

## TRANSLATIONAL SCIENCE

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

Alexis Mathian <sup>1,2</sup>, Paul Breillat <sup>2</sup>, Karim Dorgham <sup>2</sup>, Paul Bastard,<sup>3,4,5,6</sup> Caroline Charre,<sup>7,8</sup> Raphael Lhote,<sup>1</sup> Paul Quentric,<sup>2</sup> Quentin Moyon,<sup>9</sup> Alice-Andrée Mariaggi,<sup>7,8</sup> Suzanne Mouries-Martin,<sup>10</sup> Clara Mellot,<sup>2</sup> François Anna,<sup>11</sup> Julien Haroche,<sup>9</sup> Fleur Cohen-Aubart,<sup>9</sup> Delphine Sterlin <sup>2,12</sup>, Noël Zahr,<sup>13</sup> Adrian Gervais,<sup>3,4</sup> Tom Le Voyer,<sup>3,4</sup> Lucy Bizien,<sup>3</sup> Quentin Amiot,<sup>12</sup> Micheline Pha,<sup>1</sup> Miguel Hié,<sup>1</sup> Francois Chasset,<sup>14</sup> Hans Yssel,<sup>2</sup> Makoto Miyara,<sup>2,12</sup> Pierre Charneau,<sup>11</sup> Pascale Ghillani-Dalbin,<sup>12</sup> Jean-Laurent Casanova,<sup>3,4,5,6,15</sup> Flore Rozenberg,<sup>7</sup> Zahir Amoura,<sup>2,9</sup> Guy Gorochov <sup>2,12</sup>

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For numbered affiliations see end of article.

**Correspondence to** Professor Guy Gorochov; [guy.gorochov@upmc.fr](mailto:guy.gorochov@upmc.fr)

AM, PB and KD contributed equally.  
ZA and GG contributed equally.

AM, PB and KD are joint first authors.  
ZA and GG are joint last authors.

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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). Autoantibodies (AABs) neutralising IFN- $\alpha$ , IFN- $\beta$  and/or IFN- $\omega$  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- $\alpha$  were quantified by ELISA and functionally assessed by abolishment of Madin-Darby bovine kidney cell protection by IFN- $\alpha$ 2 against vesicular stomatitis virus challenge. Serum-neutralising activity against IFN- $\alpha$ 2, IFN- $\beta$  and IFN- $\omega$  was also determined with a reporter luciferase activity assay. 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- $\alpha$  antibodies are present at a frequency of 3.3% and 8.4%, respectively, in individuals with SLE. AABs neutralising IFN- $\alpha$ , unlike non-neutralising AABs, are associated with reduced IFN- $\alpha$  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- $\alpha$  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.

## 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

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anti-interferon (IFN)- $\alpha$  autoantibodies (AABs) have been reported in 5%–27% of patients with systemic lupus erythematosus (SLE), it is, however, as yet unclear whether their occurrence is pathogenic, protective or a reflection of a general tendency towards autoreactivity.

### WHAT THIS STUDY ADDS

⇒ Neutralising and non-neutralising anti-IFN- $\alpha$  AABs are present at a frequency of 3.3% and 8.4%, respectively, in patients with SLE.  
⇒ AABs neutralising IFN- $\alpha$  are associated with reduced IFN- $\alpha$  serum levels and a reduced likelihood to develop active disease.  
⇒ AABs neutralising IFN- $\alpha$  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- $\alpha$  antibodies in patients with SLE can help identify patients at risk of developing serious viral infections.

