta variants.[30] Similarly, Hoffman et al[29] found that mRNA vaccinations resulted in neutralization of Omicron variant, but with neutralizing titers 4 to 5 times lower than wild type virus, and Liu et al[31] revealed that cellular responses to the Delta and Omicron variants were more durable than antibody responses after vaccination with AdV26.COV2.S or BNT162B2.

Response to Other Vaccinations in Inborn Errors of Immunity

Increased risk of poor adaptive immune responses in patients with IEI leads to concern for decreased benefit from vaccination (Fig 1). Thus, immunogenicity of vaccines, including influenza, has been investigated in a spectrum of immunodeficiencies. Friedmann et al found that only 1 of 17 patients with common variable immunodeficiency (CVID) had a humoral response to influenza vaccination. However, most patients with CVID produced $ICOS^+$ T follicular helper cells and influenza virus-specific T cells, although at a lower magnitude than healthy controls (HC).[32] Similar studies have also revealed detectable T cell responses after influenza vaccination in patients with CVID, primary antibody deficiency (PAD), and patients with X-linked agammaglobulinemia (XLA), including in patients with severely decreased to absent antibody responses.[14,33] Some groups have hypothesized that T cell immunity, even in the setting of suboptimal serologic response, provides some protection against severe influenza disease in patients with IEI, and thus advocate for inactivated influenza vaccination.[34,35]

Response to Coronavirus Disease 2019 Vaccination in Inborn Errors of Immunity

As of April 2022, 23 studies have been published evaluating immunogenicity of COVID-19 vaccination in IEI (Table 1). Delmonte et al published one of the first cohorts comparing HC with 81 diverse patients with IEI and 2 patients with thymoma after completion of their primary vaccination series (2 doses of mRNA vaccination [n = 80] or 1 dose of AdV26.COV2.S [n = 3]). Of the patients with IEI, 85% developed detectable anti–S-antibodies after completing their primary vaccination series. Certain genetic diagnoses (including autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED]), previous use of rituximab, $CD3^+$ T cell count less than 1000, and $CD19^+$ B cell count less than 100 were associated with lower anti-spike immunoglobulin (Ig)G titers.[36] Similarly, Bergman et al assessed antibody responses to the receptor binding domain of spike (RBD) in 90 patients with IEI within a larger case series of 449 immunocompromised patients after their primary vaccination series with BNT162B2. Of the patients with IEI, 73% seroconverted after vaccination, including 68% of patients with CVID and 78% of patients

