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Original Article

Serological response after COVID-19 mRNA-1273 booster dose in immunocompromised patients, Taiwan, July to August 2021

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KEYWORDS
Serologic response;
Immuno-compromised;
Autoimmune disease;
Non-steroidal anti-inflammatory drug;
mRNA vaccine

Background: Whether immunocompromising conditions affect the immunogenicity of COVID-19 booster vaccination remains a concern, which impedes the vaccination campaign in people most vulnerable to COVID-19-associated morbidity and mortality. We aimed to evaluate the effect of immune dysfunction on immunogenicity of homologous and heterologous prime-boost COVID-19 vaccination.
Methods: Between July and August, 2021, 399 participants were randomized to receive ChAdOx1/ChAdOx1 8 weeks apart, ChAdOx1/mRNA-1273 8 weeks apart, ChAdOx1/mRNA-1273 4 weeks apart, and mRNA-1273/mRNA-1273 4 weeks apart. The anti-SARS-CoV-2 spike IgG antibody titers on the day before booster vaccination and 4 weeks after booster vaccination were compared between participants with and without immunocompromising conditions.

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Results: Among ChAdOx1-primed participants, a trend of lower anti-SARS-CoV-2 spike IgG titers before booster vaccination were found in participants with autoimmune diseases (geometric means, 34.76 vs. 84.25 binding antibody units [BAU]/mL, $P = 0.173$), compared to those without. Participants receiving immunosuppressants and/or immunomodulators had significant lower anti-SARS-CoV-2 spike IgG titers before booster vaccination than those without (geometric means, 36.39 vs. 83.84 BAU/mL; $P = 0.001$). Among mRNA-1273-boosted participants, anti-SARS-CoV-2 spike IgG titers 4 weeks after booster vaccination were similar across all the strata. Participants with autoimmune diseases and receiving immunosuppressants and/or immunomodulators, had numerically lower anti-SARS-CoV-2 spike IgG titers 4 weeks after booster vaccination compared to those without (geometric means, 1474.34 vs. 1923.23 and 1590.61 vs. 1918.38 BAU/mL; $P > 0.05$).

Conclusion: The immunogenicity of prime vaccination with ChAdOx1 decreased by immune dysfunction, but enhanced after receiving boost vaccination with mRNA-1273. Our study results support the efficacy of mRNA-1273 booster dose among immunocompromised hosts.

Introduction

The prolonged coronavirus disease 2019 (COVID-19) pandemic has affected almost 566 million individuals and led to more than 6 million deaths worldwide.[1] A high efficacy and effectiveness of COVID-19 vaccines have been shown in clinical trials and real-world observational studies; therefore, COVID-19 vaccination campaigns have been implemented around the world.[2] Individuals with immune dysfunction at increased risk of severe COVID-19 should be prioritized in the COVID-19 vaccination campaigns.[3] However, immunocompromised individuals may fail to mount adequate antibody responses after vaccination.[4] A meta-analysis demonstrated that serologic responses after COVID-19 vaccination were significantly lower in immunocompromised individuals compared with that in their immunocompetent counterparts.[5] Although the boost dose of COVID-19 vaccine consistently improved seroconversion, the concern about poorer immunogenicity after completion of COVID-19 vaccine series among immunocompromised individuals leads to increased vaccine hesitancy and impedes the vaccination campaign in this vulnerable populations.

Despite the unprecedentedly rapid development of vaccines, the availability of COVID-19 vaccines differs vastly across countries and thus there is an increasing interest in a heterologous vaccine strategy to overcome the global supply chain shortages.[6] In addition, waning of the immunity raises concerns about the durability of vaccine effectiveness and led to breakthrough infections.[7,8]

The impact of immune dysfunction on immunogenicity was mainly evaluated among individuals undergoing homologous prime-boost vaccination in previous studies.[5,7,8] Nevertheless, the immunogenicity of heterologous prime-boost vaccination among immunocompromised individuals is rarely explored. In this study, we aimed to evaluate the effect of immune dysfunction on immunogenicity of homologous and heterologous prime-boost vaccination against SARS-CoV-2.