with life-threatening COVID-19.<sup>1,2</sup> Autoantibodies (AABs) neutralising IFNs-I were also found in 7% and 15% of patients with severe and critical COVID-19 pneumonia, respectively.<sup>3–6</sup> They were also found in about a third of a cohort of patients with yellow fever vaccine-associated disease.<sup>7</sup> 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- $\alpha$ , is observed.<sup>8</sup> While anti-IFN- $\alpha$  AAbs have been reported in 5% to 27% of patients with SLE,<sup>9–12</sup> 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 autoreactivity. It has been suggested that endogenous anti-IFN- $\alpha$  AAbs may have a regulatory, protective, role against disease activity.<sup>10–11</sup> However, it is difficult to draw firm conclusions from these studies involving only small numbers of patients. Indeed, if the presence of anti-IFN- $\alpha$  AAbs has reportedly been associated with reduced downstream IFN pathway activity in patients with SLE, it was either not<sup>11</sup> or only weakly<sup>10</sup> associated with a decrease in disease activity. Anti-IFN- $\alpha$  antibodies were previously described in two patients with SLE with severe COVID-19,<sup>13</sup> 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<sup>14</sup> and the European Medicines Agency,<sup>15</sup> 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- $\alpha$  AAbs, infectious complications and disease evolution. We hypothesised that neutralising anti-IFN- $\alpha$  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 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.<sup>16–17</sup> 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- $\alpha$  AAbs were assessed. See online supplemental file 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- $\alpha$ AAbs

Auto-Abs against IFN- $\alpha$  were quantified using the anti-IFN- $\alpha$  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- $\alpha$ by IFN- $\alpha$ bioassay

Serum IFN- $\alpha$  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.<sup>18–21</sup> Serum IFN- $\alpha$

levels are expressed in IU/mL after comparison with IFN- $\alpha$ 2b reference (Introna, Shering Plough), standardised against the National Institutes of Health 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- $\alpha$  activity in healthy individuals is undetectable (ie, <2 IU/mL).<sup>22–23</sup>

### Functional evaluation of anti-IFN- $\alpha$ AAbs by VSV assay

The blocking activity of anti-IFN- $\alpha$  AAb-containing serum was assessed as previously described.<sup>24</sup> Neutralisation experiments were performed by the titration of serial dilutions of serum positive for anti-IFN- $\alpha$  AAbs against 10 IU/mL (50 pg/mL) of IFN- $\alpha$ 2b (Introna, Shering Plough), following the previously described antiviral assay. Serum and IFN- $\alpha$  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- $\alpha$  neutralisation capacity were previously inactivated at 56°C for 60 min to remove endogenous IFN- $\alpha$  activity. Neutralising titres correspond to the serum dilution at 50% CPE  $\times$  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- $\alpha$ 2 and IFN- $\omega$  at 10<sup>2</sup> pg/mL and 10<sup>4</sup> pg/mL, and IFN- $\beta$  at 10<sup>4</sup> pg/mL were determined with a reporter luciferase activity assay as previously described.<sup>4</sup>

### SARS-CoV-2 serological analysis

Serum levels of SARS-CoV-2-specific immunoglobulin G (IgG) antibodies were assessed using an ELISA specific for antinucleocapsid IgG (Euroimmun, France) or the Maverick SARS-CoV-2 Multi-Antigen Serology Panel (Genalyte, USA), according to the manufacturer's instructions, as previously described.<sup>25</sup> 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 293 T cells as previously described.<sup>25</sup>

### Statistical analysis

Qualitative variables are expressed as number (%) and quantitative variables as the mean  $\pm$  SD or median (quartiles), as appropriate. The Mann-Whitney U-test or Student's t test for continuous data and Fisher's exact or  $\chi^2$  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- $\alpha$  AAb levels as assessed by ELISA, to detect an IFN- $\alpha$ -neutralising capacity, was investigated by analysing receiver operating characteristic (ROC) curves, with the capacity to neutralise 10 IU/mL of IFN- $\alpha$  serving as the gold standard. The areas under the ROC curves (AUCs) to differentiate sera with IFN- $\alpha$ -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 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, V.8.0.1 software (GraphPad Software, San Diego, California), R software, V.3.6.3 and V.4.0.5 and the web tool easy ROC, V.1.3.1.<sup>26</sup>