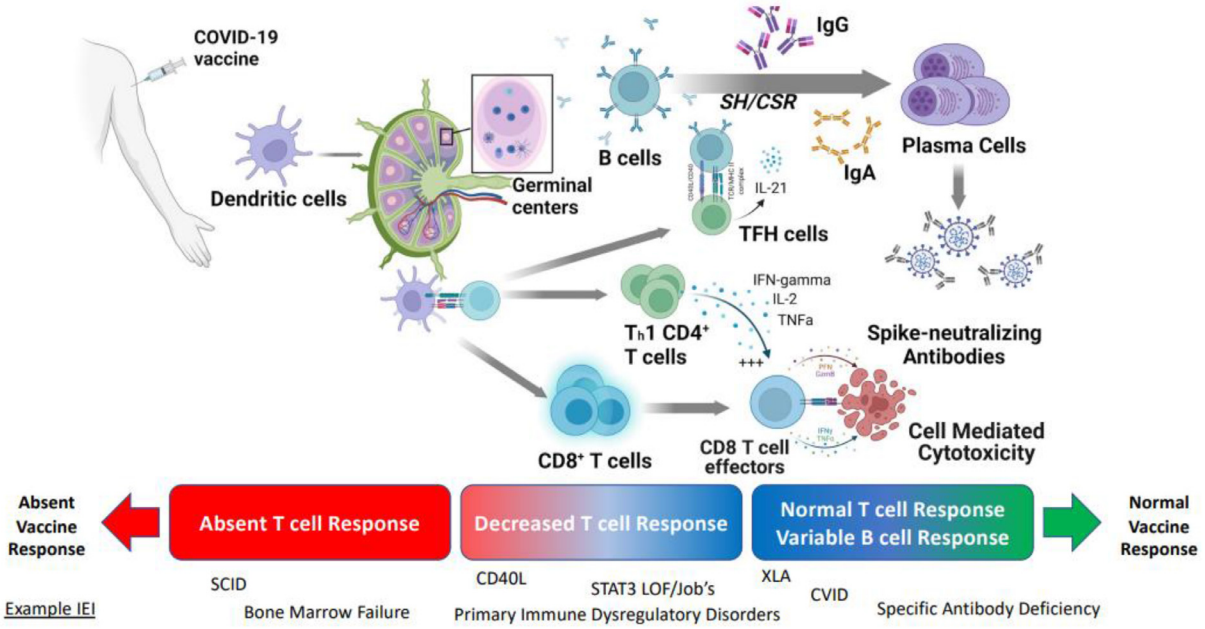

Figure 1. Overview of adaptive immune response to COVID-19 vaccination and potential disruption points for representative IEI. COVID-19, coronavirus disease 2019; CSR, class switch recombination; CVID, common variable immunodeficiency; IEI, inborn errors of immunity; IFN, interferon; Ig, immunoglobulin; IL, interleukin; SCID, severe combined immunodeficiency; SH, somatic hypermutation; TFH, T follicular helper; TNF, tumor necrosis factor.

with monogenic disease. Two patients with hypomorphic severe combined immunodeficiency owing to ARTEMIS deficiency and a patient with CARD11 deficiency did not seroconvert, though overall patients with IEI had higher seroconversion than patients with solid organ transplants or chronic lymphocytic leukemia. In a follow-up study addressing salivary spike-specific immunoglobulin G (IgG) after vaccination, patients with IEI had weaker salivary responses, although overall salivary titers did correlate with serum neutralizing capacity.[37] Lower seroconversion rates (33% for patients with CVID) were observed by Fernandez et al.[38] In the largest case series to date, van Leeuwen et al assessed 505 patients with IEI after vaccination with mRNA-1273. Overall, mild antibody deficiencies and phagocytic defects had similar seroconversion to HCs, whereas more severe IEI, including CVID and combined immunodeficiency (CID), had lower seroconversion rates.[39]

In a longitudinal study in the United Kingdom, Ponsford et al described 304 patients with IEI, 49 of whom had molecularly confirmed SARS-CoV-2 infection.[55] Of these individuals, 2 patients, both with CID, died of COVID-19 after vaccination, as compared with 9 patients who were unvaccinated. Furthermore, 67% had detectable anti-spike IgG, with humoral responses absent in 3 patients with XLA and 8 with CID, including the 2 deceased patients. Combined IgA and IgM deficiency or decreased B cell count (<50E6 cells/L) were associated with lower humoral vaccine response. Pfizer mRNA vaccination produced 50% higher postvaccination titers as compared with ChAdOx1-S NCoV-19, a replication deficiency adenoviral vector vaccine authorized internationally. Age and previous SARS-CoV-2 infection were not associated with significant differences in postvaccine titer ($P > .05$).[55] Similarly, higher antibody titers were observed by Barmettler et al and Shields et al with mRNA vaccination.[44,61] Immunogenicity of COVID-19 booster doses in IEI, for a total of 3 doses in patients receiving mRNA vaccines or 2 doses of Ad26.COV2.S, is also under investigation. Barmettler et al assessed 31 patients with PAD, 3 of whom received primary vaccination with Ad26.COV2.S after a heterologous mRNA vaccine boost. All patients increased mean anti-spike antibody levels to that of HC after primary series vaccination.[44] This finding is similar to reports of improved immunogenicity after booster doses in patients with other mechanisms of immunocompromise.[63]

Several studies have used immunophenotyping to understand the impact of B cell dysfunction on serologic response to COVID-19 vaccination in primary antibody deficiencies. In 17 patients with CVID assessed after BNT162B2 vaccination, Abo Helo et al found that patients with normal numbers of peripheral B cells and switched memory B cells mounted a serologic response. In contrast, only 5 of 7 patients with decreased switched memory B cells despite normal total B cells mounted a response, and responses were absent in patients without peripheral B cells.[40] Similar results were found by Schultz et al, with number of naive B cells serving as a predictor for response to mRNA vaccination.[64] Pulvirenti et al compared humoral responses in 34 previously SARS-CoV-2–infected patients with CVID before vaccination, 38 SARS-CoV-2–naive patients with CVID after 2 vaccinations with BNT162B2, and 20 SARS-CoV-2–convalescent patients with CVID after vaccination with BNT162B2.[56] Detection of spike-specific IgG was more common post SARS-CoV-2 natural infection as compared with post-vaccination. Furthermore, antibody response was boosted by vaccination in previously SARS-CoV-2–infected patients. The investigators postulated that SARS-CoV-2 infection primed a more efficient classical memory B cell response, whereas BNT162B2 vaccination alone induced noncanonical B cell responses in CVID characterized by $CD19^{+}CD27^{-}CD24^{-}CD38^{-}$ atypical memory B cells with low binding capacity of IgG to spike protein.[65] Similarly, Salinas et al investigated 41 patients with CVID and 6 with XLA after vaccination with BNT162B2. Anti-spike IgG was found to be higher in patients with previous infection, and vaccination boosted response in most patients for whom data were available. Patients with CVID generated atypical spike-specific B cells and undetectable RBD-specific B cells, whereas HCs generated spike-specific typical memory B cells and RBD-specific B cells.[58]

