Severely impaired humoral response against SARS-CoV-2 variants of concern following two doses of BNT162b2 vaccine in patients with systemic lupus erythematosus (SLE)

Severe COVID-19 is associated with a poor prognosis among patients with systemic lupus erythematosus (SLE). Accordingly, patients with SLE receiving immunosuppressive drugs have been prioritised for vaccination in France. However, patients with autoimmune diseases—especially those receiving anti-CD20—are now known to mount a suboptimal humoral response following COVID-19 vaccination. Furthermore, vaccine-induced humoral protection against omicron, the current dominant variant of concern (VOC) worldwide, is not known in SLE.

Patients with SLE were prospectively enrolled in the vaccine task force set up between March and May 2021 in our national centre for autoimmune diseases. Humoral vaccine responses against B (ancestral), alpha, delta and omicron variants were assessed using a specific multiplex ELISA assay (CoViDiag kit, Innobiochips, Loos, France). Humoral response was defined by a specific SARS-CoV-2 anti-spike IgG (anti-S) level in serum >260 binding antibody units (BAU)/mL, according to French Health Authorities. Data were compared between groups using Fisher’s exact test for dichotomous variables and Mann-Whitney test for continuous variables.

Fifty-five patients with SLE were enrolled in the vaccine task force. Among them, 10 had prior COVID-19 and 10 were under immunosuppressive drugs and received three-dose primary series of BNT162b2 vaccine following national recommendation. Eventually, 35 COVID-19-naive patients with SLE (43.4 (36.0, 48.6) years; 88.6% female; table 1) and 9 healthy volunteers (HV) (59.0 (56.0, 62.0) years; 88.8% female) who received two doses of BNT162b2 vaccine 4 weeks apart were screened for humoral vaccine responses at baseline, at second dose, and 2 and 5 months after second dose. The two-dose and three-dose primary series of BNT162b2 vaccine were performed following an interval of 4 weeks between doses as recommended.

Patients with SLE and HV had no detectable anti-S and anti-nucleocapsid at baseline. Two months after the second-dose vaccine, 54.3% (n=19/35), 54.3%, 42.9% and 28.6% of patients with SLE had specific anti-S titre >260 BAU/mL against B, alpha, delta and omicron variants, respectively. At the same point time, the percentage of subjects able to mount humoral response against VOC were lower in SLE as compared with HV (100% of HV for B, p=0.016; 100% for alpha; p=0.016; 88.9% for delta; p=0.023; 55.6% for omicron, p=0.235). In patients with SLE, when the humoral responses against VOC were obtained 2 months after the second dose, it was maintained at 5 months in only 10.5% (n=2/19), 10.5% (2/19), 13.3% (2/15) and 10% (1/10) for B, alpha, delta and omicron variants, respectively. Overall, 5 months after the second-dose vaccine, the percent of patients with SLE with humoral response against B (n=2/35, 5.7% vs n=7/9, 88.9% p<0.001), alpha (5.7% vs 77.8%, p<0.001) and delta (5.7% vs 55.6%, p=0.002) variants were dramatically low as compared with HV. Almost all vaccinated subjects (n=34/35, 99% patients with SLE and n=7/9, 77.8% HV, p=0.101) failed to mount long-lasting humoral response against Omicron after two doses of BNT162b2 vaccine (figure 1). Of note, 50% (n=4/8), 50% (n=4/8), 37.5% (n=3/8) and 12.5% (n=1/8) of patients with SLE who were under immunosuppressive drugs (azathioprine, mycophenolate mofetil or anti-CD20) and received three-dose primary series of BNT162b2 had a preserved humoral response for B, alpha, delta and omicron variants, respectively, 5 months after the third dose. Moreover, all but one (83.4%, n=5/6) patients with SLE who had COVID-19 6.2 (3.9–11.6) months before the first BNT162b2 dose had a sustained humoral response 5 months after the second dose against all VOC including omicron (online supplemental figures S2 and S3; online supplemental table S2).

In this 6-month prospective monocentric study, we show that more than 90% of COVID-19-naïve patients with SLE failed to reach vaccine-induced humoral response after two doses of BNT162b2. To our knowledge, this is the first evaluation of long-lasting humoral responses against VOC including omicron variant in a cohort of patients with SLE. Neutralisation activity was not determined but the threshold of 260 BAU/mL for humoral response was consistent with previous published results and a strong correlation between anti-S IgG BAU/mL, live viral neutralisation and pseudo-neutralisation activity has been reported by our group. Since our patients with SLE received no immunosuppressive drugs, the poor immune response observed...
after two vaccine doses could not be ascribed to treatment. Such vaccine failure is worrisome considering the recent onset of highly contagious SARS-CoV-2 variant such as omicron. In patients who were under immunosuppressive drugs and received 3-dose primary series of vaccine, the highly variable humoral responses may reflect the different impact of immunosuppressive agents on the vaccine immunogenicity.

In conclusion, our data show the poor immune long-lasting protection conferred by two doses of BNT162b2 vaccines in patients with SLE. Screening for humoral response to vaccination based on anti-S titers should be performed in all patients with SLE, including those who are not receiving immunosuppressive drugs. The absence of anti-SARS-CoV-2 antibodies after full vaccination might help to identify patients who are candidates for additional strategies, including anti-SARS-CoV-2 monoclonal antibody prophylaxis, to protect them from COVID-19.

Figure 1  Humoral response following two doses of anti-SARS-CoV mRNAb vaccine in COVID-19-naïve patients with SLE and healthy volunteers. Serum SARS-CoV-2 anti-spike IgG level assessed overtime against B (ancestral), beta, delta and omicron variants by using a specific quantitative ELISA assay (CoVIdiag kit, Innobiochips, Loos, France) in patients with SLE (n=35, solid line) and healthy volunteers (n=9, dotted line). Medians and first and third quartiles were showed at second dose, 2 months and 5 months after second dose. P value was calculated using Mann-Whitney U test (*p<0.05; **p<0.01; ***p<0.001). The value of 260 indicated the threshold for humoral response. BAU, binding antibody units; SLE, systemic lupus erythematosus.

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