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

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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 years-old woman diagnosed with SLE since the age of 10 years-old. 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 3 infusions of anifrolumab she developed cough, sore throat and headache and a COVID-19 was diagnosed using Polymerase Chain reaction (PCR). The 4th 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 3 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 years-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 2 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 3 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, 3 deaths were attributable to COVID-19 in non-vaccinated patients and higher rates of COVID-related serious adverse events was found in anifrolumab group(6). Moreover, although the 2 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.

Competing interests:

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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Contributors:

PB, FR, AD and FC were involved in the acquisition of data. All authors contributed to drafting and/or revising the manuscript.

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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.

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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, pericardial effusion	disseminated discoid lupus, Raynaud phenomenon, arthritis

Table 1 Main features of SLE

biological and immunological features	high titers of antinuclear antibodies, anti dsDNA , anti-Sm, anti-SSA and low C3 complement level	high titers of antinuclear antibodies , positive anti dsDNA, anti-Sm, decreased C3 complement levels and lymphopenia
Previous treatment for SLE	HCQ, CS, MTX, Thalidomide, Lenalidomide, Rituximab, ustekimumab, Belimumab	HCQ, CS, Thalidomide, MTX, Belimumab
Anifrolumab Add-on treatment	HCQ 400mg/day and CS 2mg/day	HCQ 400mg/day and CS 10mg/day
SLE at antifrolumab initiation		
SLE active manifestations	disseminated active discoid lupus, alopecia	disseminated active discoid lupus, arthritis, alopecia, 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 BNT162b2injections and one mRNA-1273 vaccine
treatment at the time of vaccination	HCQ 400mg/day, Belimumab 10mg/kg/month (since 9 months) and CS 5mg/day	HCQ 400mg/day, Thalidomide 50mg/day, CS 5mg/day
sign or symptoms	cough, sore throat and headache	cough, sore throat, headache, muscle pain
severity*	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

* adapted from NIH severity scale

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,