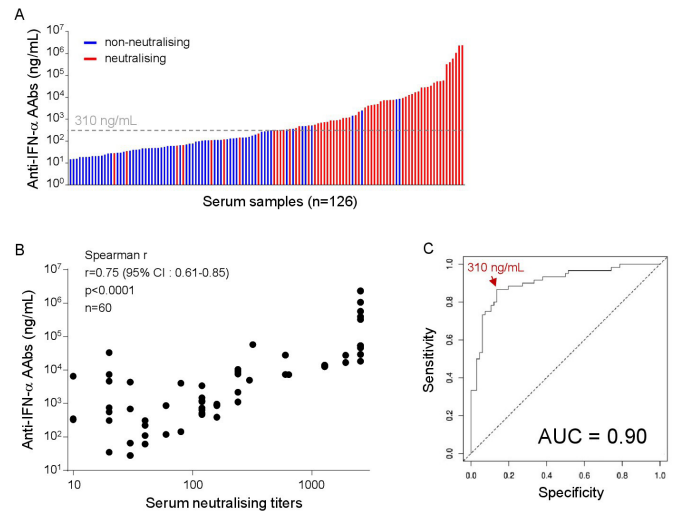
## RESULTS

### High prevalence of neutralising and non-neutralising anti-IFN- $\alpha$ AAbs in SLE

The presence of serum anti-IFN- $\alpha$  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 (IQR) time of 4.2 years (3.6–6.4) (online supplemental figure 1). There was no significant difference in terms of gender or median age between patients with ELISA-detectable anti-IFN- $\alpha$  AAbs (aIFN- $\alpha^+$ ) or not (aIFN- $\alpha^-$ ): 65 out of 71 aIFN- $\alpha^+$  patients (91.5%) versus 509 out of 538 aIFN- $\alpha^-$  patients (94.6%) were women,  $p = 0.28$  and 34.6 (26.5–46.5) years versus 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- $\alpha$  AAbs significantly abolished MDBK cell protection by IFN- $\alpha 2$  against viral challenge. Neutralisation capacity was proportional to anti-IFN- $\alpha$  AAb levels (figure 1A,B), although some rare serum samples containing high AAb levels were not endowed with neutralising activity (figure 1A). The AUC for anti-IFN- $\alpha$  AAb serum levels, differentiating between IFN- $\alpha$ -neutralising and non-neutralising sera, was 0.90 (95% CI 0.85 to 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- $\alpha$  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- $\alpha$ -neutralising AAbs are associated with increased viral risk in SLE

We next searched for comorbidities associated with the presence of anti-IFN- $\alpha$  AAbs in SLE. In order to analyse the impact of anti-IFN- $\alpha$  AAbs on the risk of viral infection in SLE, we designed a retrospective cohort study in which all patients with SLE with anti-IFN- $\alpha$  AAbs (aIFN- $\alpha^+$ ) were compared with patients without anti-IFN- $\alpha$  AAbs (aIFN- $\alpha^-$ ) at a 1:2 ratio (see online supplemental patients, materials and methods). While none of the aIFN- $\alpha^-$  patients experienced a severe COVID-19 pneumonia, five patients (7%) out of the 71 aIFN- $\alpha^+$  patients developed severe or critical COVID-19 pneumonia (table 1). The presence of anti-IFN- $\alpha$ -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



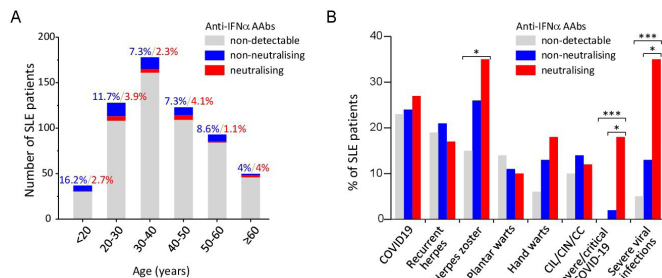
**Figure 1** Neutralising and non-neutralising anti-IFN- $\alpha$  AAbs in SLE. (A) IFN- $\alpha$  neutralisation potential contained in 126 serum samples from 71 SLE patients with anti-IFN- $\alpha$  AAbs, measured using the MDBK antiviral activity cell assay. Each vertical bar represents a serum sample.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

