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Lower disease activity but higher risk of severe COVID-19 and herpes zoster in systemic lupus erythematosus patients with pre-existing autoantibodies neutralising IFN- α

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Abstract

Objectives: Type-I interferons (IFNs-I) have potent antiviral effects. IFNs-I are also overproduced in patients with systemic lupus erythematosus (SLE). Auto-antibodies (AAbs) neutralising IFN- α , - β and/or - ω subtypes are strong determinants of hypoxemic COVID-19 pneumonia, but their impact on inflammation remains unknown.

Methods: We retrospectively analysed a monocentric longitudinal cohort of 609 patients with SLE. Serum AAbs against IFN- α were quantified by ELISA and functionally assessed by abolishment of Madin-Darby bovine kidney cells protection by IFN- α 2 against vesicular stomatitis virus challenge. Serum neutralising activity against IFN- α 2, - β and - ω was also determined with a reporter luciferase activity. SARS-CoV-2 antibody responses were measured against wild-type spike antigen, while serum-neutralising activity was assessed against the SARS-CoV-2 historical strain and variants of concerns.

Results: Neutralising and non-neutralising anti-IFN- α antibodies are present at a frequency of 3.3% and 8.4%, respectively, in individuals with SLE. AAbs neutralising IFN- α , unlike non-neutralising AAbs, are associated with reduced IFN- α serum levels and a reduced likelihood to develop active disease. However, they predispose patients to an increased risk of herpes zoster and severe COVID-19 pneumonia. Severe COVID-19 pneumonia in patients with SLE is mostly associated with combined neutralisation of different IFNs-I. Finally, anti-IFN- α AAbs do not interfere with COVID-19 vaccine humoral immunogenicity.

Conclusion: The production of non-neutralising and neutralising anti-IFN-I antibodies in SLE is likely to be a consequence of SLE-associated high IFN-I serum levels, with a beneficial effect on disease activity, yet a greater viral risk. This finding reinforces the recommendations for vaccination against SARS-CoV-2 in SLE.

Key messages:

- **What is already known on this topic:**
 - Anti-IFN- α autoantibodies (AAbs) have been reported in 5 to 27% of patients with SLE, it is however as yet unclear whether their occurrence is pathogenic, protective, or a reflection of a general tendency towards auto-reactivity.

- **What this study adds:**
 - Neutralising and non-neutralising anti-IFN- α AAbs are present at a frequency of 3.3% and 8.4%, respectively, in patients with SLE.
 - AAbs neutralising IFN- α are associated with reduced IFN- α serum levels and a reduced likelihood to develop active disease.
 - AAbs neutralising IFN- α are associated with a history of severe COVID-19 pneumonia and episodes of cutaneous herpes zoster.

- **How this study might affect research, practice or policy:**
 - Monitoring anti-IFN- α antibodies in patients with SLE can help identify patients at risk of developing serious viral infections

Introduction

Type-I interferons (IFNs-I) play a central role in the early control of viral infections. Inborn errors of IFN-I immunity were recently found in patients with life-threatening COVID-19.[1, 2] Autoantibodies (AAbs) neutralising IFNs-I were also found in 7% and 15% of patients with severe and critical COVID-19 pneumonia, respectively.[3-6] They were also found in about a third of a cohort of patients with yellow fever vaccine associated-disease.[7] However, little is known about the circumstances in which neutralising AAbs directed at IFNs-I appear and whether they might also have anti-inflammatory effects. The IFN family of cytokines is indeed involved in systemic lupus erythematosus (SLE) pathogenesis, an autoimmune disease affecting mostly young women and where persistent overexpression of IFNs-I, notably IFN- α , is observed.[8] While anti-IFN- α AAbs have been reported in 5% to 27% of patients with SLE,[9-12] it is, however, as yet unclear whether the occurrence of these AAbs in the context of SLE is pathogenic, protective or a reflection of a general tendency towards auto-reactivity. It has been suggested that endogenous anti-IFN- α AAbs may have a regulatory, protective, role against disease activity.[10, 11] However, it is difficult to draw firm conclusions from these studies involving only small numbers of patients. Indeed, if the presence of anti-IFN- α AAbs has reportedly been associated with reduced downstream IFN-pathway activity in patients with SLE, it was either not[11] or only weakly[10] associated with a decrease in disease activity. Anti-IFN- α antibodies were previously described in two patients with SLE with severe COVID-19,[13] but their clinical impact on SLE activity was not explored. Furthermore, although targeting IFN-I signalling pathways represents a promising therapeutic approach for SLE, as evidenced by the recent approval of the IFN-I receptor antagonist anifrolumab by the US Food and Drug Administration,[14] and the European Medicines Agency,[15] the potential long-term viral risk caused by this type of treatment is of concern.

In the present study, we retrospectively analysed immunological and clinical data in a monocentric longitudinal cohort of 609 patients with SLE and focused on the association between the presence and the neutralisation capacity of serum anti-IFN- α AAbs, infectious complications and disease evolution. We hypothesised that neutralising anti-IFN- α AAbs might confer an additional viral risk to patients with SLE, but could also have a disease-ameliorating effect.

Patients, Materials and Methods

Study design and patients

The retrospective longitudinal study reported here was conducted between June 2006 and June 2021 at the French National Referral Center for Systemic Lupus Erythematosus (SLE) and Antiphospholipid Antibody Syndrome and Other Autoimmune Disorders, Paris, France, regrouping out or inpatients with active or quiescent, untreated or treated disease. Serum samples were randomly obtained from patients diagnosed with SLE according to the 1997 American College of Rheumatology criteria for SLE classification or the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE.[16, 17] Patients seen in outpatient clinic or during hospital care were randomly included in the study, regardless of disease activity and treatment. Serum samples were kept frozen until anti-interferon- α AAbs were assessed. [See online supplement](#) for the designs of the clinical studies. The study was approved by the ethical committee of Sorbonne Université (CER2020-012, CER2021-011 and CER2021-099) and informed consent was obtained from all participants.

Measurement of anti-IFN- α AAbs

Auto-Abs against IFN- α were quantified using the anti-IFN- α Antibody Human ELISA Kit (Thermo Fisher, Invitrogen), according to the manufacturer's instructions. The positivity threshold of the assay was 15 ng/mL.

Determination of biological activity of IFN- α by IFN- α bioassay

Serum-IFN- α biological activity was determined by assessing the protection conferred by each patient's serum to cultured Madin-Darby bovine kidney (MDBK) cells challenged with vesicular stomatitis virus (VSV), as previously described.[18-21] Serum-IFN α levels are expressed in IU/mL after comparison with IFN- α 2b reference (Introna, Shering Plough), standardised against the National Institutes of Health (NIH) reference Ga 023-902-530 titrated under the same conditions as the SLE patients' serum samples. The lower limit of detection was 2 IU/mL. Serum-IFN- α activity in healthy individuals is undetectable (i.e., <2 IU/mL).[22, 23]

Functional evaluation of anti-IFN- α AAbs by VSV assay

The blocking activity of anti-IFN- α AAb-containing serum was assessed as previously described.[24] Neutralisation experiments were performed by the titration of serial dilutions of serum positive for anti-IFN- α AAbs against 10 IU/mL (50 pg/mL) of IFN- α 2b (Introna,

Shering Plough), following the previously described antiviral assay. Serum and IFN- α were incubated together for 30 min at room temperature before being added to MDBK-cells. End points were scored at 50% cytopathic effect (CPE). Sera to be tested for their anti-IFN- α neutralisation capacity were previously inactivated at 56°C for 60 min to remove endogenous IFN- α activity. Neutralising titres correspond to the serum dilution at 50% CPE x 10. For clinical studies, only sera with neutralisation titres >30 were considered significant.

Functional evaluation of anti-IFN-I AAbs by luciferase reporter assay.

The blocking activity against IFN- α 2 and IFN- ω at 10² pg/mL and 10⁴ pg/mL, and IFN- β at 10⁴ pg/mL, were determined with a reporter luciferase activity as previously described.[4]

SARS-CoV-2 serological analysis

Serum levels of SARS-CoV-2-specific immunoglobulin G (IgG) antibodies were assessed using an ELISA specific for anti-nucleocapsid IgG (Euroimmun, France) or the Maverick SARS-CoV-2 Multi-Antigen Serology Panel (Genalyte, USA), according to the manufacturer's instructions, as previously described.[25] The latter is designed to detect antibodies specific for five SARS-CoV-2 antigens: nucleocapsid, spike S1 receptor-binding domain (RBD), spike S1S2, spike S2 and spike S1, within a multiplex format based on photonic ring resonance technology.