Methods

Study design and participants

This is a sub-analysis of our previous study reported to compare the immunogenicity of heterologous ChAdOx1/mRNA-1273 vaccination versus standard homologous ChAdOx1/ChAdOx1 and mRNA-1273/mRNA-1273 vaccination.[13] The adenovirus vector vaccine ChAdOx1-nCoV-19 (AstraZeneca, UK) and the messenger RNA (mRNA) vaccine mRNA-1273 (Moderna, USA) were used in this study. The trial was conducted from July 1 to August 31, 2021, at two medical centers located in northern Taiwan (National Taiwan University Hospital and Taoyuan General Hospital). The full protocol has been previously published.[13] In brief, participants were eligible if they were aged 20—65 years, being generally healthy or with stable pre-existing health conditions, having prime vaccinated with either ChAdOx1 or mRNA-1273, and being scheduled for booster doses of COVID-19 vaccination. Individuals were considered as moderately or severely immunocompromised patients and excluded from participation if they had active malignancy, underwent organ transplantation, or ever received immunosuppressants, including >10 mg per day of prednisone or its dosing equivalent, B-cell depleting agents, tumor necrosis factor α inhibitors, tyrosine kinase inhibitors, or cytokine inhibitors within 90 days.

Participants being prime vaccinated with ChAdOx1 8 weeks ago were randomized to receive a homologous boost with ChAdOx1 (ChAdOx1/ChAdOx1, Group 1) or a heterologous boost with mRNA-1273 (ChAdOx1/mRNA-1273, Group 2). Participants being prime vaccinated with ChAdOx1 or mRNA-1273 4 weeks ago received mRNA-1273 (ChAdOx1/mRNA-1273 [Group 3] and mRNA-1273/mRNA-1273 [Group 4]) were also enrolled. Because the ChAdOx1 vaccine induced lower immune responses,[10] the serologic responses were evaluated among participants undergoing prime vaccination with ChAdOx1 (Groups 1—3) and those

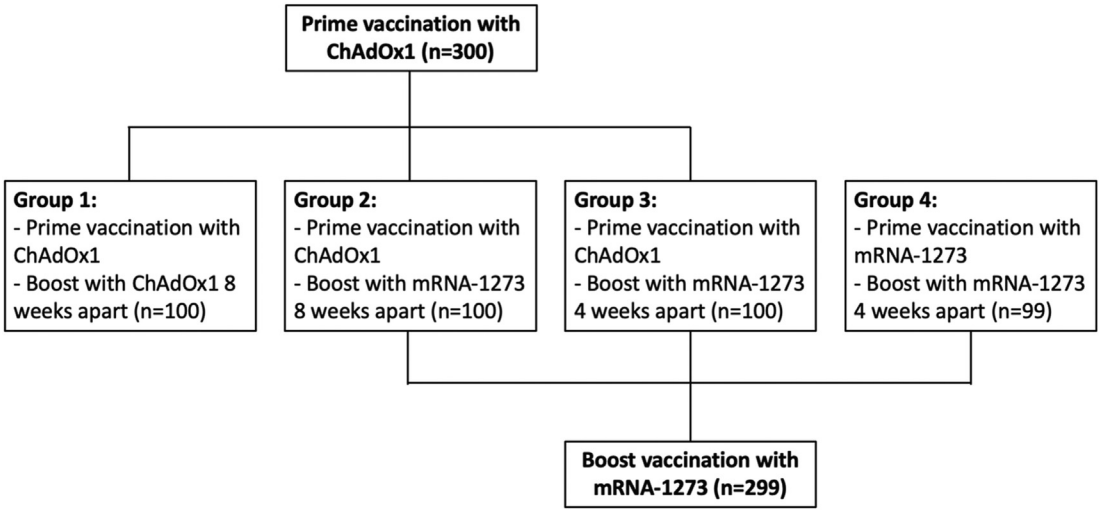

Figure 1 Study flow and groups.

