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Is there an increased risk of severe COVID-19 among patients with systemic lupus erythematosus treated with anifrolumab?

Dear Editor,

Systemic lupus erythematosus (SLE) is associated with an overexpression of type-I interferons (IFN-I)[1]. Recently, anifrolumab, a monoclonal antibody that binds IFN-I receptor subunit 1, has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency for the treatment of SLE. Life-threatening COVID-19 have been recently related to autoantibodies against IFN-I[2,3] raising the question of potentially severe COVID-19 associated with anifrolumab.

Here, we report two cases of COVID-19 which occurred in patients treated with anifrolumab for SLE. This work was approved by the ethical committee of Sorbonne Université (CER2020-012) and written informed consent was obtained from participants.

The first case was a 32-year-old woman diagnosed with SLE since the age of 10 years. The main SLE characteristics are summarized in Table 1. She developed refractory discoid lupus and previously failed multiple lines of treatment (see Table 1) and anifrolumab was started on November 2021. After three infusions of anifrolumab, she developed cough, sore throat, and headache and a COVID-19 was diagnosed using Polymerase Chain reaction (PCR). The fourth infusion of anifrolumab was postponed for 10 days that has been continued since with improvement of cutaneous lesions. Serological test performed 3 months after COVID-19 showed anti-spike (anti-S) and anti-nucleocapsid (anti-N) antibodies confirming SARS-CoV-2 infection. She reported being previously vaccinated with three injections of mRNA BNT162b2 vaccine (last in July 2021). However, retrospective analysis of a serum collected in August 2021 showed no anti-S or anti-N antibodies.

The second case was 51-year-old woman diagnosed with SLE 10 years ago. She had active cutaneous and articular involvement with failure to multiple lines (see Table 1). In September 2021, anifrolumab was started with a rapid improvement on both cutaneous and articular symptoms. Before anifrolumab initiation, she had two injections of mRNA BNT162b2 and one mRNA-1273 injection was done 2 months after, in December 2021. Retrospective analysis of a serum collected in August 2021 confirmed anti-S antibody response but no anti-N antibodies. After three anifrolumab infusions, she developed cough, sore throat, headache, muscle pain, and a COVID-19 was confirmed by PCR and serological test (2 months later). Anifrolumab infusion was postponed for 2 weeks later without SLE flare.

Anifrolumab has been associated with an increased risk of viral infections.[4] Since trials on which FDA approval was based were conducted in the COVID-19 pre-pandemic period,[5] little is known on the risk of severe COVID-19. During the long-term extension study from a phase III trial, three deaths were attributable to COVID-19 in non-vaccinated patients and higher rates of COVID-related serious adverse events were found in anifrolumab group.[6] Moreover, although the two present cases seem reassuring, it is important to note that infections occur in January 2022 when omicron variants were the most common in France. This may have contributed to a lower COVID-19 severity regarding the decreased risk of hospitalization related to omicron variants.[7] Nevertheless, additional data in larger SLE cohorts are needed to establish proper recommendations for the prevention and management of COVID-19 in patients treated with anifrolumab.

Table 1. Main features of SLE.

Characteristics	Patient n°1	Patient n°2
Sex category	F	F
Age	32	51
Ethnicity	West African	Caucasian
Chronic medical illness	Glucose-6-phosphate dehydrogenase deficiency and Farh syndrome	Depression
Historical SLE features		
Clinical involvement	Raynaud phenomenon, discoid lupus, and pericardial effusion	Disseminated discoid lupus, Raynaud phenomenon, and arthritis
Biological and immunological features	High titers of anti-nuclear antibodies, anti-dsDNA, anti-Sm, anti-SSA, and low C3 complement level	High titers of anti-nuclear antibodies, positive anti-dsDNA, anti-Sm, decreased C3 complement levels, and lymphopenia
Previous treatment for SLE	HCQ, CS, MTX, Thalidomide, Lenalidomide, Rituximab, ustekimumab, and Belimumab	HCQ, CS, Thalidomide, MTX, and Belimumab
Anifrolumab add-on treatment	HCQ 400 mg/day and CS 2 mg/day	HCQ 400 mg/day and CS 10 mg/day
SLE at antifrolumab initiation		
SLE active manifestations	Disseminated active discoid lupus and alopecia	Disseminated active discoid lupus, arthritis, alopecia, and mucosal ulcers
SLEDAI-2k	8	10
CLASI-A	23	35
Response to anifrolumab at M6		
SLEDAI-2k	2	2
CLASI-A	10	11
COVID-19		
vaccination	3 injections of mRNA BNT162b2 vaccine (reported)	2 mRNA BNT162b2 injections and one mRNA-1273 vaccine
treatment At the time of vaccination	HCQ 400 mg/day, Belimumab 10 mg/kg/month (since 9 months), and CS 5 mg/day	HCQ 400 mg/day, Thalidomide 50 mg/day, CS 5 mg/day
sign Or symptoms	Cough, sore throat, and headache	Cough, sore throat, headache, and muscle pain
severity[a]	Mild illness	Mild illness
Serological SARS-CoV-2 results		
Pre-anifrolumab	Neither anti-S nor anti-N antibodies	Anti-S antibodies
After SARS-CoV-2 infection	Anti-S and anti-N antibodies	Anti-S and anti-N antibodies

CLASI; Cutaneous LE Disease Area and Severity Index, F; female, HCQ; hydroxychloroquine, MTX; methotrexate, CS: oral costicosteroid, N; nucleocapsid, NIH; National Institutes of Health S; spike, SLE; systemic lupus erythematosus, SLEDAI; Systemic Lupus Erythematosus Disease Activity Index.
[a]Adapted from NIH severity scale.

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Astrazeneca global team was contacted to obtain vaccination status of patients who died from COVID-19 during the long-term extension study from the two phase III trials.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FC participated in advisory board related to lupus for GSK, Astrazeneca, Celgène, Principa-Bio and received consulting fees from GSK and Astrazeneca. AM and ZA received consulting fees and participated in advisory board related to lupus for GSK and Astrazeneca.

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