SARS-CoV-2 pseudoneutralisation assay

Lentiviral particles carrying the luciferase Firefly gene and pseudotyped with spikes of SARS-CoV-2 historical strain or variants of concerns (VOCs) were produced by triple transfection of 293T cells as previously described.[25]

Statistical analysis

Qualitative variables are expressed as number (%) and quantitative variables as the mean \pm standard deviation (SD) or median (quartiles), as appropriate. The Mann–Whitney U-test or Student's t-test for continuous data, and Fisher's exact or χ^2 test for categorical data were used to compare independent groups. Spearman's correlation coefficients were computed for quantitative values. The diagnostic performance of the serum-anti-IFN- α AAb levels as assessed by ELISA, to detect an IFN- α neutralising capacity was investigated by analysing receiver operating characteristic (ROC) curves, with the capacity to neutralise 10 IU/mL of IFN- α serving as the gold standard. The areas under the ROC curves (AUCs) to differentiate sera with IFN- α -neutralising capacity versus sera without were calculated. The optimal

threshold was determined using a compromise among the minimum sensitivity - specificity difference and the Youden's index. We measured the statistical association between the occurrence of severe or critical COVID-19 pneumonia in patients with SLE and different sets of neutralising anti-IFN-I capacities. Time to flare was studied by the mean of Kaplan-Meier method and compared using Log-Rank tests for patients in whom immunosuppressive and corticosteroid therapy were not increased on the day monitoring was initiated. We performed a sensitivity analysis also including patients in whom immunosuppressive or corticoid therapy was increased on the day monitoring was initiated. Crude Hazard Ratios (HRs) were calculated using the Log-Rank or Mantel-Haenszel estimate when appropriate. All tests were two-sided and $p < 0.05$ defined significance. Statistical analyses were performed using GraphPad Prism, v8.0.1 software (GraphPad Software, San Diego, California), R software, v3.6.3 and v4.0.5 and the web tool easyROC, v1.3.1.[26]

Results

High prevalence of neutralising and non-neutralising anti-IFN- α AAbs in SLE

The presence of serum anti-IFN- α AAbs was detected by ELISA in 71 (11.7%) of the 609 patients we analysed, with levels measured at least once above 500 ng/mL in 27 (38.0%) patients and were usually persistent, since they became undetectable in only 10 out of 63 (16%) patients followed for a median (interquartile) time of 4.2 years (3.6-6.4) ([supplemental figure 1](#)). There was no significant difference in terms of gender or median age between patients with ELISA-detectable anti-IFN- α AAbs (aIFN- α^+), or not (aIFN- α^-): 65 out of 71 aIFN- α^+ patients (91.5%) vs 509 out of 538 aIFN- α^- patients (94.6%) were women, $p=0.28$ and 34.6 [26.5-46.5] years vs. 37.7 [29.5-49.4], $p=0.06$, respectively). We then assessed the biological activity of these AAbs. Only 20 (28.2%) of the 71 sera with ELISA-detectable anti-IFN- α AAbs significantly abolished MDBK cell protection by IFN- α_2 against viral challenge. Neutralisation capacity was proportional to anti-IFN- α AAb levels ([figure 1A,B](#)), although some rare serum samples containing high AAb levels were not endowed with neutralising activity ([figure 1A](#)). The area under the ROC curve for anti-IFN α AAb serum levels, differentiating between IFN- α -neutralising and non-neutralising sera, was 0.90 (95%CI 0.85-0.96, [figure 1C](#)), the optimal ELISA threshold for prediction of neutralisation activity, as determined using the minimum sensitivity - specificity difference and the Youden's index, being 310 ng/mL. Proportions of patients with neutralising activity were similar in all age groups ([figure 2A](#)). In conclusion, not all anti-IFN- α AAbs have neutralisation potential. Although evaluation of serum neutralising activity remains the gold standard, simple assessments with ELISA assays are informative since a strong correlation with biological activity was observed.

Anti-IFN- α -neutralising AAbs are associated with increased viral risk in SLE

We next searched for comorbidities associated with the presence of anti-IFN- α AAbs in SLE. In order to analyse the impact of anti-IFN- α AAbs on the risk of viral infection in SLE, we designed a retrospective cohort study in which all patients with SLE with anti-IFN- α AAbs (aIFN- α^+) were compared with patients without anti-IFN- α AAbs (aIFN- α^-) at a 1:2 ratio ([see supplemental patients, materials and methods](#)). While none of the aIFN- α^- patients experienced a severe COVID-19 pneumonia, 5 patients (7%) out of the 71 aIFN- α^+ patients developed severe or critical COVID-19 pneumonia ([table 1](#)). The presence of anti-IFN- α -neutralising AAbs, unlike that of non-neutralising AAbs, was associated in a statistically significant manner with a history of severe or critical COVID-19 pneumonia, episodes of cutaneous herpes zoster,

and severe viral infection ($p=3.10^{-4}$, $p=0.03$ and $p=10^{-4}$, respectively, [figure 2B and supplemental table 2](#)). Of note, the 8 cases of severe viral infections in patients with anti-IFN- α -neutralising AAbs included 5 cases of COVID-19 pneumonia, 2 cutaneous herpes zoster and 1 varicella pneumonia. Importantly, patients had samples collected before SARS-CoV-2 infection, and anti-IFN- α AAbs were detected in all cases, prior to infection, further suggesting that they are a cause, rather than a consequence, of severe viral infection. On the other hand, aIFN- α^+ patients were not at higher risk to suffer from warts and human papillomavirus (HPV)-induced cervical lesions, as suggested by previous genetic studies on predisposition to HPV infection.[27]

Combined neutralisation of different IFN-I subtypes is associated with severe COVID-19

Given that in the general population, as well as in patients with SLE, anti-IFN- α AAbs are frequently associated with the presence of antibodies against other IFNs-I, such as IFN- β and IFN- ω , [3, 4, 9, 11] we tested whether their co-existence was associated with an increased infectious risk. Serum sampled as close as possible to the COVID-19 pandemic onset were assessed for their neutralisation capacity against IFN- α , and IFN- ω at 10^2 pg/mL and IFN- β at 10^4 pg/mL using a luciferase assay, as previously described.[4] None of the 134 sera lacking detectable levels of anti-IFN- α AAbs were able to neutralise IFN- $\alpha 2$ or IFN- β , and only 4 (3%) neutralised IFN- ω . In contrast, neutralising activities against IFN- $\alpha 2$, IFN- β and IFN- ω were more frequently detected (18 (25%), 12 (17%) and 15 (21%) sera, respectively) in the 71 sera with ELISA-detectable anti-IFN- α AAbs. A total of 30 (42%) of the 71 aIFN- α^+ sera tested neutralised at least one IFN-I, while 9 (13%) and 3 (4%) neutralised two and three IFNs-I, respectively. A high concentration of anti-IFN- α AAbs was associated with an increasing number of IFN-I neutralising abilities. Indeed, anti-IFN- α AAb concentrations in serum which neutralised at least two IFNs-I (median [Q1-Q3]; 5592 [837-70175] ng/mL) were significantly higher than those in serum which neutralised a single IFN-I (350 [72-2485] ng/mL; $p=0.009$) and in serum which did not neutralise IFN-I (53 [32-154] ng/mL; $p<10^{-4}$). Anti-IFN- α AAb concentrations in serum of these latter groups also differed significantly ($p=0.008$).

Importantly, the occurrence of severe or critical COVID-19 was significantly associated with neutralisation of IFN- $\alpha 2$ or IFN- ω ($p=0.013$ and $p=0.005$, respectively, [table 2](#)). Finally, the analysis confirmed that severe or critical COVID-19 in SLE was very significantly associated with combined neutralisation of both IFN- $\alpha 2$ and IFN- ω subtypes ($p<10^{-4}$, [table 2](#)), as recently observed in the general population.[28] Of note, the only patient with SLE in this cohort who deceased of COVID-19, had AAbs that neutralised all three IFN-I subtypes tested, suggesting

that the severity of COVID-19 pneumonia is even higher in individuals neutralising several IFN-I.[28] It should also be noted that two of the five patients who experienced a severe COVID-19 presented comorbidities conditions such as obesity, immunosuppressive therapy and renal allograft (table 1).

Anti-IFN- α -neutralising AAbs are associated with reduced SLE disease activity

We compared the clinical course of SLE in the presence or absence of anti-IFN- α AAbs (see supplemental patients, materials and methods). Patients with neutralising anti-IFN- α AAbs had reduced disease activity, less flares and less clinically active SLE, were more likely to be in remission or in lupus low disease activity states compared to patients who lacked neutralising anti-IFN- α AAbs (figure 3A). Biological markers of SLE disease activity, such as elevated anti-double stranded DNA Ab serum levels (i.e., Farr assay), decrease in complement component C3 and increase in serum IFN- α levels were also reduced in patients with neutralising anti-IFN- α AAbs compared with patients without (figure 3A). Other characteristics of lupus disease were similar between the two groups (supplemental table 3). Non-neutralising anti-IFN- α AAbs were associated with higher IFN- α serum levels and the presence of anti-RNP and anti-Sm Abs. Of the 18 patients with neutralising anti-IFN- α AAbs in whom immunosuppressive and corticosteroid therapy were not increased, none experienced a lupus flare during the following year (figure 3B). Log-Rank tests analysis showed a significantly higher risk of relapse in patients with non-neutralising anti-IFN- α AAbs, as compared with patients with neutralising anti-IFN- α AAbs (HR 4.78 [95% CI 1.02-22.40], p=0.047). The results from a sensitivity analysis, including patients in whom immunosuppressive or corticoid therapy was increased at the beginning of the follow-up, showed that only one patient out of 20 with neutralising anti-IFN- α AAbs experienced a lupus flare during the following year. In summary, non-neutralising anti-IFN- α AAbs are more prevalent and are typically associated with both unstable disease and high IFN- α serum levels. In contrast, the presence of neutralising AAbs in patients with SLE was associated with a concomitant reduction in levels of serum IFN- α and disease activity.

Anti-IFN- α AAbs do not interfere with COVID-19 vaccine efficacy

Vaccination currently represents the best option to prevent serious infections in patients with SLE. We reasoned that neutralisation of IFN- α signalling might possibly dysregulate IFN-dependent B cell responses[29] and limit vaccine-induced antibody production. In order to determine whether anti-IFN- α AAbs could interfere with COVID-19 vaccine efficacy, we performed a sub-analysis of the results we recently obtained in a cohort of patients with

SLE,[30] evaluating their SARS-CoV-2-specific immune responses after BNT162b2 vaccination in presence or absence of these AAbs. IFN-I-neutralising activity was confirmed in 50% of the 10 vaccinated aIFN- α^+ patients tested, whereas demographics and main bioclinical characteristics were similar in aIFN- α^+ and aIFN- α^- patients (supplemental table 4). Vaccine-induced anti-SARS-CoV-2 spike receptor-binding domain (RBD) IgG levels, and serum-neutralising capacity of SARS-COV-2 and its major variants, were similar in both groups, thus confirming that aIFN- α^+ patients are able to mount an efficacious anti-SARS-CoV-2 humoral vaccine response, similar to that of aIFN- α^- patients (figure 3C). In conclusion, although only a limited number of vaccinated patients with SLE could be analysed, the results nevertheless show that anti-IFN- α AAbs do not seem to interfere with COVID-19 humoral vaccine response.