undergoing boost vaccination with mRNA-1273 (Groups 2—4) (Fig. 1). Several immunocompromising conditions might contribute to dampened vaccine-induced immunity against SARS-CoV-2 infection, including old age, comorbidities, and drugs affecting immune responses (immunosuppressants and/or immunomodulators).[4] To clarify the effect of immune dysfunction on immunogenicity of COVID-19 vaccination, the serologic responses before and after boost vaccination were compared between participants with and without immunocompromising conditions. Immunosuppressants and immunomodulators in this sub-analysis included hydroxychloroquine, low-dose steroid (<10 mg per day of prednisone or its dosing equivalent), methotrexate, sulfasalazine, and non-steroidal anti-inflammatory drugs (NSAIDs). This study has been approved by the Research Ethics Committee of National Taiwan University Hospital (202106039 MINA) and Tao Yuan General Hospital (TYGH 110027), and all study participants provided written informed consent.

Laboratory investigations

Anti-SARS-CoV-2 spike IgG antibody titers were determined among all participants on the day before booster vaccination and 4 weeks after booster vaccination, with the use of Abbott SARS-CoV-2 IgG II Quant assay (06S60, Abbott, USA). This chemiluminescent microparticle immunoassay (CIMA) measures specific IgG antibodies to the receptor binding domain (RBD) of S protein on the Architect i2000SR analyzer (Abbott, USA). The IgG levels were reported as arbitrary units (AU) per milliliter, and converted to binding antibody units (BAU) per milliliter using the WHO international standard for SARS-CoV-2 immunoglobulin (BAU/mL = 0.142 × AU/mL).

Statistical analysis

Categorical variables were presented as numbers and percentages, and were analyzed using Fisher's exact test or the chi-square test. After transforming antibody titers to log values, the average values were expressed as geometric means with 95% confidence interval (CI) and compared between groups using Mann—Whitney U test. All tests were 2-tailed and a $P < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA software version 14.0 (Stata Corporation, College Station, TX, USA).

Results

Between July 1 and August 31, 2021, a total of 399 participants were enrolled in this study. There were 100, 100, 100, and 99 participants undergoing ChAdOx1/ChAdOx1 8 weeks apart (Group 1), ChAdOx1/mRNA-1273 8 weeks apart (Group 2), ChAdOx1/mRNA-1273 4 weeks apart (Group 3), and mRNA-1273/mRNA-1273 4 weeks apart (Group 4), respectively. The majority of the enrolled participants were ≤50 years with 74.7% being women (Table 1). While the most common comorbidity was hypertension (25/399, 6.3%), 16 participants had autoimmune diseases (4.0%) and 9 had solid-organ malignancy (2.3%). Eighteen (4.5%) participants received hydroxychloroquine (n = 15), sulfasalazine (6), methotrexate (2), and/or low-dose steroid (2). Fifteen (3.8%) participants received NSAIDs as immunomodulators for autoimmune diseases; 6 received nonselective or cyclooxygenase (COX)-1 selective NSAIDs, and 9 received COX-2 selective NSAIDs. The clinical characteristics were similar across participants undergoing prime vaccination with ChAdOx1 (Groups 1—3) and those undergoing boost vaccination with mRNA-1273 (Groups 2—4), except a higher proportion of male participants enrolled in Groups 2—4 (27.1% vs. 20.3%). No participants were diagnosed with SARS-CoV-2 infection during the study period.

Overall, the geometric means of anti-SARS-CoV-2 spike IgG titers before and 4 weeks after booster vaccination were 100.69 BAU/mL (95% CI, 90.89—111.54 BAU/mL) and 1140.17 BAU/mL (95% CI, 1029.65—1262.54 BAU/mL), respectively (Table 1). Compared with all participants, the anti-SARS-CoV-2 spike IgG titers before booster vaccination were lower in participants undergoing prime vaccination

Table 1 Clinical characteristics of enrolled participants.

