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Immunogenicity of repeat COVID-19 mRNA vaccinations in a patient with myasthenia gravis receiving mycophenolate, prednisone, and eculizumab

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ABSTRACT

Vaccination can prevent infection and disease due to SARS-CoV-2. Early reports indicate that immune suppressed or immune compromised populations have reduced immune responses to US emergency use authorized (EUA) vaccines. Patients with autoimmune disorders are at risk for severe COVID-19, and are frequently immune suppressed related to therapy, the underlying disease, or both. Myasthenia gravis (MG) is an autoimmune disorder characterized by antibodies that interrupt neuromuscular transmission. Chronic immune suppressive therapy is typically required. We report the case of a 74 year old woman with MG receiving mycophenolate, prednisone, and eculizumab in whom mRNA vaccination failed to elicit detectable circulating vaccine-specific IgG or IFN-γ T cell responses. Eculizumab was discontinued, and repeat vaccination with two doses of an alternative EUA mRNA vaccine led to circulating IgG specific for the receptor binding domain (RBD) of the SARS-CoV-2 spike (S) protein, and to detectable S-specific T cell responses. While it is not known if these responses will protect against SARS-CoV-2 infection or disease, a repeat course of mRNA vaccination appears to be safe and was broadly immunogenic in this individual.

1. Introduction

Vaccines are highly effective in preventing infection and disease due to SARS-CoV-2 [1]. The mRNA and recombinant adenovirus formats used in US EUA products are novel for vaccines in general use. Little is known concerning mRNA vaccine immunogenicity or efficacy in immune suppressed/immune compromised (IS/IC) populations. Data suggest that neutralizing antibodies (nAb), other functional antibodies, and virus-specific T cells contribute to protection [1]. Myasthenia gravis (MG) is an autoimmune disorder characterized by antibodies that interrupt neuromuscular transmission. Individuals with MG are at risk for severe respiratory infections, including COVID-19, due to diaphragmatic weakness and long-term immune suppressive treatment [2]. We report the case of a patient with MG for whom mRNA vaccination failed to elicit detectable circulating IgG or IFN-γ T cell responses specific for the vaccine antigen. Repeat vaccination with two doses of an alternative EUA mRNA vaccine led to IgG specific for the receptor binding domain (RBD) of the SARS-CoV-2 spike (S) protein and to detectable S-specific T cell responses.

1.1. Case report

A 74 year old woman was diagnosed with generalized MG 44 months prior to initial SARS-CoV-2 vaccination. Serologic testing showed elevated antibodies to acetylcholine receptors. For 18 months prior to and including the vaccine time course, treatment with 1440 mg mycophenolate sodium and prednisone 11 mg daily resulted in clinically stability. There was a remote history of ductal carcinoma *in situ* and Hashimoto's thyroiditis, and no history of opportunistic infection. Peripheral blood monitoring showed 8700 leukocytes and 800 lymphocytes per microliter (9%), consistent with mild lymphopenia. Three months prior to initial vaccination, the patient began treatment with eculizumab, an anti-C5 monoclonal antibody with activity in MG [3]. Eculizumab was given weekly and then biweekly per US labelling. The

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indication was adjunctive therapy to bridge elective surgery, which was uneventful. Eight weeks after surgery, BNT162b2 vaccination was started and two doses were administered 21 days apart. Eculizumab administration time points included 10 days prior to dose 1 of BNT162b2 and 3 days prior to dose 2, with the last dose given 11 days later.

Blood was initially tested 71 days after the second dose of BNT162b2. The SARS-CoV-2 RBD binding antibody level (Abbott Architect IgG II) was 19 arbitrary units (AU)/ml, with values below 50 considered negative (https://www.fda.gov/media/146371/download). QuantiFERON SARS-CoV-2 RUO (Qiagen), an S-peptide-based interferon-γ release assay (IGRA) similar to the QFT-Plus assay for *Mycobacterium tuberculosis*-specific T cells, was performed per the manufacturer. SARS-CoV-2 S peptide pool S1 and S2 net values of 0.02 international units (IU)/ml and 0.03 IU/ml were summed to 0.05 IU/ml to provide a single metric. Negative (nil) and positive (mitogen) control values were 0.02 IU/ml and >10 IU/ml, indicating negligible background lymphocyte activation and intact activation potential. Amongst 14 healthy controls (HC) studied a median of 58 days (range, 10–107) after completing BNT162b2 (10 persons) or M1273 (4 persons), median net summary response to S was 1.27 IU/ml (range, 0.34 IU/ml-2.60 IU/ml). HC median nil was 0.03 IU/ml (range, 0.02 IU/ml-0.06 IU/ml) and each mitogen control was >10 IU/ml.

