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Belimumab is not associated with COVID-19 mRNA vaccination failure in systemic lupus erythematosus

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KEY WORDS

COVID-19, systemic lupus erythematosus, belimumab, vaccination, B lymphocytes

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KEY MESSAGE

Belimumab is not associated with increased risk of SARS-CoV-2 vaccination failure in lupus patients.

DEAR EDITOR,

in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, patients with autoimmune-mediated rheumatic diseases (ARD) may have an increased risk to develop severe illness. Their malfunctioning immune system as well as the medical immunosuppression render them more susceptible for stronger and longer disease. In addition, vaccination may not be as efficacious as in the general population, which further adds to their risk of severe coronavirus 2019 disease (Covid-19).

Several immunosuppressive agents have been identified in ARD patients as well as in solid-organ transplant recipients that temper the immune response to SARS-CoV-2 vaccination. For example, the antiproliferative drug, mycophenolate mofetil, and the B-cell depleting antibody rituximab (RTX), have been associated with insufficient immunization. Understanding what medications are preventing patients from developing immunity against SARS-CoV-2 is important to be able to tailor therapies during the ongoing pandemic.

Systemic lupus erythematosus is an ARD that is highly driven by aberrant B-cell proliferation and activation. This can be attenuated by belimumab (BEL), a monoclonal antibody that binds to circulating B-cell activating factor [BAFF, also known as B-lymphocyte stimulator protein (BLyS)]. The recent approval of BEL for patients with lupus nephritis in the United States, in Europe and in other countries will likely lead to more widespread use in the near future.

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Epidemiological data on immune responses to vaccination in BEL-treated patients is sparse. Therefore, we prospectively studied the vaccination response of 50 patients from our lupus clinic. This study was approved by the local ethics committee (no. 2021-15786), and it was carried out in accordance with the Helsinki Declaration. Serum levels of IgG antibodies specific for the receptor-binding domain of the SARS-CoV-2 spike protein were measured by a chemiluminescence microparticle immunoassay (Architect SARS-CoV-2-IgG II Quant, Abbott, Wiesbaden, Germany) at the local laboratory.

30 of the 50 patients were treated with belimumab (BEL); for patient characteristics and treatment details, see Table 1. The median age was 50 years, and all but 5 patients were female. The majority of BEL patients (60%) took two other immunosuppressants, most commonly hydroxychloroquine and prednisone. Most of the patients that were not treated with BEL (50%) had single immunosuppressive therapy, most commonly hydroxychloroquine, followed by prednisone. One subject in the BEL group had no other immunosuppressant medication. Overall, hydroxychloroquine (HCQ) and prednisone (including extended-release prednisone) were the most frequently prescribed immunosuppressants (63% and 65% of all patients, respectively). There were no statistically significant differences between the BEL and no-BEL groups. There was, however, a potentially meaningful numerical difference in MMF/MPA use, with 7 of 30 patients (24%) in the BEL group taking MMF/MPA, as opposed to 7 of 20 patients (35%) in the no-BEL group.

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Most of the patients received mRNA-based vaccines: 79% BNT162b2 (Pfizer/BioNTech, Mainz, Germany) and 13% mRNA-1273 (Moderna, Cambridge, Massachusetts, USA). 8% were immunized with a vector-based vaccine (AZD1222, AstraZeneca, Hamburg, Germany).

A positive antibody response (> 50 AU/ml) was observed in 80% of BEL patients after two vaccinations and in 90% of BEL patients after three vaccinations. Only two BEL-treated subjects failed to produce antibodies even after three vaccinations, and these had been previously treated with rituximab. There were no statistically significant differences between the antibody levels of both groups (see Table).

To our knowledge, this is the largest number of patients treated with BEL and immunized against SARS-CoV-2 that has been reported so far. Several previous studies of the vaccination response in ARD patients included between 3 and 17 BEL-treated patients [1–8] with discordant results regarding median antibody levels. However, as in our study, the overall response rate to mRNA-based vaccines was very high with BEL. Of note, in a study of an inactivated SARS-CoV-2 vaccine (CoronaVac), 13 out of 30 BEL-treated patients did not seroconvert.

Antibody levels do not directly translate into protection from infection, and this is a major limitation of this study as well as similar studies that report humoral and cellular responses, but not infection rates. Furthermore, the relatively small number of subjects precludes analyses of potential interactions with other

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immunosuppressants, such as MMF/MPA. On the other hand, the cohort that was currently studied represents "real world" lupus patients, and it is remarkable that none of these patients, regardless of belimumab treatment, were hospitalized with COVID-19. Of note, it was recently shown that antibody levels after vaccination do correlate with protection against SARS-CoV-2 infection in patients with autoimmune diseases.

Taken together, the data presented herein as well as the data reported by others suggest that there is no reason to fear vaccination failures in lupus patients with belimumab. Still, given the high rates of breakthrough infections even in vaccinated healthy persons, it is imperative to closely observe lupus patients with SARS-CoV-2 infection and be wary of the possibility of severe illness.

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DISCLOSURES

J.W.M. received honoraria from GlaxoSmithKline unrelated to this work. S.-C.B.-L., P.C., and D.K. declare nothing to disclose.

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TABLE

SARS-CoV-2 vaccines, number of vaccinations, intervals between vaccinations, and anti-SARS-CoV-2 antibody levels.

Vaccination	Overall, N = 147	BEL, N = 88	no BEL, N = 59	p-value
Vaccine type				0.2
AstraZeneca	12 (8.2%)	10 (11%)	2 (3.4%)	
Biontech	116 (79%)	66 (75%)	50 (85%)	
Moderna	19 (13%)	12 (14%)	7 (12%)	
No. of vaccinations				>0.9
2	5 (10%)	3 (10%)	2 (10%)	
3	43 (86%)	26 (87%)	17 (85%)	
Days between 1st and 2nd shot	42 (33, 56)	41 (36, 50)	42 (31, 61)	0.7
Anti-SARS-CoV-2 IgG after second shot (AU/ml)	812 (130, 5,358)	265 (91, 5,410)	3,382 (1,152, 5,061)	0.078
Days between 2nd and 3rd shot	194 (168, 215)	196 (182, 220)	186 (158, 214)	0.4
Anti-SARS-CoV-2 IgG after third shot (AU/ml)	3,405 (1,386, 11,032)	2,657 (906, 5,382)	6,258 (3,010, 12,858)	0.12

Days and antibody levels are given as medians with interquartile ranges. Statistical significance between the BEL and no-BEL groups was assessed by Wilcoxon rank sum exact test.