Discussion

The COVID-19 outbreak has illustrated the fact that a previously poorly recognised form of autoimmunity underlies some severe forms of COVID-19 disease,[3-7] although the mechanisms driving the appearance of the anti-IFN-I AAbs and their potential broader medical impact remain unknown. Besides reported SLE-associated cases,[9-12, 31] these AAbs have also been found in patients with thymoma,[32] myasthenia gravis [33, 34] or affected by various primary immune deficiencies.[35-39] However, their potential inflammatory disease-ameliorating effects until now remained unexplored.

Here we analysed a longitudinal cohort of 609 patients SLE, a disease driven by IFN- α , evolving by successive phases of relapses and remissions affecting from 29 to 367 per 100,000 individuals in North America and Europe.[40] We show that the prevalence of anti-IFN- α antibodies is particularly elevated in this population. As expected, we confirm that this novel form of autoimmunity is associated with a greater risk to contract severe COVID-19 disease. We also highlight its association with herpes zoster. It should be emphasised that AAbs directed to human IFN- α were first observed in a patient with varicella-zoster disease,[41] but that link had been not confirmed as yet. More recently the administration of anifrolumab, a human monoclonal antibody that binds IFN-I receptor subunit, was associated with an increased incidence of herpes zoster,[42] which confirms that IFN-I blockade impairs varicella-zoster recurrences control. Unlike others [43], we did not observe reactivation of either type 1 and 2 herpes simplex virus or cytomegalovirus in patients with anti-IFN-I AAbs. We also show that IFN- α autoimmunity appears to have a beneficial effect on inflammatory disease activity.

The analysis of this cohort of patients with SLE might provide some clues regarding the mechanism underlying the development of anti-IFN-I AAbs. Overall, the results suggest that abnormally elevated IFN-I levels elicit an AAb response that eventually matures from non-neutralising to neutralising in some patients with SLE. This evolution might be predicted from our observation of two distinct clinical presentations associated with anti-IFN-I AAbs; either, (1) elevated IFN-I levels, instable SLE disease and non-neutralising anti-IFN-I AAbs, or (2) low IFN-I levels, quiescent SLE disease and neutralising anti-IFN-I AAbs. This interpretation is in line with the observation that patients treated with IFN- α or IFN- β are also prone to develop AAbs targeting these cytokines.[44-46] Future longitudinal studies will be necessary to explore the relationship between neutralisation activity and somatic hypermutation-driven molecular evolution that may underlie in vivo promotion of neutralising anti-IFN-I AAbs. Our study also has immediate implications in terms of medical management: (1) considering their prevalence in SLE, affected patients should be screened for the presence of anti-IFN-I

AAbs, (2) because the biological activity of these AAbs, is correlated with their serum concentration, their mere titration might, in most instances, inform on their clinical relevance (3) since anti-COVID-19 vaccination is well tolerated in SLE [30] and since its efficacy is not impaired by anti-IFN-I AAbs, patients with SLE carrying these AAbs should be vaccinated against COVID-19 as a priority, and (4) preventive and/or early curative antiviral treatment [47] should also be considered in cases of SARS-CoV-2 infection in patients with SLE with serum anti-IFN-I AAbs. Finally, our results have also implications regarding innovative therapeutic options that are currently being tested in SLE.[48] Because viral risk seems likely associated with the neutralisation of more than one IFN-I subtype, we would argue that anti-IFN intervention in SLE and other diseases might not concomitantly target all IFNs. Long-term placebo-controlled assessment of patients treated with anifrolumab, that interferes with all IFNs-I besides IFN- α , was recently reported.[49] A total of seven deaths were attributed to infections (4 pneumonia and 3 COVID-19) in anifrolumab-treated subjects, as compared to none in the group of patients receiving placebo [49]. The interpretation of these data should however take into account the large number of patients treated with anifrolumab, compared to those receiving placebo, as well as the fact that the observation period spanned the first year of the pandemic prior to vaccination and implementation of effective treatments for severe COVID-19. Our own study also dates back to the pre-vaccination era of the pandemic and none of the patients who developed severe or critical COVID-19 in our cohort had been vaccinated against SARS-CoV-2. The forthcoming anifrolumab safety data collected in patients vaccinated against SARS-CoV-2 should provide more important insights.

The main limitation of our study is associated with its design that was limited to a retrospective analysis of clinical data. However, there is arguably no reason to expect that clinical flares would tend to be better recorded in one group of patients or the other, characterised by the presence or absence of anti-IFN- α AAbs, because this biomarker was never recorded prior to the present study, and therefore had no impact on medical care. An additional limitation, pertaining to the estimation of viral risk, was study size. Even in a study that comprised several hundred patients affected by a rare disease, cases that present both anti-IFN- α AAbs and a history of COVID-19 constitute only a small subset. As a result, only few severe or critical COVID-19 cases were recorded, but it was nevertheless possible to establish a significative link between presence of AAbs against IFN-I and COVID-19 severity, furthermore taking into account that the majority of patients with SLE are women, often young, and therefore at lower risk of severe infection. It should also be underlined that the link between anti-IFNs-I and COVID-19 has been confirmed in different studies including a cohort of 3,595 patients

hospitalised with critical COVID-19 pneumonia.[4, 5, 50-59] Our study setup was not designed to estimate the prevalence of anti-IFN- α AAbs among patients with SLE with severe COVID-19 pneumonia. Other factors will obviously contribute to an enhanced risk of developing a severe COVID-19, as suggested by the presence of associated comorbidities in 2 out of the 5 patients with anti-IFN- α AAbs who developed a severe COVID-19 in the cohort.[60] Finally, although we report that the presence of neutralising anti-IFN- α AAbs did not interfere with the induction of vaccine-induced antibody responses, we could not analyse the effect of these AAbs on the development of SARS-CoV-2-specific T cell immunity, and this point will therefore require further study since it was recently reported that a small proportion of individuals with such AAbs might not be fully protected by the vaccine.[61] A final limitation, which is not addressed here, is associated with the genetic evolution of SARS-CoV-2 which may alter its IFN-I sensitivity.

In summary, while neutralising anti-IFN-I AAbs seem to confer increased viral susceptibility, they are also associated with reduced SLE disease activity. It is tempting to not only speculate that immunisation against IFN- α could be a consequence of elevated levels of this cytokine recurrently observed in patients with SLE with active disease, but also that neutralising anti-IFN-I autoimmunity is progressively acquired in these patients.

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Conflict of interests

AM has received grant/research support from Sobi; participated in advisory board related to lupus for AstraZeneca; received payment for expert testimony for GSK; received support for attending meetings and/or travel from AstraZeneca and GSK; received consulting fees, speaking fees and honoraria from AstraZeneca and GSK. FC has received grant/research support from AstraZeneca; participated in advisory board related to lupus for AstraZeneca, GSK, Celgene and Principabio; received speaking fees and honoraria from AstraZeneca and GSK. ZA has received grant/research support from GSK, AstraZeneca, Roche, Novartis, Amgen; participated in advisory board related to lupus for GSK, AstraZeneca, Kezar, Amgen, Otsuka; received consulting fees, speaking fees and honoraria from AstraZeneca and GSK. The other authors have no conflicts of interest to report.

1 **Table 1: Demographics, IFN-I neutralising capacities and severity of SARS-CoV-2 infection in 17 patients with SLE tested positive for**
2 **circulating serum anti-IFN- α AAbs.**
3

Pts	gender/ Age (years)	Chronic medical illness	Daily treatment			Maximal aIFN- α AAbs (ng/mL) [§]	Pre-COVID-19 anti-IFN humoral immunity [#]						Description of COVID-19 signs or symptoms	Severity*
			HCQ	Pred (mg/d)	Is		aIFN- α AAbs (ng/mL) [‡]	IFN neutralisation capacities ^{&}						
								IFN- α 10 ² pg/mL	IFN- α 10 ⁴ pg/mL	IFN- β 10 ⁴ pg/mL	IFN- ω 10 ² pg/ml	IFN- ω 10 ⁴ pg/mL		
#30	F/61	APS, CKD, Hyp, CVD	+	5	MTX BMB	49	0	-	-	-	-	-	Headache, nausea, vomiting and cough	1
#32	F/26	Ren Al	+	5	MMF TAC	108	0	-	-	+	-	-	Asymptomatic	1
#29	F/48	Ob	+	-	-	98	35	-	-	-	-	-	Myalgia and fever	1
#64	F/36	-	+	-	-	37	37	-	-	-	-	-	Anosmia, myalgia and fever	1
#42	F/46	-	+	6	-	51	51	-	-	-	-	-	Asymptomatic	1
#16	H/57	Hyp, CKD	+	-	MMF	75	55	-	-	-	-	-	Headache, myalgia and fever	1
#63	F/39	CKD	-	5	MMF	368	198	-	-	-	-	-	Asymptomatic	1
#55	F/61	-	+	-	-	241	241	-	-	-	-	-	Pneumonia ROT (NC 3L/min)	3
#52	F/41	-	-	-	-	520	260	-	-	+	-	-	Asymptomatic	1
#8	F/41	Hyp, Ren Al, Ma Tu (CR)	+	5	MMF TAC	600	600	-	-	+	-	-	Asymptomatic	1
#24	F/38	-	-	10	-	8968	625	-	-	+	+	+	Asymptomatic	1
#26	F/45	Ob, Ren Al	+	40	MMF TAC RTX	1.1x10 ⁴	763	+	-	+	+	-	ARDS (ECMO)	5
#58	F/29	CKD	+	5	MMF	3.0x10 ⁴	1060	-	-	+	+	-	Anosmia, cough, myalgia and fever	1
#3	F/54	Ow, Hyp	+	-	-	2.8x10 ⁴	1.2x10 ⁴	+	+	-	-	-	Pneumonia requiring monitoring	2
#40	F/29	Ob	+	9	-	8.8x10 ⁴	8.8x10 ⁴	+	+	-	+	+	Pneumonia ROT (HCM 12L/min)	4
#25	F/44	-	+	-	-	5.7x10 ⁵	3.2x10 ⁵	+	+	+	+	+	Pneumonia ROT (NC 5L/min)	3
#34	M/47	Thymoma (CR since 17 yrs)	+	-	-	3.2 x10 ⁶	2.3x10 ⁶	+	+	-	+	+	Pneumonia ROT (non- invasive ventilation)	4

4 [§]Corresponds to the maximum level of serum anti-IFN- α AAbs assessed by ELISA during the follow-up of SLE.