Variable	Overall (n = 399)	Prime with ChAdOx1 (n = 300)	Boost with mRNA-1273 (n = 299)
Age, n (%)			
≤50 years	312 (78.2)	233 (77.7)	235 (78.6)
≤60 years	382 (95.7)	288 (95.7)	287 (96.0)
Female, n (%)	298 (74.7)	239 (79.7)	218 (72.9)
Comorbidities, n (%)			
Hypertension	25 (6.3)	20 (6.7)	17 (5.7)
Diabetes under treatment	12 (3.0)	11 (3.7)	8 (2.7)
Autoimmune diseases[a]	16 (4.0)	13 (4.3)	12 (4.0)
Hypothyroidism	8 (2.0)	8 (2.7)	7 (2.3)
Chronic viral hepatitis[b]	13 (3.2)	9 (3.0)	8 (2.7)
Chronic lung disease	8 (2.0)	6 (2.0)	8 (2.7)
Chronic kidney disease[c]	2 (0.5)	2 (0.7)	1 (0.3)
Solid organ malignancy	9 (2.3)	7 (2.3)	7 (2.3)
Immunosuppressants and/or immunomodulators, n (%)			
Hydroxychloroquine, low-dose steroid, methotrexate, and/or sulfasalazine	18 (4.5)	12 (4)	13 (4.3)
NSAIDs	15 (3.8)	10 (3.3)	12 (4.0)
SARS-CoV-2 anti-spike IgG, geometric mean (95% CI), BAU/mL			
Baseline visit (prior to booster vaccination)	100.69 (90.89–111.54)	81.08 (73.41–89.56)	–
Follow-up visit (4 weeks after booster vaccination)	1140.17 (1029.65–1262.54)	–	1902.76 (1774.13–2040.72)

Abbreviations: BAU, binding antibody units; CI, confidence interval; COX-2, cyclooxygenase-2; NSAID, Non-steroidal anti-inflammatory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Autoimmune diseases included ankylosing spondylitis, antiphospholipid syndrome, autoimmune thyroiditis, rheumatoid arthritis, seronegative spondyloarthritis, Sjögren's syndrome, and systemic lupus erythematosus.

[b] Chronic viral hepatitis included hepatitis B and C infections for more than 6 months.

[c] Chronic kidney disease was defined as reduced glomerular filtration rate or kidney damage (<60 ml/min/1.73 m^2 of body-surface area) for more than 3 months.

with ChAdOx1 (geometric means, 81.08 vs. 100.69 BAU/mL), and the titers 4 weeks after booster vaccination were higher in participants undergoing boost vaccination with mRNA-1273 (geometric means, 1902.76 vs. 1140.17 BAU/mL).

The serologic responses compared between participants with and without immunocompromising conditions are shown in Tables 2 and 3. Among participants undergoing prime vaccination with ChAdOx1, SARS-CoV-2 anti-spike IgG titers before booster vaccination were similar across different age and sex stratifications (Table 2). Compared with healthy participants aged ≤50 years, participants with immunocompromising conditions (i.e. those aged >50 years, having comorbidities, or using immunosuppressants and/or immunomodulators) had similar anti-SARS-CoV-2 spike IgG titers before booster vaccination (geometric means, 75.36 vs. 82.87 BAU/mL; $P = 0.429$). However, numerically lower anti-SARS-CoV-2 spike IgG titers before booster vaccination were found in participants with autoimmune diseases compared to those without (geometric means, 34.76 vs. 84.25 BAU/mL; $P = 0.173$). The participants receiving hydroxychloroquine, low-dose steroid, methotrexate, and/or sulfasalazine had statistically significantly lower anti-SARS-CoV-2 spike IgG titers before booster vaccination compared with those not receiving (geometric means, 36.39 vs. 83.84 BAU/mL; $P = 0.001$), especially in those receiving hydroxychloroquine (geometric means, 38.48 vs. 82.97 BAU/mL; $P = 0.009$) and sulfasalazine (geometric means, 21.96 vs. 82.90 BAU/mL; $P < 0.001$). The participants receiving NSAIDs also had statistically significantly lower anti-SARS-CoV-2 spike IgG titers before booster vaccination compared with those not receiving (geometric means, 39.04 vs. 83.15 BAU/mL; $P = 0.007$), especially in those receiving COX-2 selective NSAIDs (geometric means, 27.88 vs. 83.49 BAU/mL; $P < 0.001$).