Although early studies focused mainly on seroconversion, several studies have in addition evaluated functional activity of anti-spike antibodies. A hierarchy of functional tests have included the following: (1) anti-spike RBD antibody; (2) trimeric anti-spike antibody; (3) neutralizing activity of antibodies against spike protein by

Table 1
Immunogenicity of COVID-19 Vaccines in Patients With IEI

Author	Total number of patients with IEI	Vaccine	IEI diagnosis	Humoral immunity findings	Cellular immunity findings
Abo Helo et al[40]	17	BNT162B2	CVID	65%[a]	NR
Amodio et al[41]	21	BNT162B2	XLA, CVID, antibody deficiency	95% anti-spike RBD antibody, 86% anti-trimeric spike Ab	76%[b]
Antoli et al[42]	28	BNT162B2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S	CVID	71.4%	71%
Arroyo-Sanchez et al[43]	18	BNT162B2, mRNA-1273, ChAdOx1	CVID	83% any, 50% neutralizing	83%
Barmettler et al[44]	62	BNT162B2, mRNA-1273, Ad26.COV2.S	Primary antibody deficiency	59.7% after initial series; 14x higher after booster 2erologic response	NR
Barrios et al[45]	17	BNT162B2	CVID	70.5%	82%
Bergman et al[46]	78	BNT162B2	CVID, XLA, CID, "monogenic"	73%	
Bradley et al[47]	1	BNT162B2	WAS	100%	100%
Delmonte et al[36]	81	BNT162B2, mRNA-1273, Ad26.COV2.S	SCID, APECED, CD40L, CID, CVID, FOXN1, hypogammaglobulinemia, MagT1, immune dysregulation, RAG, RALD, SASH3, STAT 3 LOF, STAT3 GOF, WAS, WHIM, XLA	85%	NR
Fernandez-Salinas et al[38]	33	BNT162B2	CVID	33%	NR
Goda et al[48]	30	ChAdOx1 BNT162b2 Booster	CVID	83% Any after booster 80% Neutralizing after mRNA booster	53% after ChAdOx1 83% after mRNA booster
Gupta et al[49]	10	BNT162B2	CVID	NR	Lower SARS-CoV-2 tetramer-specific CD8+ T cells, lower CD8+ granzyme+ perforin+ T cells
Hagin et al[50]	26	BNT162B2	XLA, hypogammaglobulinemia, STAT1 GOF, CVID, STAT3 LOF, NFKB1, Complement deficiency, IgG2 deficiency, CVID	69%	73%
Jalil, Abraham et al[51]	1	BNT162B2	CVID	100%	NR
Jalil, Rowane et al[52]	1	BNT162B2	MagT1	100%	NR
Oshiro et al[53]	1	Coronovac	XLA	0%	100%
Pham et al[54]	33	BNT162B2, mRNA-1273	Hypo/agammaglobulinemia, XLA, CVID, SAD, Good syndrome, CD40L, CTLA4 haploinsufficiency, PIK3R1 deficiency, ataxia telangiectasia, ATP6AP1 deficiency	48% anti RBD-specific Ab; 6% with ACE2 receptor blocking activity > 50%	77% with detectable T cell specificity
Ponsford et al[55]	156	BNT162B2, mRNA-1273, ChAdOx1	CVID, hypogammaglobulinemia, CID, SAD, DiGeorge, XLA, STAT1 GOF, APECED, CD40L, CGD, CTLA4, complement 2 deficiency, ADA2, IFNGR1, CHH, STAT3 LOF, idiopathic CD4+ T cell lymphopenia, WAS	67%	NR
Pulvirenti et al[56]	58	BNT162B2	CVID	34% post-vaccination; 100% post-infection and vaccination serologic response	1/9 after immunization, 0/3 convalescent and immunized
Romano et al[57]	5	BNT162B2, mRNA-1273	CVID	80%	NR
Salinas et al[58]	47	BNT162B2	CVID, XLA	20%	70% CVID, 83% XLA
Sauerwein et al[59]	73	BNT162B2	CVID, PAD	48% of CVID, 77% of PAD	CVID nonresponders have defective vaccine specific activation of CXCR5-negative CD4+ memory T cells and defective T follicular helper cells. CVID responders and PAD have intact vaccine specific activation of CXCR5-CD4+ memory T cells
Schulz-Cherry et al[60]	25	mRNA-1273, BNT162B2	SAD, subclass deficiency, CVID, "other"	73%	NR