( $p = 3.10^{-4}$ ,  $p = 0.03$  and  $p = 10^{-4}$ , respectively, figure 2B and online supplemental table 2). Of note, the eight cases of severe viral infections in patients with anti-IFN- $\alpha$ -neutralising AAbs included five cases of COVID-19 pneumonia, two cutaneous herpes zoster and one varicella pneumonia. Importantly, patients had samples collected before SARS-CoV-2 infection, and anti-IFN- $\alpha$  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- $\alpha^+$  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.<sup>27</sup>

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

Given that in the general population, as well as in SLE patients, anti-IFN- $\alpha$  AAbs are frequently associated with the presence of antibodies against other IFNs-I, such as IFN- $\beta$  and IFN- $\omega$ ,<sup>3 4 9 11</sup> we tested whether their coexistence 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- $\alpha$ , and IFN- $\omega$  at  $10^2$  pg/mL and IFN- $\beta$  at  $10^4$  pg/mL using a luciferase assay, as previously described.<sup>4</sup> None of the 134 sera lacking detectable levels of anti-IFN- $\alpha$  AAbs was able to neutralise IFN- $\alpha 2$  or IFN- $\beta$ , and





**Figure 2** Anti-IFN- $\alpha$  AAbs and viral infections in SLE. (A) Serum anti-IFN- $\alpha$  AAb levels, as determined by ELISA, in SLE patients (n=609) according to age. Indicated proportions of IFN- $\alpha$  neutralisation activity were assessed using the MDBK cell assay. (B) History of viral infections in relation with neutralisation activity of serum anti-IFN- $\alpha$  AAbs. P values were calculated using the Fisher's exact test.  $p < 0.05$  was considered significant. \* $p < 0.05$  and \*\*\* $p < 0.001$ . CIL/CIN/CC, cervical intraepithelial lesions or cervical intraepithelial neoplasia or cervical cancer; IFN, interferon; SLE, systemic lupus erythematosus.

only 4 (3%) neutralised IFN- $\omega$ . In contrast, neutralising activities against IFN- $\alpha 2$ , IFN- $\beta$  and IFN- $\omega$  were more frequently detected (18 (25%), 12 (17%) and 15 (21%) sera, respectively) in the 71 sera with ELISA-detectable anti-IFN- $\alpha$  AAbs. A total of 30 (42%) of the 71 aIFN- $\alpha^+$  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- $\alpha$  AAbs was associated with an increasing number of IFN-I neutralising abilities. Indeed, anti-IFN- $\alpha$  AAb concentrations in serum which neutralised at least two IFNs-I (median (Q1–Q3); 5592 (837–70 175) 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- $\alpha$  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 the neutralisation of IFN- $\alpha 2$  or IFN- $\omega$  ( $p = 0.013$  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- $\omega$  subtypes ( $p < 10^{-4}$ , [table 2](#)), as recently observed in the general population.<sup>28</sup> Of note, the only patients 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.<sup>28</sup> 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- $\alpha$ -neutralising AAbs are associated with reduced SLE disease activity