Among participants undergoing boost vaccination with mRNA-1273, anti-SARS-CoV-2 spike IgG titers 4 weeks after booster vaccination were similar across the strata (Table 3). Compared with healthy participants aged ≤50 years, participants with immunocompromising conditions (i.e. those aged >50 years, having comorbidities, or using immunosuppressants and/or immunomodulators) had similar anti-SARS-CoV-2 spike IgG titers 4 weeks after booster vaccination (geometric means, 1769.66 vs. 1946.41 BAU/mL; $P = 0.255$). Only participants with autoimmune diseases and receiving hydroxychloroquine, low-dose steroid, methotrexate, and/or sulfasalazine had numerically lower anti-SARS-CoV-2 spike IgG titers 4 weeks after booster vaccination compared to those without (geometric means,

Table 2 The immunogenicity of prime vaccination with ChAdOx1 before boost vaccination and characteristics of recipients in this study.

Variable	SARS-CoV-2 anti-spike IgG, geometric means (95% CI), BAU/mL	*P* value
Overall (n = 300)	81.08 (73.41–89.56)	
Immunocompromising conditions[a] (n = 69)		0.429
Yes	75.36 (60.03–94.61)	
No	82.87 (74.20–92.57)	
Age ≥50 years (n = 67)		0.809
Yes	82.95 (67.30–102.30)	
No	80.55 (71.89–90.26)	
Male (n = 61)		0.066
Yes	67.48 (52.30–87.05)	
No	84.97 (76.37–95.54)	
Hypertension (n = 20)		0.193
Yes	103.70 (65.68–163.80)	
No	79.67 (71.95–88.22)	
DM under treatment (n = 11)		0.145
Yes	118.30 (73.27–191.00)	
No	79.92 (72.20–88.48)	
Hypothyroidism (n = 8)		0.799
Yes	93.03 (26.48–326.90)	
No	80.78 (73.20–89.14)	
Chronic viral hepatitis[b] (n = 9)		0.828
Yes	76.16 (41.43–140.00)	
No	81.24 (73.41–89.91)	
Chronic lung disease (n = 6)		0.119
Yes	140.60 (39.95–494.70)	
No	80.18 (72.59–88.56)	
Chronic kidney disease[c] (n = 2)		0.099
Yes	224.00 (0.22–224104)	
No	80.53 (72.90–88.96)	
Solid organ malignancy (n = 7)		0.825
Yes	87.16 (32.09–236.70)	
No	80.94 (73.22–86.48)	
Autoimmune diseases[d] (n = 13)		0.173
Yes	34.76 (19.34–62.47)	
No	84.25 (76.31–93.03)	
Ankylosing spondylitis (n = 2)		0.309
Yes	13.24 (0.01–36252.12)	
No	82.07 (74.38–90.57)	
Antiphospholipid syndrome (n = 2)		0.536
Yes	46.70 (0.01–154558.39)	
No	81.38 (73.66–89.92)	
Autoimmune thyroiditis (n = 3)		0.173
Yes	40.84 (1.94–860.40)	
No	81.65 (73.92–90.18)	
Rheumatoid arthritis (n = 4)		0.016
Yes	28.59 (4.71–173.50)	
No	82.23 (74.49–90.78)	
Seronegative spondyloarthritis (n = 4)		0.090
Yes	38.83 (20.10–75.04)	
No	81.89 (74.09–90.52)	
Sjögren's syndrome (n = 5)		0.059
Yes	39.07 (11.20–136.30)	
No	82.09 (74.31–90.69)	
Systemic lupus erythematosus (n = 1)		0.859
Yes	69.39 (–)	
No	81.12 (73.42–89.63)	
Hydroxychloroquine, low-dose steroid, methotrexate, and/or sulfasalazine (n = 12)		0.001
Yes	36.39 (20.12–65.81)	
No	83.84 (75.89–92.61)	
Hydroxychloroquine (n = 9)		0.009
Yes	38.48 (20.43–72.49)	
No	82.97 (75.07–91.71)	
Low-dose steroid (n = 2)		0.447
Yes	23.39 (0.001–88,656,975)	
No	81.76 (74.07–90.25)	
Methotrexate (n = 2)		0.332
Yes	15.56 (0.001–332930.42)	
No	81.99 (74.29–90.48)	
Sulfasalazine (n = 5)		<0.001
Yes	21.96 (5.02–96.07)	
No	82.90 (75.17–91.42)	
NSAID (n = 10)		0.007
Yes	39.04 (16.70–91.28)	
No	83.15 (75.34–91.78)	
COX-2 inhibitor (n = 8)		<0.001
Yes	27.88 (11.31–67.72)	
No	83.49 (75.68–92.10)	
NSAID except COX-2 inhibitor (n = 2)		0.319
Yes	150.00 (60.16–373.90)	
No	80.75 (73.07–89.23)	

