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Short communication

Response to mRNA COVID-19 vaccination in three XLA patients

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ABSTRACT

X-linked agammaglobulinemia (XLA) is an inborn error of immunity characterized by insufficient production of immunoglobulins and lack of measurable antibody response to vaccines. The rise of novel infections limits the protective effect of immunoglobulin replacement in immunodeficient patients though. While XLA patients are not expected to mount an antibody response to COVID-19 vaccination, it has been demonstrated that XLA patients can mount a T-cell response to COVID-19 vaccines, similar to the influenza vaccine. We present three patients with XLA who received an mRNA COVID-19 vaccine. One patient demonstrated positive antibody response. Many XLA patients do not receive routine vaccinations due to ongoing immunoglobulin replacement therapy and lack of native antibody production, but in addition to T-cell response to vaccination, select XLA patients may mount a positive antibody response. Therefore, COVID-19 vaccination should be encouraged for all XLA patients.

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1. Introduction

X-linked agammaglobulinemia (XLA) was one of the first identified inborn errors of immunity (IEI) characterized by defective B-cell development resulting in B-cell lymphopenia (usually < 2 %) due to mutations in the Bruton tyrosine kinase (*BTK*) gene on the X-chromosome [1]. This results in significantly reduced levels of all immunoglobulins and ineffective specific antibody production. Milder mutations in *BTK* have been associated with some residual function resulting in older age of diagnosis, higher than expected immunoglobulin levels, and increased B cells counts compared to other mutations considered more severe [2,3]. The primary treatment for XLA is immunoglobulin replacement, either intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG), which offers protection against many vaccine-preventable diseases with high titers, except for certain viral antigens such as each yearly circulating influenza strain [4]. Antibody deficiencies are most commonly associated with risk of bacterial sinopulmonary infections, but patients with XLA have also demonstrated increased risk of viral infections, such as chronic

enterovirus meningoencephalitis [5]. While patients with XLA typically do not mount significant antibody response to vaccination, it has been shown that they can produce normal virus-specific T-cell responses to the inactivated influenza vaccine [6]. Due to the risk of vaccine associated illness, it is generally recommended to avoid live vaccination in patients with XLA, and routine inactivated vaccines are typically not given due to the lack of response and ongoing treatment with immunoglobulin replacement.[7] Yearly inactivated influenza vaccine is recommended in virtually all patients with XLA due to the low antibody levels for current influenza strains in the supplemental immunoglobulin preparations.[4,7] Data on response to COVID-19 vaccination in patients with immunodeficiency is growing, several case series and studies have now been published demonstrating encouraging results for humoral and cellular response to the vaccines in this group.[8–10] We present 3 patients (one previously reported[8]) with XLA, to further demonstrate the effectiveness and heterogeneity of antibody response to COVID-19 vaccination in IEI. All patients had no prior history of COVID-19 infection.

Patient case information was obtained from retrospective chart review as part of an institutional review board approved study.

2. Case series

Patient #1 is 47-year-old male with XLA and bronchiectasis receiving IVIG 40 g monthly. Current immunomodulation includes hydroxychloroquine for chronic lower extremity rash likely

Abbreviations: XLA, X-linked agammaglobulinemia; *BTK*, Bruton tyrosine kinase; IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin; MFI, mean fluorescent intensity.

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consistent with erythema nodosum. The patient has a known pathogenic hemizygous variant in *BTK* (c.763C > T, p.Arg255) resulting in a premature stop codon. Flow cytometry demonstrated absent CD19+ and CD20+ B-cells. Btk protein expression was reduced in monocytes (patient’s MFI = 1.23, control MFI = 4.31), consistent with XLA. His most recent immunoglobulin levels (on IVIG) were IgG 1090 mg/dL, IgA < 1 mg/dL, and IgM < 5 mg/dL. Two weeks following his second dose of Pfizer mRNA COVID-19 vaccination, in May 2021, SARS-CoV-2 spike antibodies were negative (<0.80 U/mL) as well as negative SARS-CoV-2 nucleocapsid antibodies. See Table 1.

Patient #2 is a 44-year-old male with XLA and bronchiectasis on IVIG 30 g every 3 weeks, with no additional immunomodulation. This patient was previously reported in a case series on response to COVID-19 vaccination in patients with immunodeficiency.[8] He has a variant in the *BTK* gene (c.1657delA, p.Ser553Alafs*3) creating a frame shift starting at codon Ser553 and resulting in a premature stop codon. He demonstrated absent CD19+ and CD20+ B-cells by flow cytometry and decreased Btk protein expression in monocytes (patient’s MFI = 2.36, control MFI = 7.88). Most recent immunoglobulin levels (on IVIG) were IgG 1060 mg/dL, IgA < 1 mg/dL, and IgM < 5 mg/dL. SARS-CoV-2 spike (<0.40 U/mL) and nucleocapsid antibodies were negative in March 2021, >4 weeks after the second dose of the Pfizer mRNA COVID-19 vaccine. See Table 1.