(*continued*)

Table 1 (*Continued*)

Author	Total number of patients with IEI	Vaccine	IEI diagnosis	Humoral immunity findings	Cellular immunity findings
Shields et al[61]	168	BNT162B2, ChAdOx1	CVID, PAD, SAD, XLA, hyper IgM, CID, thymoma	55%	46.20%
Squire et al[62]	11	BNT162B2, mRNA-1273	CVID, XLA, WAS, DiGeorge, hypogammaglobulinemia	91%	NR
van Leeuwen et al[39]	505	mRNA-1273	CVID, PAD, XLA, CID, phagocytic defects	RBD-specific binding antibodies: 98.3% IgG subclass deficiency: 100% undefined antibody deficiency, 100% phagocytic defect, 15% XLA, 91% CID, 81% CVID	88% overall, 67% in CVID

Abbreviations: APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CID, combined immunodeficiency; COVID-19, coronavirus disease 2019; CVID, common variable immunodeficiency; IEI, inborn errors of immunity; Ig, immunoglobulin; mRNA, messenger RNA; NR, not reported; PAD, primary antibody deficiency; RBD, receptor binding domain; SAD, specific antibody deficiency; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; XLA, X-linked agammaglobulinemia.

[a]Percentage of persons with detectable SARS-CoV-2 spike-specific antibodies.

[b]Percentage of persons with detectable SARS-CoV-2 spike-specific T cells.

pseudoneutralizing antibody/angiotensin-converting enzyme 2 receptor blocking activity; and (4) in vitro viral neutralizing antibody assays. Amodio et al investigated 21 patients with XLA, CID, and unclassified antibody deficiency who received BNT162B2.[41] Both HC and patients with IEI had an increase in anti-spike antibody levels; however, levels were lower in patients with IEI, and antitrimeric antibodies, which correlate with neutralization, were present in HC but absent in patients with IEI.[66] The presence of less effective antibody by neutralization or pseudoneutralization in patients with IEI was also found in large case series recently published by Shields et al and van Leeuwen et al.[39,61] Similarly, in a study by Pham et al, 33 patients with humoral defects were evaluated post-BNT162b2 or mRNA-1273 vaccine. Although 16 of 33 subjects had detectable RBD-specific IgG responses, only 2 of 16 had an angiotensin-converting enzyme 2 receptor block activity more than 50%, suggesting that many patients with IEI have suboptimal neutralization activity against SARS-CoV-2.[54]

Many studies have sought to evaluate spike-specific T cell responses after vaccination, especially in patients who are expected to have poor or absent antibody responses. Amodio et al revealed that all HC had T cell responses, but only 16 of 21 patients with IEI had detectable cellular immune responses. Of note, in the patients with IEI who have a T cell response, the magnitude of their T cell response seemed to be greater than HC which may be a compensatory mechanism for poorer antibody responses.[41] Similarly, Arroyo-Sanchez et al evaluated 18 patients with CVID, including 1 patient who received ChAdOX1-S.[43,67] Although 83% of patients with CVID also have an anti-spike T cell response, the magnitude of both antibody and cellular responses in CVID was lower than HC. Hagin *et al.* published a series of 26 patients, including CID, immune dysregulation, and XLA. They found that 73% of patients exhibited a cellular response.[50] With specific regard to cytotoxic $CD8^+$ T cells, Gupta et al revealed that SARS-CoV-2–specific tetramer$^+$ $CD8^+$ T cells and functional $CD8^+$ $107a^+$ granzyme B^+ perforin$^+$ T cells were significantly lower in 5 patients with CVID after BNT162B2 compared with HCs ($P \leq .0003$).[49] Van Leeuwen et al also noted spike-specific T cell responses that were comparable to HCs by Ifn-g release assay, with exception of patients with CVID (67% responders vs 88% in HCs). Finally, in 168 patients with IEI evaluated by Shields et al, 46% of individuals had detectable T cell responses. Importantly, the presence of T cell response was associated with improved antibody responses.[61]