5 [#]Tested on a serum collected during the COVID-19 pandemic or the 6 months preceding its onset.

6 [‡]Assessed by ELISA.

7 [&]The capacity of the serum with anti-IFN- α AAbs to neutralise 10² pg/mL of IFN- α or - ω and 10⁴ pg/mL of IFN- α , - ω or - β were evaluated in a neutralisation assay developed in HEK293T cells using a
8 luciferase system in the presence of serum 1:10 from patients.

9 ^{*}Categorisation of COVID-19 severity (see supplemental table 1). Encoding: 1 for asymptomatic infection, mild or moderate illness; 2 for moderate hospitalised illness; 3 for severe illness; 4 for critical
10 illness and 5 for death.

11 aIFN- α AAbs, anti-interferon-alpha Autoantibodies; APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome; BMB, belimumab; CKD, chronic kidney disease; CR, complete
12 remission; CVD, chronic vascular disease; ECMO, extracorporeal membrane oxygenation; F, female; HCM, high concentration mask; HCQ, hydroxychloroquine; Hyp, Hypertension; IFN, interferon; Is,
13 immunosuppressant; M, male; Ma Tu, malignant tumor; MDBK, Madin Darby Kidney cells; MMF, mycophenolate mofetil; MTX, methotrexate; NC, nasal canula; Ob, obesity; Ow, overweight; pred,
14 prednisone; pts, patients; Ren Al, renal allograft; ROT, requiring oxygen therapy; RTX, rituximab; SLE, systemic lupus erythematosus; TAC, tacrolimus; yrs, years.

15 **Table 2. Risk of severe or critical COVID-19 pneumonia in patients with SLE, carrying**
 16 **different sets of neutralising IFN-I activities.**

	Severe /critical COVID-19			
	Neutralising	n (%)	OR [95%CI]	P value
Anti-IFN- α 2	No (n=47)	1 (2)	15.3 [2.1-190.3]	0.013
	Yes (n=16)	4 (25)		
Anti-IFN- β	No (n=51)	3 (6)	3.2 [0.5-17.0]	0.239
	Yes (n=12)	2 (17)		
Anti-IFN- ω	No (n=50)	1 (2)	21.8 [2.8-269.5]	0.005
	Yes (n=13)	4 (31)		
Anti-IFN- α 2 and anti-IFN- β	No (n=58)	3 (5)	12.2 [1.6-75.4]	0.046
	Yes (n=5)	2 (40)		
Anti-IFN- β and anti-IFN- ω	No (n=57)	3 (5)	9.0 [1.2-52.2]	0.067
	Yes (n=6)	2 (33)		
Anti-IFN- α 2 and anti-IFN- ω	No (n=58)	1 (2)	228.0 [11.2-2726]	<10 ⁻⁴
	Yes (n=5)	4 (80)		

19 Serum samples carrying anti-IFN- α AAbs as detected by ELISA were assessed for their neutralisation capacity against
 20 10² pg/mL IFN- α and IFN- ω and 10⁴ pg/mL IFN- β using a luciferase assay. Patients tested for anti-IFN-I activity
 21 more than 6 months before the onset of the COVID-19 pandemic and/or lost to follow-up on May 10 2021 were
 22 excluded from the analysis.

23 The numbers and proportion of patients with severe or critical COVID-19 pneumonia are shown for each neutralising
 24 IFN-I subgroups.

25 P values were calculated using the Fisher's exact test.

26 anti-IFN- α AAbs, anti-interferon-alpha autoantibodies; IFN, interferon; n, number of patients; SLE, systemic lupus
 27 erythematosus.

28 **Figure 1. Neutralising and non-neutralising anti-IFN- α AAbs in SLE.** **A.** IFN- α
29 neutralisation potential contained in 126 serum samples from 71 patients with SLE with anti-
30 IFN- α AAbs, measured using the MDBK antiviral activity cell assay. Each vertical bar represents
31 a serum sample. Samples are distributed along the x-axis according to the increasing serum level
32 of anti-IFN- α AAbs. Optimal cut-off point of anti-IFN- α AAb serum concentration, associated
33 with IFN- α neutralising capacity (310 ng/mL), as determined using the minimum sensitivity –
34 specificity difference and the Youden’s index is indicated (*horizontal dashed grey line*). **B.**
35 Correlation between anti-IFN- α AAbs serum concentrations and serum neutralisation titres. Each
36 dot represents an individual. Only neutralising samples were analysed (n=60). Spearman’s rank
37 correlation coefficient was used. **C.** Diagnostic performance of serum anti-IFN- α AAbs
38 measured by ELISA to predict neutralisation of 10 IU/mL (50 pg/mL) of IFN- α 2. Area under
39 receiver operating characteristics (ROC) curve (AUC) is indicated. The optimal cut-off point (red
40 arrow), determined using the minimum sensitivity – specificity difference and the Youden’s index
41 is represented. IFN, interferon; MDBK, Madin-Darby bovine kidney; SLE, systemic lupus
42 erythematosus.
43

44 **Figure 2. Anti-IFN- α AAbs and viral infections in SLE. A.** Serum anti-IFN- α AAb levels, as
45 determined by ELISA, in patients with SLE (n= 609) according to age. Indicated proportions of
46 IFN- α neutralisation activity were assessed using the MDBK cell assay. **B.** History of viral
47 infections in relation with neutralisation activity of serum anti-IFN- α AAbs. P values were
48 calculated using the Fisher's exact test. $p < 0.05$ was considered significant. *, $p < 0.05$ and ***,
49 $p < 0.001$. CIL/CIN/CC, cervical intraepithelial lesions or cervical intraepithelial neoplasia or
50 cervical cancer; IFN, interferon; SLE, systemic lupus erythematosus.
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Figure 3. SLE Disease activity and BNT162b2 vaccine immunogenicity. **A.** SLE activity assessed with the SLEDAI-2K score (left), clinical and biological markers of SLE disease activity (middle) and IFN- α serum levels (right) according to anti-IFN- α AAbs status. *Left and right*, columns represent the mean values of disease activity and IFN- α serum levels and vertical lines show positive SD. **B.** Kaplan-Meyer analysis of the risk to develop SLE flares in relation to baseline anti-IFN- α AAb status. Red, neutralising aIFN- α^+ ; blue, non-neutralising aIFN- α^+ (positivity ELISA threshold: 15 ng/mL); grey, aIFN- α^- . Vertical ticks indicate patients who remained flare-free but did not have a full year of clinical follow-up (censored data). Curves were compared using Log-Rank tests. Crude Hazard Ratios (HR) were calculated. $P < 0.05$ was considered significant. **C.** BNT162b2-vaccinated patients (two injections) evaluated at day 42 after first injection. *Left*, comparison of anti-RBD IgG serum levels measured by photonic ring immunoassay in patients with (n=9) and without (n=19) serum anti-IFN- α AAbs. Pink solid circles and empty circles represent IFN-I neutralising aIFN- α^+ and non-neutralising aIFN- α^+ patients, respectively. Median values, first and third quartiles are indicated. P values were calculated using the Mann-Whitney U test. *Right*, Serum with (n=10) or without (n=19) anti-IFN- α AAbs tested for neutralisation of D614G SARS-CoV-2 and variants B.1.1.7 (alpha), B.1.351 (beta), B.1.1.28 (gamma) and B.1.617.2 (delta). Patients were defined as “non-neutralisers” or “neutralisers” according to the absence or presence of neutralising activity at first serum dilution (1/30). The Mann-Whitney U test for continuous variables and the Fisher’s exact test for categorical variables were used for bivariable analysis. $p < 0.05$ was considered significant. *, $p < 0.05$. IFN- α AAbs, anti-interferon-alpha autoantibodies; SLE, systemic lupus erythematosus.

