Attenuated response to fourth dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series

Severe, occasionally fatal breakthrough COVID-19 infections despite vaccination have been reported in patients with autoimmune disease,[1] bringing vaccine efficacy in this population into question. Recently, the Food and Drug Administration authorised a third vaccine dose in immunocompromised patients who previously received two mRNA vaccines. We previously reported augmented antibody titers in 89% of patients with autoimmune disease after third SARS-CoV-2 vaccination dose[2]; herein, we describe antibody response in patients who received two additional SARS-CoV-2 vaccine doses after completion of initial series.

Patients with autoimmune diseases were recruited for our observational study as previously reported.[3] We identified 18 patients ≥18 years of age who completed initial SARS-CoV-2 vaccine series (mRNA or adenovirus vector) and subsequently obtained two additional doses (AD) of SARS-CoV-2 vaccine between 30 April 2021 and 8 July 2021, six of whom were included in a previous report on response after three dose-vaccination.[2] Participants with prior COVID-19 infection were excluded. Serial semiquantitative SARS-CoV-2 antibody testing

Table 1 Vaccines administered, autoimmune diagnoses, immunosuppressive regimens and perivaccination management with serial antispike antibody responses

Age/sex	Diagnosis	Immunosuppression	Initial vaccine series	Meds held or modified preinitial Vaccine	Pre-AD1 antibody U/mL*	Additional vaccines	PostAD1 antibody U/mL*	PostAD2 antibody U/mL*	Therapy held periAD†
62F	Myositis	Mycophenolate‡ Prednisone	Pfizer	No	Negative§	AD1: Pfizer AD2: Pfizer	–	<0.4	No
56F	Mucous membrane pemphigoid	Mycophenolate‡	Pfizer	No	<0.4	AD1: J&J AD2: Moderna	<0.8	<0.4	No
67F	Systemic sclerosis	Mycophenolate‡	Pfizer	No	<0.4	AD1: Pfizer AD2: Pfizer	<0.4	2.1	Yes
73M	Myasthenia gravis	Mycophenolate‡ Prednisone	Moderna	No	<0.4	AD1: Pfizer AD2: Pfizer	–	21.8	–
44F	Inflammatory arthritis¶	Abatacept Hydroxychloroquine Methotrexate Prednisone	Pfizer	No	<0.4	AD1:Pfizer AD2: J&J	<0.4	27.1	Yes
55M	Inflammatory arthritis¶	Infliximab Mycophenolate‡	Pfizer	No	Negative§	AD1: Pfizer AD2: Pfizer	<0.8	46.5	Yes
64F	Myositis	Mycophenolate‡	Pfizer	No	Negative§	AD1: Pfizer AD2: Pfizer	38.1	120.9	Yes
53F	Inflammatory arthritis¶	Adalimumab Mycophenolate‡ Prednisone	Pfizer	No	<0.4	AD1: Moderna AD2: Moderna	229	134	No
55M	Sarcoidosis	Infliximab Mycophenolate‡ Prednisone	Pfizer	No	<0.4	AD1: Moderna AD2: Moderna	2.40	1276	Yes
40F	Inflammatory bowel disease	Adalimumab Hydroxychloroquine Methotrexate	Pfizer	No	178.4	AD1: Moderna AD2: Pfizer	601.2	1750	No
49F	Overlap CT disease**	Belimumab Methotrexate Prednisone	Pfizer	No	<0.4	AD1: Pfizer AD2: Pfizer	16.4	>2500	–
68F	Proliferative nephritis	Mycophenolate‡ Prednisone	Moderna	No	<0.4	AD1: J&J AD2: Moderna	714	>2500	–
53F	Sjögren's syndrome	Azathioprine	J&J	No	<0.4	AD1: Pfizer AD2: Pfizer	>250	>2500	Yes
55F	Minimal change disease	Mycophenolate‡	J&J	No	<0.4	AD1: Moderna AD2: Moderna	>2500	>2500	No
74M	Myositis	Mycophenolate‡	Pfizer	No	Negative§	AD1: Moderna AD2: Moderna	>2500	>2500	Yes
42F	Overlap CT disease**	Hydroxychloroquine Mycophenolate‡	Pfizer	No	<0.4	AD1: Pfizer AD2: Pfizer	–	>2500	Yes
65F	Inflammatory arthritis	Abatacept	J&J	No	Negative§	AD1: Pfizer AD2: Pfizer	–	>2500	Yes
52M	Overlap CT disease**	Hydroxychloroquine Mycophenolate‡	J&J	No	18.6	AD1: Pfizer AD2: Pfizer	>2500	>2500	Yes