After tests for vaccine immunogenicity returned negative, the patient sought repeat vaccination. At 85 days after completing BNT162b2, they received M1273, with a second dose 29 days later. Side effects were minimal. Immune response were tested 16 days after the second dose of M1273. The serum anti-SARS-CoV-2 RBD IgG level was 2999 AU/ml, considered positive. IGRA re-test 32 days after completing M1273 showed a net summary response to S peptides of 0.38 IU/ml IFN-γ, with nil and mitogen responses of 0.03 IU/ml and >10 IU/ml.

2. Discussion

The SARS-CoV-2 pandemic has been particularly impactful for IS/IC populations. Passive immunization, selected immune suppressive drugs, and antivirals have a positive effect on disease course after infection, with less efficacy data available for IS/IC persons [4]. Prevention is preferred, and several vaccines have been authorized worldwide. There is currently controversy concerning homologous or heterologous booster doses for IS/IC patients, with case reports showing immunogenicity and apparent safety [5].

Diverse IS/IC cohorts show lower ELISA responses than HC after EUA vaccination [6,7]. Circulating nAb is a candidate correlate of protection (CoP) and the ELISA-like binding assay used here correlates with nAb [8]. The elicitation of anti-RBD in this case indicates that B cell priming has occurred, and hopefully that long-lived antibody secreting and B-memory cells have also developed. S-specific T cell responses are readily detected after mRNA vaccination [9], with little data are available for IS/IC individuals. It is biologically expected that CD4 T cells and antibodies arise in concert. The IGRA test used here does not distinguish T cell subsets and alternative tests would be required to determine if both CD4 and CD8 T cell responses occurred. Overall, a repeat series of a heterologous but biologically similar mRNA vaccine can be well tolerated and elicit B and T cell responses, without required interruption of chronic immune suppression.

Mycophenolic acid is an antagonist of inosine-5′-monophosphate dehydrogenase that inhibits lymphocyte proliferation. Use can lead to peripheral blood lymphopenia, a variety of opportunistic infections, and poor responsiveness to vaccines including SARS-CoV-2 mRNA vaccination [10]. Corticosteroids such as prednisone have myriad effects including susceptibility to infection and diminished vaccine immunogenicity. In this patient, chronic receipt of mycophenolate and low-dose prednisone was combined with temporary use of eculizumab during the first vaccine series with BNT162b2. Complement activity is required for host defense to some *Neisseria* species in the infection context, but complement antagonism or deficiencies have not been associated with poor responses to vaccines. The BNT162b2 and M1273 products used sequentially also differ in mRNA content per dose, administration interval between doses, and details of the lipid nanoparticle formulations. The immune mechanism leading to apparent success with a repeat vaccination likely involves repeated antigen exposure, possibly modulated by cessation of anti-complement therapy, but overall remains unknown.

This report is limited by inclusion of a single patient and several other factors. The safety of booster vaccination may vary per patient. It is not known if the immune responses achieved by this patient are functionally protective against infection, viral shedding, or disease. There are no published interpretive criteria for the IGRA T cell assay used, and IGRA tests for SARS-CoV-2 have not achieved US Food and Drug Administration approval or EUA status. The heterogeneity of IS/IC individuals including influences from their underlying diseases precludes generalizations concerning booster vaccination. The durability of vaccine-elicited immune responses in this setting is unknown. Additionally, the safety and immunogenicity of the mRNA and adenovirus products, if used as boosters, may vary depending on vaccine identity, sequence, intervals, and number of doses.

In summary, two doses of M1273, three months after a standard course of BNT162b2, resulted in peripheral T- and B-cell conversion in a person dependent on mycophenolate and prednisone therapy to maintain MG clinical remission. A contribution of the transient eculizumab therapy to the lack of response to BNT162b2 cannot be ruled out, but vaccine hyporesponsiveness was more likely related to mycophenolate and prednisone. Maneuvers to increase host immunity may not be feasible in many IS/IC patients, and vaccine dose increases, extra doses, strong adjuvants, or heterologous prime/boost vaccine strategies are already used for other vaccine indications. These may be reasonable for SARS-CoV-2. Overall, pre-arming patients with circulating antibody and antigen-specific T cells is likely to be clinically beneficial. Additional studies of the safety, immunogenicity and clinical efficacy of homologous and heterologous SARS-CoV-2 vaccines are urgently required to better protect susceptible persons from the pandemic.

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Declaration of competing interest

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