We compared the clinical course of SLE in the presence or absence of anti-IFN- $\alpha$  AAbs (see online supplemental patients, materials and methods). Patients with neutralising anti-IFN- $\alpha$  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 with patients who lacked neutralising anti-IFN- $\alpha$  AAbs ([figure 3A](#)). Biological markers of SLE disease activity, such as elevated antidouble-stranded DNA Ab serum levels (ie, Farr assay), decrease in complement component C3 and increase in serum IFN- $\alpha$  levels were also reduced in patients with neutralising anti-IFN- $\alpha$  AAbs compared with patients

without ([figure 3A](#)). Other characteristics of lupus disease were similar between the two groups (online supplemental table 3). Non-neutralising anti-IFN- $\alpha$  AAbs were associated with higher IFN- $\alpha$  serum levels and the presence of anti-RNP and anti-Sm Abs. Of the 18 patients with neutralising anti-IFN- $\alpha$  AAbs in whom immunosuppressive and corticosteroid therapy were not increased, none experienced a lupus flare during the following year ([figure 3B](#)). Log-Rank test analysis showed a significantly higher risk of relapse in patients with non-neutralising anti-IFN- $\alpha$  AAbs, as compared with patients with neutralising anti-IFN- $\alpha$  AAbs (HR 4.78 (95% CI 1.02 to 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- $\alpha$  AAbs experienced a lupus flare during the following year. In summary, non-neutralising anti-IFN- $\alpha$  AAbs are more prevalent and are typically associated with both unstable disease and high IFN- $\alpha$  serum levels. In contrast, the presence of neutralising AAbs in patients with SLE was associated with a concomitant reduction in levels of serum IFN- $\alpha$  and disease activity.

### Anti-IFN- $\alpha$ 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- $\alpha$  signalling might possibly dysregulate IFN-dependent B cell responses<sup>29</sup> and limit vaccine-induced antibody production. In order to determine whether anti-IFN- $\alpha$  AAbs could interfere with COVID-19 vaccine efficacy, we performed a subanalysis of the results we recently obtained in a cohort of patients with SLE,<sup>30</sup> 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- $\alpha^+$  patients tested, whereas demographics and main bioclinical characteristics were similar in aIFN- $\alpha^+$  and aIFN- $\alpha^-$  patients (online supplemental table 4). Vaccine-induced anti-SARS-CoV-2 spike RBD IgG levels, and serum-neutralising capacity of SARS-CoV-2 and its major variants, were similar in both groups, thus confirming that aIFN- $\alpha^+$  patients are able to mount an efficacious anti-SARS-CoV-2 humoral vaccine response, similar to that of aIFN- $\alpha^-$  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- $\alpha$  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,<sup>3–7</sup> 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,<sup>9–12 31</sup> these AAbs have also been found in patients with thymoma,<sup>32</sup> myasthenia gravis<sup>33 34</sup> or affected by various primary immune deficiencies.<sup>35–39</sup> However, their potential inflammatory disease-ameliorating effects until now remained unexplored.

Here, we analysed a longitudinal cohort of 609 patients with SLE, a disease driven by IFN- $\alpha$ , evolving by successive phases of relapses and remissions affecting from 29 to 367 per 100 000 individuals in North America and Europe.<sup>40</sup> We show that the prevalence of anti-IFN- $\alpha$  antibodies is particularly

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

Pts	Gender/age (years)	Chronic medical illness	Daily treatment			Maximal aIFN- $\alpha$ AAbs (ng/mL)*	Pre-COVID-19 anti-IFN humoral immunity†						Description of COVID-19 signs or symptoms	Severity‡
			HCQ	Pred (mg/d)	Is		IFN neutralisation capacities¶							
							IFN- $\alpha$			IFN- $\omega$				
						aIFN- $\alpha$ AAbs (ng/mL)§	10 <sup>2</sup> pg/mL	10 <sup>4</sup> pg/mL	IFN- $\beta$ 10 <sup>4</sup> pg/mL	10 <sup>2</sup> pg/mL	10 <sup>4</sup> 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 3 L/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	1.1×10 <sup>4</sup>	763	+	-	+	+	-	ARDS (ECMO)	5
58	F/29	CKD	+	5	MMF	3.0×10 <sup>4</sup>	1060	-	-	+	+	-	Anosmia, cough, myalgia and fever	1
3	F/54	Ow, Hyp	+	-	-	2.8×10 <sup>4</sup>	1.2×10 <sup>4</sup>	+	+	-	-	-	Pneumonia requiring monitoring	2
40	F/29	Ob	+	9	-	8.8×10 <sup>4</sup>	8.8×10 <sup>4</sup>	+	+	-	+	+	Pneumonia ROT (HCM 12 L/min)	4
25	F/44	-	+	-	-	5.7×10 <sup>5</sup>	3.2×10 <sup>5</sup>	+	+	+	+	+	Pneumonia ROT (NC 5 L/min)	3
34	M/47	Thymoma (CR since 17 years)	+	-	-	3.2×10 <sup>6</sup>	2.3×10 <sup>6</sup>	+	+	-	+	+	Pneumonia ROT (non-invasive ventilation)	4