Though general vaccine response rates have been reassuring, the durability of immunity in patients with IEI has been a critical question. To this end, several recent studies have evaluated longitudinal efficacy of COVID-19 vaccination in patients with IEI. Ponsford et al noted that increased time since vaccination was associated with falling titers, similar to trends in HC. Shields et al also found a gradual decrease in titers in the 6 months after vaccination, although higher titers were observed in patients who received BNT162b2 vs ChAdOx1-S. Di Fusco et al evaluated the rate and severity of breakthrough infections in immunocompromised patients who received BNT162b2 vaccination during late 2020 to mid-2021. In their cohort, 7 of 3190 (0.22%) of patients with IEI had breakthrough infections in the 8-month study period. This rate was comparable with patients with rheumatologic conditions and patients receiving antimetabolite therapy but lower than solid organ transplant recipients.[68] There were 11 breakthrough cases observed by Shields et al in a case series of more than 500 patients with IEI, 10 of them occurred in recipients of ChAdOx1-S.[61]

In addition to prevention, Bradley et al published a notable case report of a male adult with Wiskott-Aldrich syndrome who had persistent COVID-19 with undetectable humoral and equivocal T cell response to SARS-CoV-2 on day 140 of illness who was subsequently treated for COVID-19 with 2 doses of BNT162B2. Vaccines were well tolerated. Two weeks after completion of his series, he had detectable anti-spike cellular and humoral responses with declining SARS-CoV-2

viral load on respiratory polymerase chain reaction. He was finally SARS-CoV-2 virus clear at 72 days after his first vaccine dose and 218 days after his initial positive test result.[47]

Safety of Coronavirus Disease 2019 Vaccinations in Inborn Errors of Immunity

To date, COVID-19 vaccines have had an excellent safety profile in patients with IEI (Table 2). Reactogenicity to mRNA vaccines is common in patients with IEI and seems to occur more frequently than in the general population (Table 2). Common symptoms include fever, myalgias, and fatigue, but severity does not seem to be increased in patients with IEI. Given the high rates of reactogenicity and the rare inflammatory events after COVID-19 vaccines, safety of the vaccines in patients with IEI with autoimmune or autoinflammatory complications has been a particular concern for clinicians. Importantly, several publications have noted limited to no marked flaring of autoinflammatory disorders after COVID-19 vaccination. Peet et al evaluated 130 patients with a variety of autoinflammatory disorders who received one or more doses of COVID-19 vaccines (ChAdOx1-S or BNT162B2), and no serious adverse reactions or hospitalizations were reported after vaccination.[69] Of note, most of these patients did not interrupt immunomodulatory therapy during vaccination. Furthermore, substantial inflammatory disease flares have not been found after receipt of mRNA vaccines. In the limited number of patients with IEI complicated by autoimmunity or primary immunodysregulatory disorders, vaccinations have been similarly well tolerated without worsening of autoimmune conditions. In addition, studies of patients with autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease have described excellent tolerance of COVID-19 vaccines without notable induction of disease flares.[70–72]

Serious adverse events after COVID-19 vaccination have included anaphylaxis, myocarditis, idiopathic thrombocytopenic purpura, and vaccine-associated immune thrombotic thrombocytopenia.[74–76] These events have been extremely rare, and to date, there has been no evidence that patients with IEI are at higher risk for adverse events after COVID-19 vaccinations. As immune thrombocytopenia (ITP) and vaccine-associated immune thrombotic thrombocytopenia seem to be antibody mediated, it is possible that use of immunoglobulin replacement therapy may provide some risk reduction against these adverse effects. However, given the small number of patients with IEI who have been vaccinated, the true risk of these adverse effects remains unclear. ITP and vaccine-induced thrombotic thrombocytopenia (VITT) seem to be more highly associated with adenoviral vaccines, and accordingly, in patients with thrombotic risks or history of ITP, avoidance of adenoviral vaccines would be prudent.