Abbreviations: BAU, binding antibody units; CI, confidence interval; COX-2, cyclooxygenase-2; NSAID, Non-steroidal anti-inflammatory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Participants with immunocompromising conditions were defined as those aged >50 years, having comorbidities, or using immunosuppressants and/or immunomodulators. Participants without immunocompromising conditions were defined as healthy participants aged ≤50 years.

[b] Chronic viral hepatitis included hepatitis B and C infections for more than 6 months.

[c] Chronic kidney disease was defined as reduced glomerular filtration rate or kidney damage (<60 mL/min/1.73 m^2. of body-surface area) for more than 3 months.

[d] Autoimmune diseases included ankylosing spondylitis, autoimmune thyroiditis, rheumatoid arthritis, seronegative spondyloarthritis, Sjögren's syndrome, and systemic lupus erythematosus.

Table 3 The immunogenicity of boost vaccination with mRNA-1273 and characteristics of recipients in this study.

Variable	SARS-CoV-2 anti-spike IgG, geometric means (95% CI), BAU/ml	*P* value
Overall (n = 299)	1902.76 (1774.13–2040.72)	
Immunocompromising conditions[a] (n = 71)		0.255
Yes	1769.66 (1516.06–2065.69)	
No	1946.41 (1799.32–2105.53)	
Age >50 years (n = 64)		0.181
Yes	1737.23 (1471.36–2051.14)	
No	1950.72 (1806.02–2107.00)	
Male (n = 81)		0.749
Yes	1938.61 (1677.05–2240.97)	
No	1889.55 (1743.97–2047.28)	
Hypertension (n = 17)		0.772
Yes	1824.61 (1248.70–2666.15)	
No	1907.59 (1776.32–2048.57)	
DM under treatment (n = 8)		0.572
Yes	1685.18 (948.87–2992.87)	
No	1909.14 (1778.60–2049.27)	
Hypothyroidism (n = 7)		0.855
Yes	1984.47 (1072.52–3671.85)	
No	1900.84 (1770.86–2040.35)	
Chronic viral hepatitis[b] (n = 8)		0.814
Yes	1809.04 (1160.56–2819.87)	
No	1905.41 (1774.30–2046.22)	
Chronic lung disease (n = 8)		0.549
Yes	2163.44 (1512.15–3095.25)	
No	1896.03 (1765.23–2036.52)	
Chronic kidney disease[c] (n = 0)		–
Yes	–	
No	1902.76 (1774.13–2040.72)	
Solid organ malignancy (n = 7)		0.379
Yes	2329.18 (1221.63–4440.83)	
No	1893.53 (1764.36–2032.15)	
Autoimmune diseases[d] (n = 12)		0.142
Yes	1474.34 (1069.83–2031.80)	
No	1923.23 (1790.05–2066.32)	
Ankylosing spondylitis (n = 1)		0.165
Yes	811.71 (–)	
No	1908.22 (1779.21–2046.60)	
Antiphospholipid syndrome (n = 0)		–
Yes	–	
No	1902.76 (1774.13–2040.72)	
Autoimmune thyroiditis (n = 3)		0.886
Yes	1808.63 (402.61–8124.79)	
No	1903.74 (1774.19–2042.75)	
Rheumatoid arthritis (n = 3)		0.578
Yes	1562.98 (775.18–3151.40)	
No	1906.57 (1776.56–2046.09)	
Seronegative spondyloarthritis (n = 4)		0.206
Yes	1293.73 (619.99–2699.61)	
No	1912.77 (1782.46–2052.61)	
Sjögren's syndrome (n = 4)		0.197
Yes	1283.70 (466.90–3529.41)	
No	1912.97 (1782.99–2052.44)	
Systemic lupus erythematosus (n = 1)		0.662
Yes	1454.19 (–)	
No	1904.48 (1775.35–2043.00)	
Hydroxychloroquine, low-dose steroid, methotrexate, and/or sulfasalazine (n = 13)[d]		0.283
Yes	1590.61 (1195.34–2116.58)	
No	1918.38 (1784.78–2061.97)	
Hydroxychloroquine (n = 10)		0.478
Yes	1661.01 (1187.42–2323.49)	
No	1911.76 (1779.42–2053.94)	
Low-dose steroid (n = 1)		0.165
Yes	811.71 (–)	
No	1908.22 (1779.21–2046.60)	
Methotrexate (n = 1)		0.540
Yes	1306.34 (–)	
No	1905.17 (1776.03–2043.70)	
Sulfasalazine (n = 4)		0.480
Yes	1533.40 (688.88–3413.24)	
No	1908.35 (1778.18–2048.06)	
NSAID (n = 12)		0.981
Yes	1894.94 (1234.55–2908.57)	
No	1903.09 (1772.12–2043.74)	
COX-2 inhibitor (n = 6)		0.179
Yes	1362.55 (611.99–3033.60)	
No	1915.86 (1785.82–2055.37)	
NSAID except COX-2 (n = 6)		0.190
Yes	2635.34 (1737.10–3998.05)	
No	1890.07 (1760.56–2029.10)	