FIGURE 1

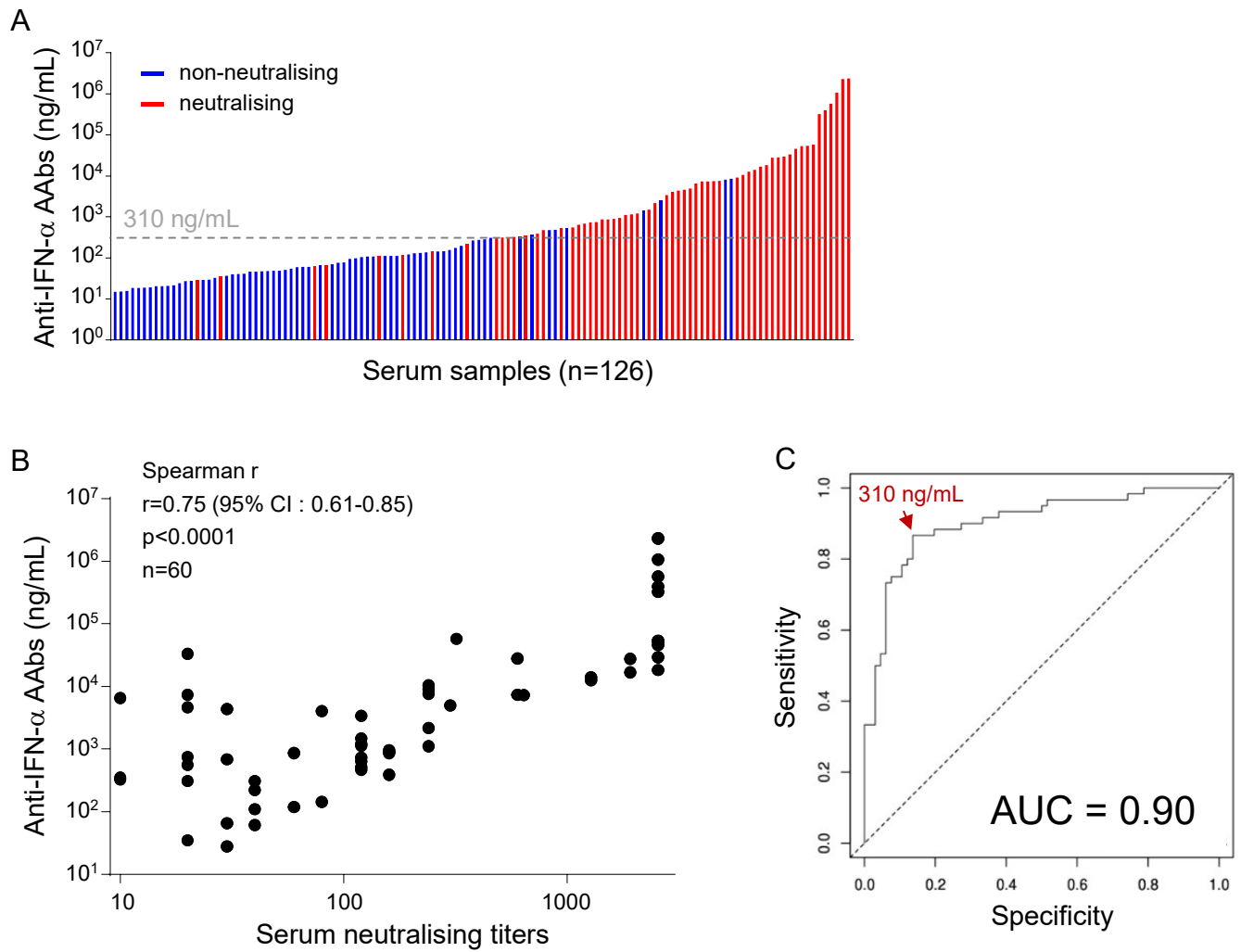


FIGURE 2

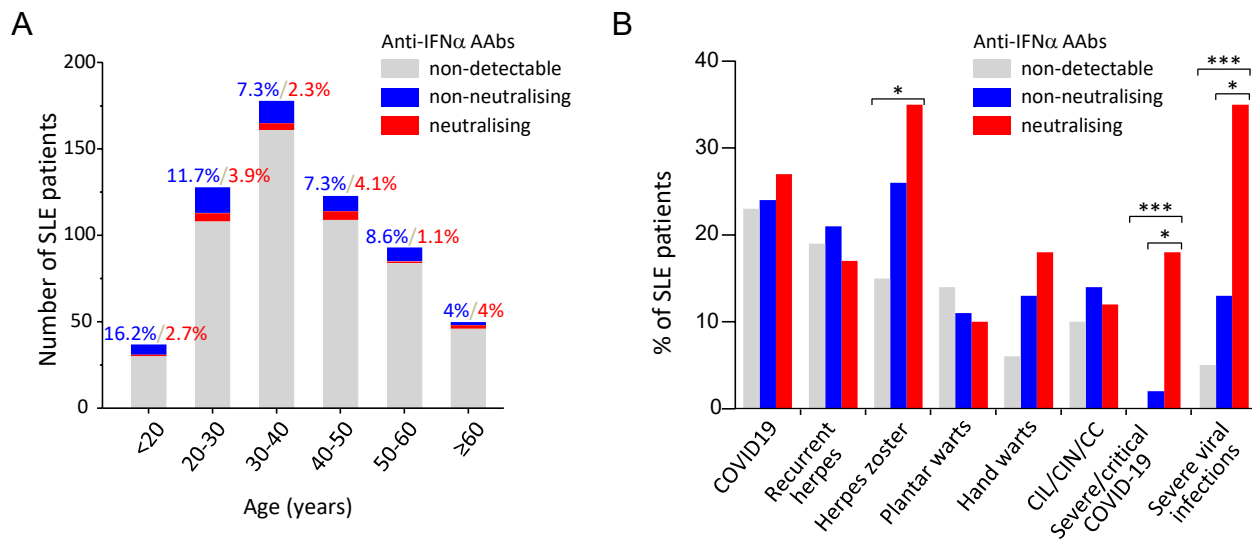
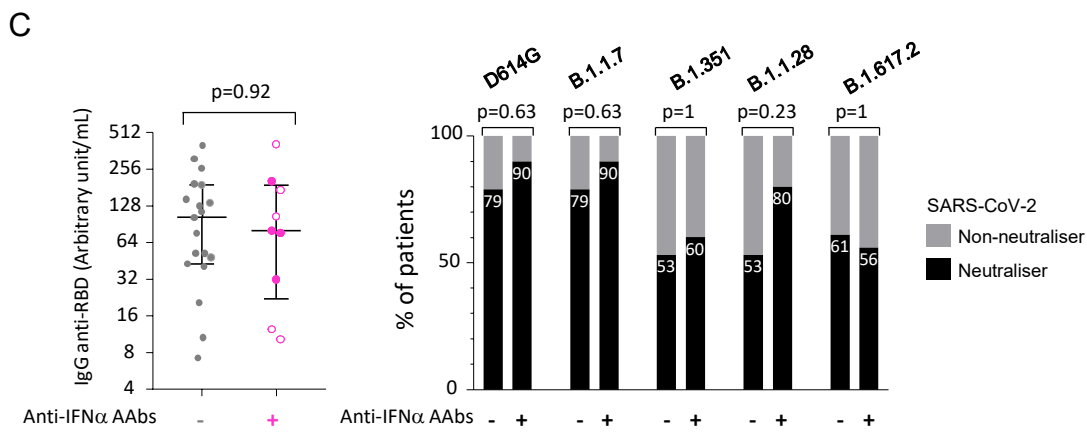
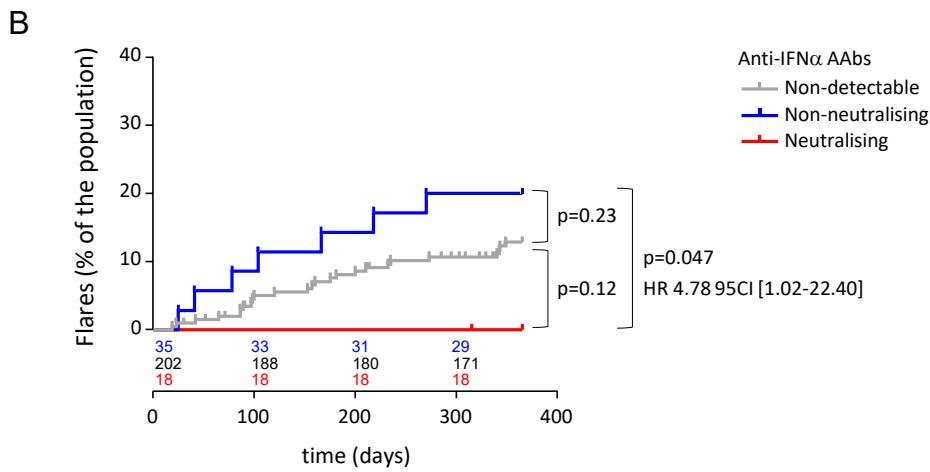
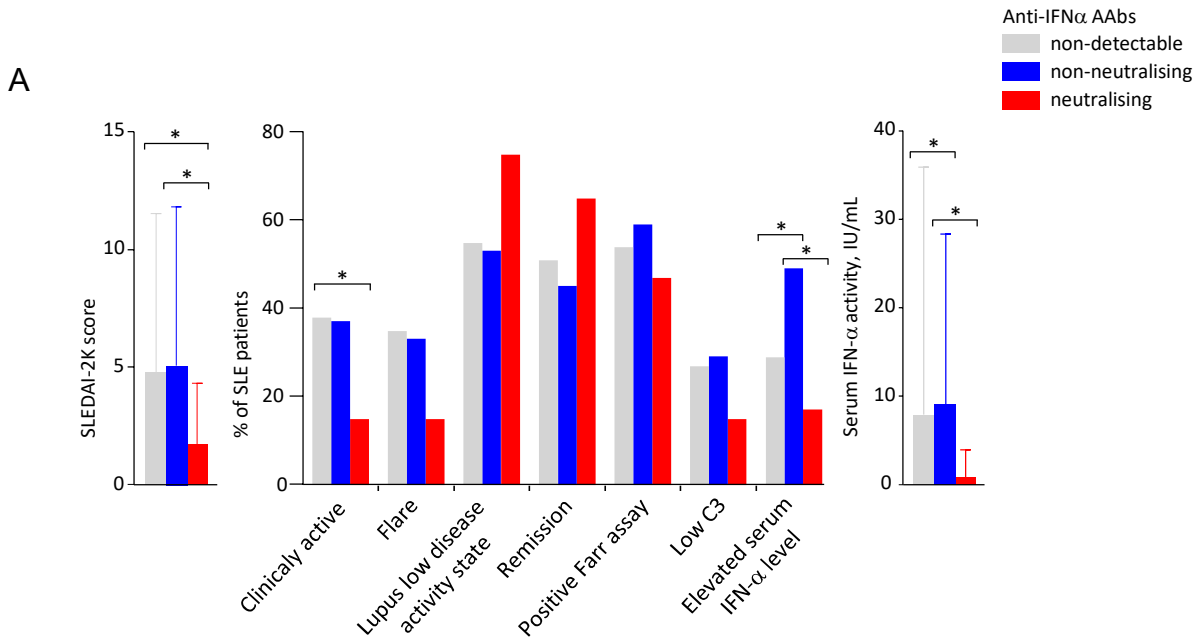


FIGURE 3



Supplemental Materials

Supplemental Patients, Materials and Methods.