Immunosuppression and Coronavirus Disease 2019 Vaccine Responses

Many patients with IEI require immunosuppressive therapy for management of autoimmune or autoinflammatory disease, and many such therapies could affect the efficacy and safety of vaccines. B cell-targeting therapies have well described impacts on antibody production, and T cell-targeting therapy may decrease induction of cytotoxic responses and T follicular helper cells. Delmonte *et al.* noted that overall use of immunomodulators in patients with IEI did not significantly affect the chances of antibody responses after COVID-19 vaccination, though patients treated with rituximab in the previous 5 years uniformly failed to generate SARS-CoV-2 antibodies after 2 vaccinations ($P > .05$).[36] Notably, 4 patients receiving Janus kinase inhibitors had intact antibody responses. Studies of COVID-19 vaccine responses in non-IEI immunosuppressed populations have revealed similar outcomes.[15,46,77,78] However, data from van Leeuwen et al

Table 2
Adverse Reactions to COVID-19 Vaccines in Patients With IEI

Author	Total number of patients with IEI	COVID-19 vaccine(s)	Serious reactions	Reactogenicity
Amodio et al[41]	21	BNT162b2	None	Fever 38%, myalgia 19%, malaise 14%
Antoli et al[42]	28	BNT162B2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S	None	Most common was pain/redness/swelling at the injection site, and fever, more common after dose 2
Arroyo-Sanchez et al[43]	18	mRNA-1273, BNT162b2, ChAdOx1-S	None	NR
Bergman et al[46]	90	BNT162b2	3, all unlikely related	Lower than HC
Bradley et al[47]	1	BNT162b2	None	Mild (flu like)
Delmonte et al[36]	81	mRNA-1273, BNT162b2, Ad26.COV2.S	None	Mild-moderate systemic systems (fever, fatigue, myalgias) in 22% after D1, 53% after D2. Increased local reaction compared with HC; otherwise comparable with HC
Goda et al[48]	30	ChAdOx1 BNT162b2 Booster	None	
Hagin et al[50]	26	BNT162b2	None	13 (50%): local pain (9), fever (3), adenopathy (1)
Oshiro et al[53]	1	SinoVAC	None	None
Pham et al[54]	33	mRNA-1273, BNT162b2	None	Mild-moderate in 14 of 33 (42%)
Ponsford et al[55]	284	mRNA-1273, BNT162b2, ChAdOx1-S	None	Not reported
Romano et al[57]	5	mRNA-1273, BNT162b2	None	Mild-moderate systems in 5 of 5
Schultz-Cherry et al[60]	25	mRNA-1273, BNT162b2	None	Mild-moderate in 70%
Squire et al[73]	37	mRNA-1273, BNT162b2, Coronavac, ChAdOx1-S, Ad26.COV2.S	None	Dose 1: 48% mild Dose 2: 54% mild, 30.8% moderate, 15.4% severe
van Leeuwen et al[39]	505	mRNA-1273	9, including 1 patient with cerebral hemorrhage 2 mo post-vaccination, 1 with dyspnea, 1 with tinnitus	Not reported
Total	1134		3 possibly related events	38%-70%

Abbreviations: COVID-19, coronavirus disease 2019; HC, healthy control; IEI, inborn errors of immunity; mRNA, messenger RNA; NR, not reported.

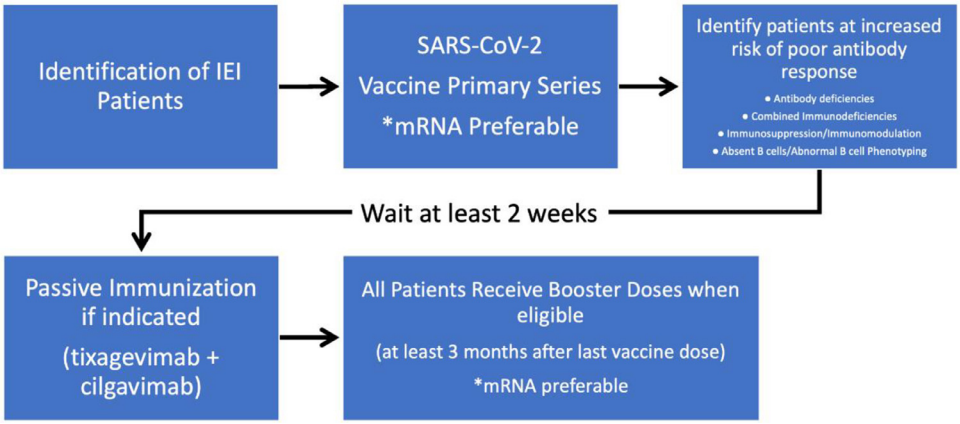

Figure 2. Proposed workflow for active and passive COVID-19 immunization in patients with IEI. COVID-19, coronavirus disease 2019; IEI, inborn errors of immunity; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

revealed that COVID-19 vaccine nonresponders with IEI had statistically significantly increased autoimmune cytopenias, granulomatous lymphocytic interstitial lung disease, and use of immunosuppressive medications, including in a multivariable logistic regression model, as compared with responders (P <.0001).[39] A meta-analysis by Ramirez et al of more than 11,000 patients with autoimmune conditions revealed humoral and cellular responses in 85% of patients overall, but neutralizing antibody responses were less robust than in HC. Anti-B cell therapy was also associated with poorer antibody responses (37% overall from 9 studies) consistent with data from patients with IEI.[79]