Patient #3 is 64-year-old male with XLA on IVIG 45 g monthly, on no additional immunomodulation. On flow cytometry, his absolute CD19+ B-cell count was 1 cell/mL and CD20+ B-cells are essentially absent (0.12 %). Genetic testing revealed a missense variant in exon 2 of the *BTK* gene (c.76A > G, p.Lys26Glu), encoding the pleckstrin homology (PH) domain. Btk protein expression was reported as present intracellularly in B-cells and monocytes, and intracellular Btk protein expression appeared to be normal in monocytes. This patient has a strong family history of XLA, with diagnosis in 2 maternal cousins as well as his great-grandson. The patient’s most recent immunoglobulin levels (on IVIG) were IgG 896 mg/dL, IgA < 1 mg/dL, and IgM < 5 mg/dL. In April 2021,

2 weeks after 2 doses of Moderna mRNA COVID-19 vaccine, the patient had evidence of antibody response to the vaccine with positive SARS-CoV-2 spike antibodies (118 U/mL) and negative SARS-CoV-2 nucleocapsid antibodies (consistent with vaccination and not prior infection). See Table 1.

3. Discussion

With the onset of the COVID-19 pandemic, many patients with immunodeficiency have had significant concerns regarding risk of infection, complications, mortality, as well as effectiveness of prophylaxis and treatment strategies for COVID-19. Initially reported cases of COVID-19 infection in patients with congenital agammaglobulinemia suggested a mild course without significant complication but a more recent review of published cases of COVID-19 infection in XLA patients indicates that a cause for concern is not unfounded.[11,12] Ponsford et al identified 28 XLA patients with COVID-19 infection reported in the literature. Overall, 79 % (22/28) were admitted to the hospital with median length of stay of 22 days, 3 of which were admitted the intensive care unit. There was 1 reported death which equated to a 4 % overall mortality rate. [12].

Vaccination against COVID-19 infection has demonstrated dramatic effect on improving adverse outcomes, including hospitalizations and deaths, in the US population overall.[13] While there is less specific data on outcomes in patients with IEI, there has been growing data on the response to COVID-19 vaccination in immunodeficient patients. As expected, majority with XLA have not produced measurable antibody responses to COVID-19 vaccination, yet when assessed, almost all had positive T-cell response. Outcomes of vaccination in XLA patients identified from literature review are summarized in Table 2.[8,9,14–20] More recently, van Leeuwen et al published the response to mRNA COVID-19 vaccination a cohort of adult patients with IEI. Nineteen patients with XLA were included, 3 of which had positive antibody response.[10] Our case series supports their findings, that certain subsets of XLA patients may be able to produce a humoral, in addition to a cellular

Table 1
XLA Patient Characteristics and Response to mRNA COVID-19 Vaccination.

Patient #	Age (yrs)	Mutation in BTK	Intracellular Btk Protein Expression	Absolute B-cell Count (cells/mL)	SARS-CoV-2 Spike Ab (U/mL)	SARS-CoV-2 Nucleocapsid (Total Ab)
1	47	c.763C > T, p.Arg255	↓	0	Negative (<0.80)	Negative
2	44	c.1657delA, p.Ser553Alafs*3	↓	0	Negative (<0.40)	Negative
3	64	c.76A > G, p.Lys26Glu	Normal	1	Positive (118)	Negative

Ab = antibodies.

Table 2
Response to COVID-19 Vaccination in Reported XLA Patients.

Paper	Number of XLA patients Assessed	Type of Vaccine Received	Number with Positive Antibody Response (%)	Number with Positive Cellular Response (%)
Oshiro et al [17]	1	CoronaVac	0 (0 %)	1 (100 %)
Ponsford et al [18]	3	AstraZeneca or mRNA	0 (0 %)	NA
Shields et al [19]	9	AstraZeneca or mRNA	0 (0 %)	NR
Squire & Joshi [8]	1	Pfizer mRNA	0 (0 %)	NA
Hagin et al [9]	4	Pfizer mRNA	0 (0 %)	4 (100 %)
Salinas et al [14]	6	Pfizer mRNA	0 (0 %)	5 (83 %)
Bergman et al [15]	4	Pfizer mRNA	0 (0 %)	NA
Delmonte & Bergerson et al [16]	1	Moderna mRNA	0 (0 %)	NA
Pham et al [20]	1	Moderna mRNA	0 (0 %)	1 (100 %)
van Leeuwen et al [10]	19	Moderna mRNA	3 (15 %)	19 (100 %)

XLA = X-linked agammaglobulinemia; NA = not assessed; NR = not reported.

immune response, due to residual B-cell function. While majority of patients with XLA have classical features, there can be a heterogeneity in presentation and severity based on the *BTK* mutation. [2,3] A known mutation in the *BTK* gene may not exclude the ability for patients with XLA to mount a positive antibody response to vaccination. Btk protein expression may help differentiate those with the ability to respond, as patient #3 who had normal intracellular Btk expression in monocytes and who did mount a humoral immune response, as compared to decreased Btk expression found in patients #1 and #2.

While studies have demonstrated rising anti-SARS-CoV-2 antibodies in commercially available immunoglobulin products[21], it is unlikely that the results in patient #3 are due to spike antibodies in differing lots or IVIG products. All three patients received vaccination at the beginning of 2021 when COVID-19 vaccines first became available to high-risk patients (between March–May 2021), which would not have been enough elapsed time for vaccinated plasma donors to contribute to the currently available IVIG at the time. As the nucleocapsid antibodies were negative, this indicates that the positive spike antibodies were not due to natural infection antibodies either. It still remains unclear what antibody level is needed for protection and whether passive immunity itself would be enough to prevent infection, especially in the context of variant strains. Our report provides additional support for the safety and efficacy of mRNA COVID-19 vaccination in patients with XLA. Therefore, COVID-19 vaccination should be encouraged in patients with XLA.

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Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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