Abbreviations: BAU, binding antibody units; CI, confidence interval; COX-2, cyclooxygenase-2; NSAID, Non-steroidal anti-inflammatory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Participants with immunocompromising conditions were defined as those aged >50 years, having comorbidities, or using immunosuppressants and/or immunomodulators. Participants without immunocompromising conditions were defined as healthy participants aged ≤50 years.

[b] Chronic viral hepatitis included hepatitis B and C infections for more than 6 months.

[c] Chronic kidney disease was defined as reduced glomerular filtration rate or kidney damage (<60 ml/min/1.73 m^2 of body-surface area) for more than 3 months.

[d] Autoimmune diseases included ankylosing spondylitis, autoimmune thyroiditis, rheumatoid arthritis, seronegative spondyloarthritis, Sjögren's syndrome, and systemic lupus erythematosus.

1474.34 vs. 1923.23 and 1590.61 vs. 1918.38 BAU/mL; both $P > 0.05$). While anti-SARS-CoV-2 spike IgG titers 4 weeks after booster vaccination were comparable between participants receiving and not receiving NSAIDs (geometric means, 1894.94 vs. 1903.09 BAU/mL, $P = 0.981$), those receiving COX-2 selective NSAIDs had numerically lower titers (geometric means, 1362.55 vs. 1915.86 BAU/mL, $P = 0.179$).

Discussion

In this study to evaluate the effect of immune dysfunction on immunogenicity of homologous and heterologous prime-boost vaccination, we found that the serologic responses were lower in ChAdOx1-primed participants with autoimmune diseases and receiving immunosuppressants and/or immunomodulators. After boosting with mRNA-1273 vaccine, the serologic responses enhanced across all the strata with only numerically lower but not statistically different serologic responses in participants with immunocompromising conditions.

Individuals with immune dysfunction, including organ transplant recipients, people living with HIV, and people with autoimmune diseases, malignancies, and immunosuppressants use, are at higher risk for severe COVID-19 outcomes. Furthermore, individuals with immune dysfunction also have greater risk of breakthrough SARS-CoV-2 infections and prolonged shedding of SARS-CoV-2.[14,15] Therefore, immunocompromised patients are prioritized for COVID-19 vaccination. In a meta-analysis including 26 studies investigating the immunogenicity of 2-dose mRNA COVID-19 vaccination, the seroconversion rates in immunocompromised patients had been reported 48% lower than those in immunocompetent controls, especially organ transplant recipients with a 67% lower risk of seroconversion.[16] Although the seroconversion rates in patients with autoimmune diseases were lower than their counterparts, the pooled analysis showed no statistically significant difference between 2 groups. On the other hand, the seroconversion rates in patients with malignancies were significant lower than the controls, especially in those with hematological malignancies. Our study only included participants with stable pre-existing medical conditions, thus only a numerical decrease in serologic responses before boost vaccination was observed in participants with autoimmune diseases.