Immunoglobulin Replacement Therapy and Coronavirus Disease 2019 Vaccination

Patients with IEI frequently receive immunoglobulin replacement therapy (IGRT) providing protection against many circulating and vaccine-preventable illnesses. The delay from plasma donation to product (typically approximately 9 to 10 months) may affect coverage of emerging viral variants. In addition, IGRT adversely affects active vaccination against pathogens that are targeted by donor antibodies.[80] Studies evaluating SARS-CoV-2 antibody titers in commercial immunoglobulin products have revealed an increasing trend in titers over time, but with lot-to-lot variability.[81,82] A more recent study by Miller et al revealed that the upward trend in neutralizing antibodies has continued in commercially available products in 2021.[83] Thankfully, Delmonte et al did not note any difference in response to COVID-19 vaccination in patients with IEI who were receiving IGRT vs those who were not.[36] Many other case series similarly revealed preserved antibody and cellular responses after vaccination in patients receiving IGRT.[40,56,58,62] Given the safety of the vaccines in patients with IEI and the potential benefit of cellular responses, it is felt that vaccination of those receiving IGRT is advisable. Longitudinal studies of SARS-CoV-2 titers in commercially available immunoglobulin preparations will be useful to understand the potential impact of IGRT on diagnostics and risk of COVID-19 in patients receiving this therapy.

Passive Immune Therapies Against Coronavirus Disease 2019

Passive immunotherapies, including monoclonal antibodies targeting the spike RBD of SARS-CoV-2, have been developed and are indicated for acute treatment, post-exposure prophylaxis, and longer-term preventative therapy of COVID-19. Preventative therapy, currently authorized as tixagevimab co-packaged with cilgavimab, is specifically intended for those who are not expected to mount adequate responses to active vaccination, and therefore would be appropriate for patients with IEI. During the delta variant surge, use of monoclonal antibody therapy for breakthrough infections in high-risk patients reduced hospitalization by 77%, and the number needed to treat to prevent hospitalization of 1 immunocompromised patient was 12.[84] Furthermore, in patients with high risk of severe COVID-19 owing to APECED, monoclonal antibody therapy has been used successfully to prevent disease progression.[85] Unfortunately, evasion of monoclonal antibody therapy with emerging variants develops rapidly. High-risk patients were found to have 74% reduction in progression to severe COVID-19 after receiving sotrovimab; however, the FDA has recently reversed emergency use authorization because of lack of efficacy against emerging Omicron subvariants.[86] In contrast, bebtelovimab has recently received FDA emergency use authorization and maintains activity against the new Omicron BA.2 subvariant.[87] The full impact of monoclonal therapies on vaccine efficacy remains unclear, though case reports of successful seroconversion with vaccination post-monoclonal antibody therapy support active immunization in this setting.[60] Presently, vaccine doses are recommended at least 2 weeks before giving a preventative monoclonal antibody therapy to minimize the chance of interference (Fig 2), though large studies of vaccine efficacy with or without monoclonal antibody therapy have not been performed.

Limitations and Future Needs

Much progress has been made to understand COVID-19 vaccine responses in patients with IEI, but many questions remain unanswered. Ideal vaccine regimens, timing of boosters, and the duration of protection after vaccination in IEI remain unclear. To date, most of the studies have been conducted in the United States and Europe, and therefore little data are available regarding the numerous additional platforms and vaccines used around the world.[88] At this time, only 1 study in 1 patient addresses Coronovac, which uses a whole inactivated virus.[53] The preponderance of data are from mRNA vaccines which pose an international vaccination challenge given the need for cold chain and freezer storage. With the prevalence of IEI globally, and the observed increased immunogenicity of mRNA vaccinations in this patient population, distribution and availability to patients with immunodeficiency are critical. Fortunately, preliminary data on uptake of COVID-19 vaccination in patients with IEI are encouraging. Ponsford et al reported that 93% of 302 patients with IEI in the United Kingdom had received their second dose by September 2021, whereas only 14 patients declined.[55]

Efficacy and immunogenicity may be mildly compromised in patients with IEI, but COVID-19 vaccines with available data seem to have a favorable safety profile, even in the setting of autoimmune and autoinflammatory diseases. Thus, although benefit may be limited in some patients, risk is also minimal for non-live vaccination platforms.