Supplemental Figure 1: Kinetics of anti-IFN- α AAb levels between the first and last serum analysis.

Supplemental Table 1: Categorisation of COVID-19 severity adapted from the NIH categorial scale of severity [1] and following Bastard et al..[2]

Supplemental Table 2: Impact of anti-IFN- α AAbs on viral infectious comorbidities during the clinical course of patients with SLE.

Supplemental Table 3: Disease characteristics associated with neutralising IFN- α capacities at baseline in patients with SLE.

Supplemental Table 4: Demographics and characteristics at baseline in patients with SLE receiving the mRNA BNT162b2 vaccine

Supplemental Patients, Materials and Methods.

Study design and patients

Disease characteristics associated with anti-IFN- α AAbs in patients with SLE

Demographics, SLE clinical characteristics, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA–SLEDAI),[3-5] SLEDAI-2K,[6] routine laboratory testing and therapeutic regimen were collected from electronic medical files of the visit to the clinic recorded on the day blood was drawn (Day 0). Routine testing to determine anti-dsDNA (double stranded DNA) Ab (antibody) titres (Farr assay, Trinity Biotech; cut-off value: 9.0 IU/mL), anti-ribonucleoprotein Abs (anti-RNP, anti-Sm, anti-SSA/Ro60, anti-Ro52/TRIM21, anti-SSB [Luminex FIDIS™, Theradiag]), as well as laboratory analyses (complement C3 levels (Optilite®, Binding Site; cut-off value: 0.78g/L), complete blood counts, serum creatinine, proteinuria, leukocyturia, hematuria and IFN- α serum levels were run. Fever was defined as a body temperature above 38.5°C, weight loss as a loss of at least 5% of body weight, and cytopenia as leukopenia <3 G/L or thrombocytopenia <100 G/L. Leukopenia related to drugs or benign ethnic causes were not scored in the SLEDAI. The class of lupus nephritis was recorded according to ISN/RPS-2003.[7] Lupus flares were defined according to the SELENA-SLEDAI Flare Index.[4, 5] The term “clinical” SLEDAI (cSLEDAI) refers to symptoms, signs and routine laboratory testing and disregards only scores contributed by the presence of anti-dsDNA Abs and/or low complement.[8] According to their cSLEDAI-2K scores, patients were divided into groups with inactive (patients with a cSLEDAI-2K=0) or clinically active SLE (patients with a cSLEDAI-2K \geq 1 or suffering from clinical manifestations related to SLE, but not recorded in the SLEDAI-2K [e.g. myelitis, hepatitis...]). Remission was defined according to the DORIS,[8] following Wilhelm et al. [9] and Ugarte-Gil et al. [10] without physician global assessment (PGA) and serum C4 analysis in patients with cSELENA-SLEDAI=0 treated with prednisone 0-5mg/day (treatment with an immunosuppressant and/or hydroxychloroquine (HCQ) were allowed). Lupus low disease activity state (LLDAS) was defined as patients with a SLEDAI-2K \leq 4, with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity, without new lupus disease activity, compared with the previous assessment and with corticosteroid treatment up to 7.5 mg/day of prednisone (treatment with an immunosuppressant and/or hydroxychloroquine (HCQ) were allowed).[10, 11] In case of multiple serum samples at different dates for the same patient, only the oldest one was included and established as day 0. Basic demographic data (age and sex) were collected for all patients. Data regarding lupus disease were collected for all patients with detectable anti-IFN- α AAbs, as well as for the

randomly-selected 60% of the cohort for patients without detectable anti-IFN- α AAbs. The analysis was performed by grouping patients according to the presence of neutralising or non-neutralising anti-IFN- α AAbs at day 0, tested in an antiviral assay using MDBK cells.[12] Kinetics over time of anti-IFN- α AAb response was determined in all the available serum samples of patients who were tested positive at least once.

Impact of anti-IFN- α AAbs on the risk of lupus flare during patient follow-up

Patients in whom immunosuppressive and corticosteroid therapies were not increased at baseline, were followed for one year, starting at day 0. A lupus specialist performed physical medical examination at day 0, month 6 and 12 and recorded flares that occurred between visits or were present during examination. Between two outpatient visits (at month 3 and month 9), patients were contacted by phone, and specific questions were asked to monitor lupus flares. Patients with suspected lupus symptoms or flares were invited to call their physician and were subsequently seen for a confirmatory diagnosis. Lupus flares were defined according to the SELENA-SLEDAI Flare Index.[4, 5] Time elapsed between day 0 and the lupus flare was recorded. Patients were grouped at day 0 according to the presence of neutralising or non-neutralising anti-IFN- α AAbs, tested in an antiviral assay using MDBK cells.[12] Additionally, we performed a sensitivity analysis in which patients with an increase of immunosuppressive or corticosteroid therapy at baseline were also included.

Impact of anti-IFN- α AAbs on the risk of viral infectious comorbidities and lupus severity

In order to analyse the impact of anti-IFN- α AAbs on the risk of viral infection and disease severity in SLE, we designed a retrospective cohort analysis in which all anti-IFN- α^+ SLE patients were compared with anti-IFN- α^- patients at a 1:2 ratio. Anti-IFN- α^+ patients were defined as patients tested positive by ELISA for the presence of anti-IFN- α AAbs at least once during their follow-up, and anti-IFN- α^- patients as those who always tested negative. The absence of anti-IFN- α AAbs was verified on a sample collected between October 2019 and June 2021 (i.e., just before or during the COVID-19 pandemic). Spanning their entire medical follow-up, patients tested positive at least once for the presence of neutralising anti-IFN- α AAbs were assigned to the neutralising group. Each anti-IFN- α^+ patient was paired with two anti-IFN- α^- patients randomly selected from the cohort, matched for gender, age (\pm 5 years) and lupus duration (\pm 5 years) at the last visit. The analysis was performed by grouping patients according to the presence of neutralising or non-neutralising anti-IFN- α AAbs, tested in an antiviral assay using MDBK cells.[12]

Demographics, duration of clinical follow-up, chronic medical illness, past or present lupus nephritis, SLICC/ACR Damage Index (SDI),[13] treatment regimen and viral infectious comorbidities were recorded retrospectively by analysis of the medical records and phone contact with patients during the month of the last follow-up, arbitrarily set at April 30 2021 +/- 10 days. This date was chosen because of the progressive extension of the SARS-CoV-2 vaccine coverage of patients with SLE during the first months of 2021 in France. A severe viral infection was defined as any viral infection leading to death or hospitalisation of the patient. Herpes labialis and genitalis were defined as the occurrence of clusters of inflamed papules and vesicles on the outer surface of the mouth or genitals, usually associated with pain. Herpes zoster was defined as the occurrence of a cutaneous vesicular eruption on an erythematous base presenting along dermatome(s) and usually associated with pain. In case of a typical description, a virological confirmation was not mandatory. Recurrent herpes labialis or genitalis infections were defined as more than 2 episodes per year of herpes reactivation. History of human papillomavirus (HPV)-induced cervical lesions such as low and high grade cervical squamous intraepithelial lesions (CIL), cervical intraepithelial neoplasia (CIN) and cervical cancer (CC) were recorded and referred to as “CIL/CIN/CC”. In France, screening for cervical squamous intraepithelial lesions and cervical cancer is strongly recommended and practiced by a majority of women with SLE. The screening is performed by a Pap smear every three years in women between 25 and 29 years of age. For women aged 30 to 65, the more effective human HPV-high risk (HPV-HR) test is performed 3 years after the last cytological examination with a normal result. A new test is carried out every 5 years, until the age of 65, if the previous test result is negative. For women who had not had a Pap smear in the 3 years nor an HPV-HR test in the 5 years preceding the study, the data on cervical lesions were considered missing. SARS-CoV-2 infection was always confirmed by a SARS-CoV-2 carriage in a nasopharyngeal swab or bronchoalveolar lavage fluid, determined by real-time reverse transcription-PCR analysis and/or serological IgG test. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) was recorded according to the NIH categorial scale of severity,[1] following Bastard et al. [2] and adding a category of COVID-19 patients hospitalised due to the severity of the SARS-CoV-2 infection without the need for an oxygen support nor the transfer to an intensive care unit. The most severe condition during the course of the clinical illness was recorded. The clinical spectrum of SARS-CoV-2 infection ranged from asymptomatic infection, mild or moderate illness, moderate hospitalised illness, severe illness to critical illness and death (**Supplemental table 1**). To detect asymptomatic SARS-CoV-2 infections, patients were tested for SARS-CoV-2 antibody responses using serum samples obtained during the first semester of 2021. Patients with missing data on SARS-CoV-2

infections, i.e., in the absence of recent medical examination and/or telephone contact prior to May 10 2021 were excluded for the analysis.