Individuals with immune dysfunction are vulnerable to COVID-19 breakthrough infection due to a significant waning of immune responses to vaccination.[14] A prospective study found individuals with immunosuppression had decreases in the IgG antibodies of 65% as compared with those without immunosuppression 6 months after 2-dose COVID-19 vaccination.[17] The poorer serologic responses and swiftly waning immunity after COVID-19 vaccination in immunocompromised patients prompt additional strategies to confer improved seroprotection, such as the administration of a heterologous booster and a third vaccine dose.[18,19] Another meta-analysis included 82 studies and evaluated the efficacy of COVID-19 vaccination in immunocompromised individuals.[5] After one vaccine dose, achieving seroconversion was less likely in patients with organ transplantation (risk ratio [RR] for seroconversion, 0.06), hematological cancers (RR, 0.40), immune mediated inflammatory disorders (RR, 0.53), and solid cancers (RR, 0.55) compared with immunocompetent controls. A second dose of COVID-19 vaccine improved seroconversion rates in patients with organ transplantation (RR, 0.39), hematological cancers (RR, 0.63), immune mediated inflammatory disorders (RR, 0.75), and solid cancers (RR, 0.90). Our study also consistently showed improved seroconversion after boost vaccination and decreasing differences in serologic responses across all patient groups, including those with immunocompromising conditions.

Previous studies demonstrated that immunosuppressants and/or immunomodulators, such as NSAID, reduced both the proinflammatory cytokine and antibody responses to SARS-CoV-2 infection in the mouse model.[20] While analgesics/antipyretics have been used either prophylactically or therapeutically to reduce the vaccine-induced systemic adverse events, there is a possibility that analgesics/antipyretics may compromise vaccine immunogenicity. In most clinical trials, participants were allowed to use analgesics/antipyretics to relieve COVID-19 vaccine-induced systemic adverse events. In a phase 1/2 study of ChAdOx1, 10% of participants received prophylactic acetaminophen prior to vaccination and vaccine reactogenicity was lower in participants received prophylactic acetaminophen compared with those did not.[21] NSAID could impair the antigen presenting function of dendritic cells, and the possible correlation of NSAID use and decreasing antibody response to ChAdOx1 had been postulated.[22–24] Nevertheless, there were no studies systemically evaluating the impact of analgesics/antipyretics on immunogenicity.[24] In our study, all participants received NSAIDs for autoimmune diseases. Therefore, a dampened antibody response to COVID-19 vaccination observed in participants receiving NSAIDs may be also related to autoimmune disease itself.

Our study provided the information on the effects of immune dysfunction and medication on the immunogenicity of homologous and heterologous prime-boost vaccination. However, this study has limitations. First, we enrolled relative young participants being healthy and with stable medical conditions in this study. Therefore, the case number of participants with moderate to severe immune suppression was relative small, and might limit the generalizability to elderly population and more pronounced immune compromised hosts. Second, we did not study the cellular immunity in this study and the prevalence of COVID-19 in Taiwan was low during the study period.[25,26] Therefore, whether the ability of protection against SARS-CoV-2 in participants with immune suppression after vaccination was unable to clarified. Although not all participants received SARS-CoV-2 PCR testing in this study, none of them had COVID-19 associated symptoms and were diagnosed with SARS-CoV-2 infection. Therefore, the serologic responses were more likely to be vaccine-induced immunity rather than infection-induced immunity. The data linking response to protection against SARS-CoV-2 infection remain currently limited and evolving, particularly among the immunocompromised populations.[16]

In conclusion, we found that immune dysfunction decreased immunogenicity of prime vaccination. However, the immunogenicity improved without significant

differences after receiving boost vaccination with mRNA-1273. Individuals with immune dysfunction should be prioritized for COVID-19 mRNA-1273 booster vaccination.

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Conflict of Interest

The authors have no conflicts of interest relevant to this article.

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