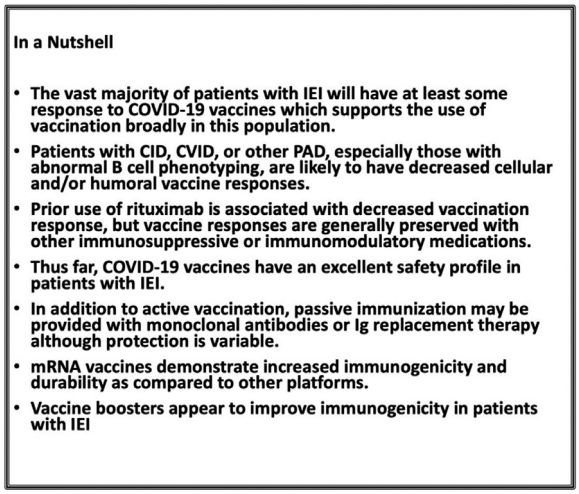

Figure 3. COVID-19 vaccination in IEI: key points. CID, combined immunodeficiency; COVID-19, coronavirus disease 2019; CVID, common variable immunodeficiency; IEI, inborn errors of immunity; Ig, immunoglobulin; mRNA, messenger RNA; PAD, primary antibody deficiency.

Vaccination, especially if an mRNA vaccine is available, should be strongly recommended to most, if not all, patients with IEI. Given the stronger immunogenicity observed in mRNA vaccines (mRNA-1273 and BNT162B2) compared with adenovirus-based vaccines, including in patients with IEI, and the association between adenoviral vaccines and very rare but serious complications owing to VITT, mRNA vaccines should be preferred in the IEI population when available.[61]

Conclusion

COVID-19 continues to pose a great risk to patients with IEI; and vaccination against SARS-CoV-2 remains the best preventative tool in reducing hospitalizations and deaths. In 26 available studies where 1439 patients with IEI have been vaccinated against SARS-CoV-2, overall serologic response rate is favorable at 72%. Adaptive immune responses are heterogeneous, with poorer antibody responses in B cell dysfunctional and aplastic patients, but cellular immunity may offer compensatory protection. Studies to date of breakthrough infections after vaccination do give cause for optimism, including in patients with IEI (Fig 3).[39] As the data rapidly evolve, professional organizations will continue to be an essential source for updated guidance, including resources listed in eTable 1. Additional longitudinal studies of vaccine efficacy in IEI are currently underway (NCT04852276) and it is hoped to provide further guidance to clinicians and patients regarding best methods to prevent COVID-19 in this population.[42,45,48,51,52,57,59,73]

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2022.06.009

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eTable 1
Online Resources for COVID-19 Vaccination in IEI

Organization	Web resource
American Academy of Allergy Asthma & Immunology	https://www.aaaai.org/Tools-for-the-Public/Conditions-Library/Related-Conditions/COVID-resources
American Cancer Society	https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections/covid-19-vaccines-in-people-with-cancer.html
American College of Allergy, Asthma, & Immunology	https://acaai.org/news/allergy/
American College of Rheumatology	https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Disesases-Summary.pdf
American College of Rheumatology	https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf
American Society of Transplantation	https://www.myast.org/sites/default/files/ast%20ishlt%20guidance%20vaccine%2008132021FINAL%20DRAFT2.pdf https://www.myast.org/covid-19-vaccine-faq-sheet
European Society for Immunodeficiency	https://esid.org/COVID-19/ESID-COVID-19-Statement
Immune Deficiency Foundation	https://primaryimmune.org/news/covid-19-update-vaccines-monoclonal-antibodies-antivirals; https://primaryimmune.org/news-category/covid-19?page=1
International Organization for the Study of Inflammatory Bowel Disease	https://ioibd.org/wp-content/uploads/2021/01/gutjnl-2020-324000.full_pdf
International Society of Heart and Lung Transplantation	https://ishlt.org/covid-19-information
National Comprehensive Cancer Network	https://www.nccn.org/covid-19
US Centers for Disease Control and Prevention	https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised; https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html
World Health Organization	https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons

Abbreviations: COVID-19, coronavirus disease 2019; IEI, inborn errors of immunity.

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