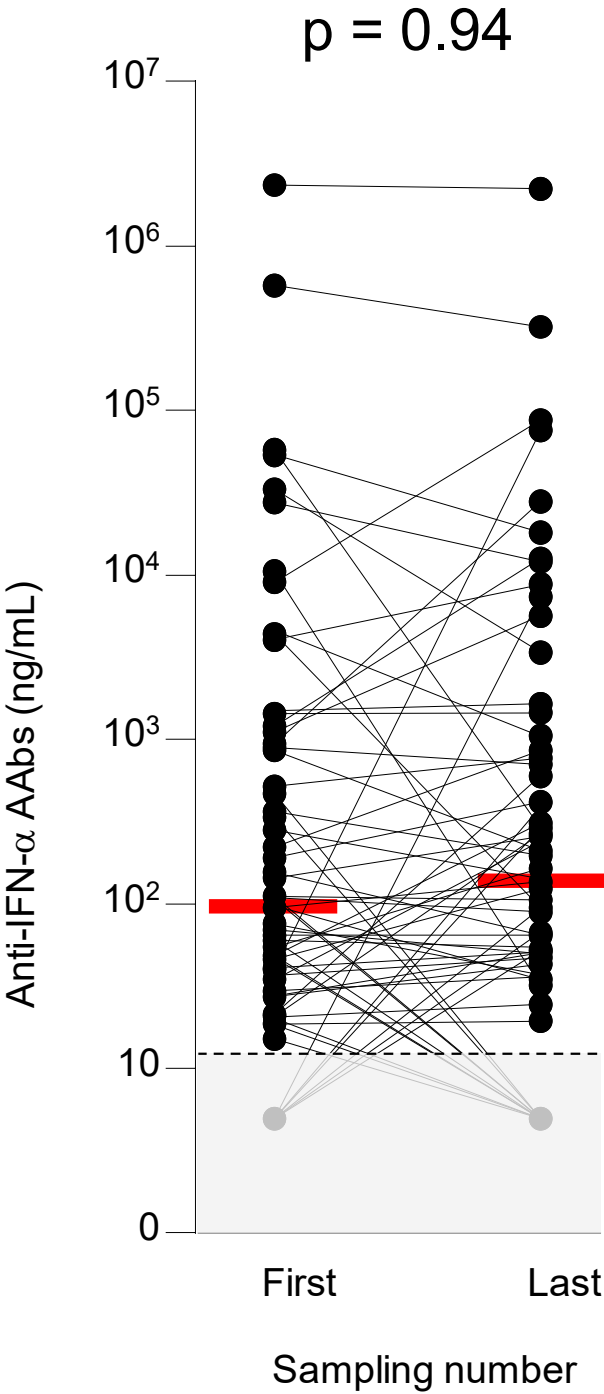
In a specific analysis, we characterised the infectious risk conferred by the different IFN-I neutralising activities. Patients included in the study on the impact of anti-IFN- α AAbs on the risk of viral infectious comorbidities were tested for serum anti-IFN- α AAbs by ELISA and anti-IFN-I activity using a luciferase assay on a serum sampled as close as possible to the COVID-19 pandemic (i.e., during the pandemic or the 6 months preceding its onset). Patients tested for anti-IFN-I activity more than 6 months before the onset of the COVID-19 pandemic and/or lost to follow-up on May 10 2021 were excluded from this comparative analysis.

Impact of anti-IFN- α AAbs on BNT162b2 vaccine-induced humoral responses in patients with SLE

In order to analyse the impact of anti-IFN- α AAbs on SARS-CoV-2 Pfizer/BioNTech (BNT162b2) vaccination, we performed a sub-analysis of the results we recently obtained in a cohort of patients with SLE, evaluating their SARS-CoV-2-specific immune responses after BNT162b2 vaccination.[14] A total of 10 patients with circulating anti-IFN- α AAbs prior to vaccination were matched (1: 2) with patients without anti-IFN- α AAbs of the same cohort, according to the following factors known or suspected to impact the humoral response against the vaccine: gender, immunosuppressive treatment, age, serum IgG level and naive B cell frequencies (if available) the day of the first vaccination. Anti-SARS-CoV-2 antibody responses against wild-type spike antigen were measured with the Maverick SARS-CoV-2 multi-antigen serology panel (Genalyte, USA), according to the manufacturer's instructions, while serum-neutralising activity was assessed against the original SARS-CoV-2 strain and variants of concerns (VOCs) at day 42 following the first vaccination.

None of the patients included in the study had previously received IFN for therapeutic purposes.

Supplemental Figure 1. Kinetics of anti-IFN- α AAb levels between the first and last serum analysis. At least two serum samples were available for 63 patients with anti-IFN- α AAbs. Median (Q1-Q3) follow-up time elapsed between first and last blood draws was 4.2 years (3.6-6.4). Serum anti-IFN- α AAb levels were assessed by ELISA. Each dot represents a patient and red lines indicate median values. Black dotted line indicates anti-IFN- α ELISA-positivity threshold (15 ng/mL). P values were calculated using the Wilcoxon matched-pairs signed rank test.



Supplemental Table 1. Categorisation of COVID-19 severity adapted from the NIH categorial scale of severity [1] and following Bastard et al.[2]

Categories	Description
<i>No COVID-19</i>	No symptoms of COVID-19, negative for antigen-, reverse transcription-PCR-based SARS-CoV-2 diagnostic tests if practiced, negative for serology-based SARS-CoV-2 diagnostic tests.
<i>Asymptomatic infection/Mild or Moderate illness</i>	Individuals with none (<i>asymptomatic</i>) or any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) without (<i>mild illness</i>) or with (<i>moderate illness</i>) evidence of lower respiratory disease (shortness of breath, dyspnea or abnormal chest imaging) who have SpO ₂ ≥94% on room air in the absence of oxygen therapy
<i>Moderate Hospitalised illness</i>	Individuals hospitalised for SARS-CoV-2 infection who have SpO ₂ ≥94% on room air [#]
<i>Severe illness</i>	Individuals hospitalised with pneumonia who have SpO ₂ <94% on room air and requiring oxygen therapy by nasal cannula ≤6L/min
<i>Critical illness</i>	Individuals hospitalised with pneumonia who have SpO ₂ <94% on room air and requiring oxygen therapy by nasal cannula > 6L/min or high concentration mask or high-flow-oxygen-therapy or non-invasive ventilation or invasive mechanical ventilation or extracorporeal membrane oxygenation or individuals hospitalised with septic shock, and/or multiple organ dysfunction.
<i>Death</i>	Death secondary to COVID-19

[#]e.g., pneumonia requiring monitoring or diarrhea requiring rehydration.

SpO₂, oxygen saturation measured by pulse oximetry; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 disease 2019, COVID-19.

Supplemental Table 2. Impact of anti-IFN- α AAbs on viral infectious comorbidities during the clinical course of patients with SLE.

	Anti-IFN- α AAbs ^a				
	Negative N=142	Positive ^b			
		Non-neutralising N=47	<i>p value</i> ^d	Neutralising ^c N=24	<i>p value</i> ^e
Women	127 (89)	42 (89)	<i>1</i>	20 (83)	<i>0.48</i>
Age, years, median (Q1-Q3)	40.2 (32.5-49.9)	40.5 (30.0-50.2)	<i>0.93</i>	42.2 (30.8-48.9)	<i>0.87</i>
Duration of clinical follow-up, years, median (Q1-Q3)	13.3 (7.3-20.3)	13.3 (7.9-17.3)	<i>0.75</i>	15.1 (9.8-21.3)	<i>0.35</i>
Geographical origins of ancestors					
European	60 (42)	19 (40)	<i>0.20</i>	9 (38)	<i>5.10⁻³</i>
West African and Caribbean	30 (21)	16 (34)		11 (46)	
North African	35 (25)	6 (13)		0 (0)	
Asian	10 (7)	5 (11)		2 (8)	
Others	7 (5)	1 (2)		2 (8)	
Chronic medical illness					
Ever smoker	26/141‡ (18)	7 (15)	<i>0.66</i>	4/18 (22)	<i>1</i>
Obesity	25/139 (18)	6/45 (13)	<i>0.65</i>	5/23 (22)	<i>0.77</i>
Diabetes	3 (2)	0 (0)	<i>0.57</i>	0/23 (0)	<i>1</i>
Malignant tumor	10 (7)	6 (13)	<i>0.23</i>	1/23 (4)	<i>1</i>
Kidney transplant	3/141 (2)	3 (6)	<i>0.17</i>	1/23 (4)	<i>0.47</i>
Lupus characteristics					
Lupus nephritis	54 (38)	19 (40)	<i>0.86</i>	8/23 (35)	<i>0.82</i>
SLICC Damage Index, median (Q1-Q3)	1 (0-2)	0.5 (0-1)	<i>0.66</i>	0 (0-1)	<i>0.24</i>
Treatment regimen at last follow-up					
HCQ	120/141 (85)	38 (81)	<i>0.50</i>	20/23 (87)	<i>1</i>
Prednisone	87/141 (62)	27 (57)	<i>0.61</i>	18/23 (78)	<i>0.16</i>
Prednisone \geq 10 mg/day	13/141 (9)	6 (13)	<i>0.57</i>	3/23 (13)	<i>0.47</i>
Prednisone, mg/d, median (Q1-Q3)	5 (0-5)	5 (0-5)	<i>0.71</i>	5 (3.5-5.5)	<i>0.13</i>
Immunosuppressive agent†	60/141 (43)	24 (51)	<i>0.32</i>	7/23 (30)	<i>0.36</i>
Infectious comorbidity					
Severe viral infection#	7 (5)	6 (13)	<i>0.09</i>	8/23 (35)	<i>10⁻⁴</i>
Hospitalised COVID-19	1/132 (1)	1/44 (2)	<i>0.44</i>	5/22 (23)	<i>2.10⁻⁴</i>
Severe or critical COVID-19	0/132 (0)	1/44 (2)	<i>0.25</i>	4/22 (18)	<i>3.10⁻⁴</i>
COVID-19	31/133 (23)	11/44 (25)	<i>0.84</i>	6/22 (27)	<i>0.79</i>
Recurrent herpes labialis or genitalis	27 (19)	10 (21)	<i>0.83</i>	4/23 (17)	<i>1</i>
Herpes Zoster	21 (15)	12 (26)	<i>0.12</i>	8/23 (35)	<i>0.03</i>
Periungual and palmar warts	9/139 (6)	6 (13)	<i>0.21</i>	4/22 (18)	<i>0.08</i>
Plantar warts	20/139 (14)	5 (11)	<i>0.63</i>	2/20 (10)	<i>0.74</i>
HPV-induced cervical lesions	12/120 (10)	6/42 (14)	<i>0.57</i>	2/17 (12)	<i>0.69</i>

Values are expressed as n (%), unless stated otherwise.

Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables were used.

Statistically significant data ($p < 0.05$) are highlighted in bold.

† Excluding antimalarials and prednisone.

‡ Positive assay/number of patients assessed.

Viral infection resulting in hospitalisation or death.

^a Anti-IFN- α AAbs were assessed using ELISA test.

^b Serum with anti-IFN- α AAbs > 15 ng/mL.

^c Serum with anti-IFN- α AAbs > 15 ng/mL displaying an IFN- α neutralising titre > 30 in the antiviral assay.

^d Estimated by comparing non-neutralising serum with anti-IFN- α AAbs negative serum.

^e Estimated by comparing neutralising serum with anti-IFN- α AAbs negative serum.

COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019; HCQ, hydroxychloroquine; HPV, Human Papillomavirus; IFN, interferon; Q1, first quartile; Q3, third quartile; SLICC, Systemic Lupus International Collaborating Clinics

Supplemental Table 3. Disease characteristics associated with neutralising IFN- α capacities at baseline in patients with SLE.

	anti-IFN- α AAbs ^a					
	Negative n=326	positive ^b		neutralising ^c n=20	p value ^e	p value ^f
		non-neutralising n=51	p value ^d			
Women	301 (92)	45 (88)	0.41	17 (85)	0.21	0.70
Age, years, median (Q1-Q3)	36.1 (29.1-37.3)	33.9 (26.1-45.6)	0.39	36.3 (28.6-43.9)	0.96	0.58
Disease duration, years, median (Q1-Q3)	7.5 (2.9-12.7)	6.1 (2.1-12.7)	0.92	10.0 (5.3-15.4)	0.18	0.26
Remission	167 (51)	23 (45)	0.45	13 (65)	0.26	0.19
Lupus low disease activity state	180 (55)	27 (53)	0.76	15 (75)	0.10	0.11
Flare	113 (35)	17 (33)	0.85	3 (15)	0.07	0.12
SLEDAI-2K score, mean (\pm SD)	4.8 (6.7)	5.1 (6.8)	0.81	1.8 (2.6)	0.04	0.05
Clinically active SLE	126 (38)	19 (37)	0.87	3 (15)	0.03	0.09
Positive Farr test	175/324 [‡] (54)	30 (59)	0.55	9/19 (47)	0.64	0.43
Low C3	85/315 (27)	15 (29)	0.74	3 (15)	0.30	0.24
Lymphocytes, G/L, median (Q1-Q3)	1.3 (0.9-1.7)	1.1 (0.7-1.4)	0.07	1.8 (1.0-2.2)	0.10	0.03
Serum IFN- α activity, IU/mL, mean (\pm SD)	7.9 (28.0)	9.1 (19.4)	0.01	1.1 (3.0)	0.20	0.01
Elevated serum IFN- α level ^g	93/317 (29)	19/39 (49)	0.02	3/18 (17)	0.30	0.04
Clinical involvement						
Fever	29 (9)	6 (12)	0.45	0 (0)	0.39	0.17
Weight loss or anorexia	18 (6)	4 (8)	0.52	2 (10)	0.33	1
Lymphadenopathy	27 (8)	2 (4)	0.40	0 (0)	0.39	1
Active cutaneous lupus	53 (16)	8 (16)	1	2 (10)	0.75	0.71
Active lupus serositis	31 (10)	1 (2)	0.11	0 (0)	0.24	1
Active lupus arthritis	69 (21)	11 (22)	1	2 (10)	0.39	0.33
Active lupus nephropathy	36 (11)	6 (12)	0.81	0 (0)	0.25	0.17
Class III or IV	20 (6)	5 (10)	0.36	0 (0)	0.62	0.31
Class V	17 (5)	1 (2)	0.49	0 (0)	0.61	1
Active neuropsychiatric lupus	10 (3)	2 (4)	0.67	0 (0)	1	1
Cytopenia	32 (10)	5 (10)	1	0 (0)	0.24	0.31
Treatment regimen						
HCQ use	275 (84)	45 (88)	0.67	16 (80)	0.54	0.45
HCQ blood concentration, ng/mL, median (Q1-Q3)	867 (184-1381)	1087 (446-1426)	0.12	671 (428-1115)	0.44	0.11
Prednisone use	177 (54)	33 (65)	0.18	15 (75)	0.10	0.57
Prednisone use, mg/d, median (Q1-Q3)	5 (0-7)	5 (0-9)	0.22	5 (4-5)	0.48	0.79
Prednisone \geq 10 mg/j	70 (21)	13 (25)	0.59	2 (10)	0.27	0.20
Immunosuppressive agent use [†]	85 (26)	19 (37)	0.13	5 (25)	1	0.41
Biological tests						
Positive anti-RNP Abs	97 (30)	24 (47)	0.02	5/18 (28)	1	0.18
Positive anti-Ro/SSA 52 Abs	84 (26)	15 (29)	0.61	4/18 (22)	1	0.76
Positive anti-Ro/SSA 60 Abs	118 (36)	22 (43)	0.35	4/18 (22)	0.31	0.16
Positive anti-La/SSB Abs	30 (9)	6/50 (12)	0.60	5/18 (28)	0.03	0.14
Positive anti-Sm Abs	44 (13)	13 (25)	0.03	1/18 (6)	0.49	0.09

Values are expressed as n (%), unless stated otherwise.

The Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables were used for bivariable analysis.

Statistically significant data are highlighted in bold.

[†]Excluding antimalarials and prednisone. Immunosuppressant therapy was mycophenolate mofetil for 48 (44%) patients, methotrexate for 38 (35%), azathioprine for 18 (17%), cyclophosphamide for 4 (4%) and rituximab for 1 (1%). One patient was receiving calcineurin inhibitor in addition to mycophenolate mofetil and four patients were receiving belimumab in addition to MTX.

[‡]Positive assay/number of patients assessed

^aAnti-IFN- α AAbs were assessed using ELISA.

^bSerum with anti-IFN- α AAbs >15 ng/mL.

^cSerum with anti-IFN- α AAbs >15 ng/mL displaying an IFN- α neutralising titre >30 in the antiviral assay.

^dEstimated by comparing non-neutralising serum with anti-IFN- α AAbs negative serum.

^eEstimated by comparing neutralising serum with anti-IFN- α AAbs negative serum.

^fEstimated by comparing non-neutralising serum with neutralising serum.

^gSerum displaying an IFN- α biological activity \geq 2 IU/mL.

AAbs, autoantibodies; Abs, antibodies; HCQ, hydroxychloroquine; IFN, interferon; RNP, ribonucleoprotein; Sm, Smith; SSA, Sjögren's-syndrome-related antigen A; SSB Sjögren's-syndrome-related antigen B; Q1, first quartile; Q3, third quartile; SD, standard deviation; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Supplemental Table 4. Demographics and characteristics at baseline in patients with SLE receiving the mRNA BNT162b2 vaccine

	Anti-IFN- α AAbs ^a		p value
	Negative n=20	Positive ^b n=10	
Women	16 (80)	8 (80)	1
Age, years, median (Q1-Q3)	43 (36-54)	42 (29-47)	0.47
Disease duration, years, median (Q1-Q3)	17 (13-30)	11 (9-20)	0.13
anti-IFN- α AAb level, ng/mL, median (Q1-Q3)	0 (0-0)	407 (182-38120)	-
Neutralising* IFN- α , - β and - ω	-	0 (0)	-
Neutralising IFN- α and - β	-	1 (10)	-
Neutralising IFN- α and - ω	-	1 (10)	-
Neutralising IFN- α only	-	2 (20)	-
Neutralising IFN- ω only	-	1 (10)	-
<i>Treatment regimen</i>			
HCQ use	17 (85)	8 (80)	1
Prednisone use	10 (50)	7 (70)	0.44
Prednisone use \geq 10mg/day	3 (15)	3 (30)	0.37
Immunosuppressive agent use [†]	12 (60)	7 (70)	0.70
COVID-19 previous to the vaccination	0 (0)	1 (10)	0.33
Received a two-dose regimen of BNT162b2	20 (100)	9 (90) [‡]	0.33

Values are expressed as n (%), unless stated otherwise.

Patients were vaccinated at baseline against SARS-CoV-2 with Pfizer/BioNTech (BNT162b2) vaccine and received the second dose at day 21–28, unless contraindicated.

The Mann-Whitney U test for continuous variables and the Fisher's exact test for categorical variables were used for bivariable analysis.

*The capacity of the serum displaying anti-IFN- α AAbs to neutralise 10^2 pg/mL of IFN- α or IFN- ω and 10^4 pg/mL of IFN- β were evaluated in a neutralisation assay developed in HEK293T cells using a luciferase system in the presence of serum 1:10 from patients,

[†]Excluding antimalarials and prednisone and including mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, belimumab and tofacitinib.

[‡]One patient contracted COVID-19 three months before vaccination and received only one dose of vaccine.

^aAnti-IFN- α serum AAbs were assessed using an ELISA test.

^bSerum with anti-IFN- α AAbs >15 ng/mL.

COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019; HCQ, hydroxychloroquine; IFN, interferon; Q1, first quartile; Q3, third quartile.

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