- denotes missing data.
*Roche Elecsys anti-RBD pan-Ig≥0.8 units/mL is considered positive (upper ceiling expanded from>250 to >2500 U/mL per manufacturer).
†Pre-AD1 median number of doses held for mycophenolate 6, 23 doses of azathioprine held by one patient, and two abatacept infusion held by one patient. Pre-AD2 median number (IQR) of doses of mycophenolate 14 (10–14), 23 doses of azathioprine and 2 abatacept infusion held by one patient.
‡Mycophenolate includes mycophenolic acid and mycophenolate mofetil.
§Self-reported values.
¶Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, reactive arthritis, or inflammatory bowel disease associated arthritis.
**Denotes a combination of two or more defined rheumatic diagnoses.
AD, additional dose; J&J, Johnson and Johnson; RBD, receptor binding domain.

was completed on the Roche Elecsys anti-SARS-CoV-2 S enzyme immunoassay, which measures total antibody to the SARS-CoV-2 S-receptor binding domain protein (positive ≥0.8 U/mL) and a consistent correlate of plasma neutralising capacity.[4] Participants provided informed consent electronically.

Thirteen participants were female, with a median (IQR) age of 56 (52–66) years (table 1). The most common autoimmune diagnoses included inflammatory arthritis (n=4), myositis (n=3) and overlap connective tissue disease (n=3). Participants completed initial vaccine series with two doses of Pfizer (n=11), Moderna (n=2) or single dose of Janssen/Johnson and Johnson (J&J) (n=5). Mycophenolate was the most common immunosuppressive therapy (13/18) with median (IQR) daily dose of 2500 mg (1125, 3000 mg). All participants reported continuation of immunosuppression without interruption or modification during the initial vaccine series.

There were 16/18 participants with negative anti-spike antibody response at a median of 84 (31–90) days after initial vaccine series. Participants reported the following additional vaccinations: AD 1 (AD1): Pfizer (n=11), Moderna (n=5), J&J (n=2), followed by AD 2 (AD2) of Pfizer (n=11) or Moderna (n=6) or J&J (n=1). Most participants (11/18) reported temporarily withholding of immunosuppressive therapy in the period surrounding the AD. Among those who completed antibody testing after AD1 (12/18), antispike antibodies increased above the threshold of positivity in eight participants and remained negative in two participants at a median (IQR) of 24 (14–31) days. Antibody testing was performed at a median (IQR) of 32 (28–34) days after AD2 in all participants, with median (IQR) antispike antibody titre of 1750 U/mL (26–2500). Both participants with persistently negative response reported use of mycophenolate and did not undergo perivaccination interruption of therapy.

This study has several limitations including small sample size, convenience sampling and lack of data on cellular response. Furthermore, most participants continued immunosuppressive therapy during initial vaccine series but modulated therapy around the time of AD which confounds results and limits interpretation of our findings; larger studies are required for systematic evaluation. We cannot exclude asymptomatic COVID-19 infection as we did not complete antinucleocapsid testing. Participants who initially received the J&J vaccine received a total of three doses while those who initially received mRNA vaccine received a total of four doses, which limits comparability. We did not routinely collect baseline disease activity or severity and the reason for participants receiving two AD, as opposed to a single AD, is unknown.

This is the first case series describing antibody responses to two AD of SARS-CoV-2 vaccines in patients with autoimmune disease on immunosuppression. While most patients demonstrated an augmented antibody response, our findings suggest that a subset of patients who do not withhold immunosuppression continue to have an impaired vaccine response despite four vaccine doses; this is similar to findings in other immunosuppressed populations.[5] Both non-responders reported use of mycophenolate and continued therapy during the peri-vaccination period, which is consistent with findings that temporary interruption in immunosuppression can augment the humoral response,[2 6] although, a recent case report demonstrated seroconversion following four vaccine doses without interruption of immunosuppression.[7] More studies are needed to identify patients who may benefit from antibody monitoring, refinement in vaccination schedule, adjustment of perivaccination immunosuppression, or other strategies such as prophylactic therapies to better protect this vulnerable population.

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