\*Corresponds to the maximum level of serum anti-IFN- $\alpha$  AAbs assessed by ELISA during the follow-up of SLE.

†Tested on a serum collected during the COVID-19 pandemic or the 6 months preceding its onset.

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

§Assessed by ELISA.

¶The capacity of the serum with anti-IFN- $\alpha$  AAbs to neutralise 10<sup>2</sup> pg/mL of IFN- $\alpha$  or - $\omega$  and 10<sup>4</sup> pg/mL of IFN- $\alpha$ , - $\omega$  or - $\beta$  were evaluated in a neutralisation assay developed in HEK293T cells using a luciferase system in the presence of serum 1:10 from patients.

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

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- $\alpha$  were first observed in a patient with varicella-zoster disease,<sup>41</sup> 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,<sup>42</sup> which confirms that IFN-I blockade impairs varicella-zoster recurrences control. Unlike others,<sup>43</sup> 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- $\alpha$  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

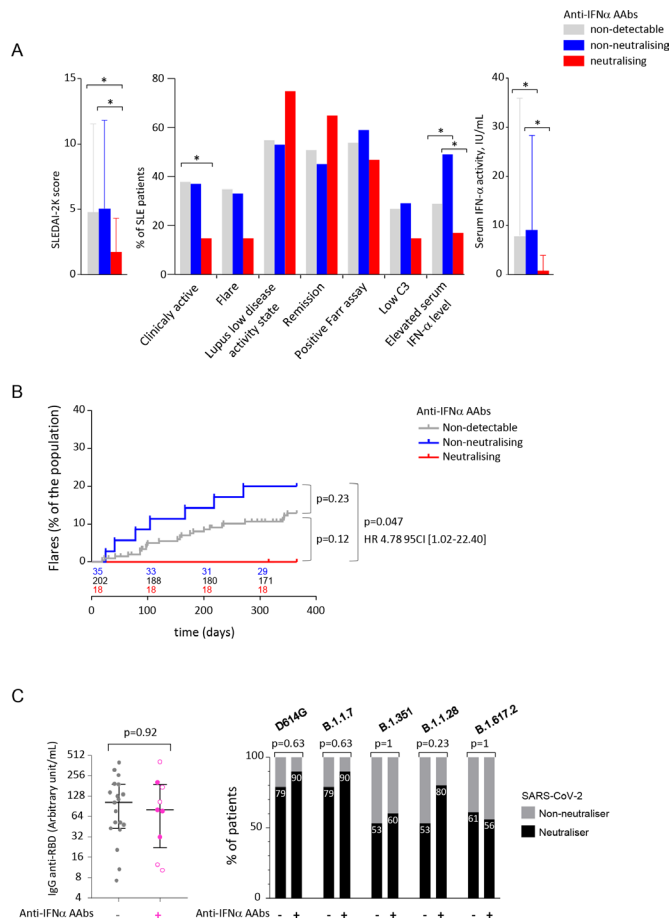
**Table 2** Risk of severe or critical COVID-19 pneumonia in patients with SLE, carrying different sets of neutralising IFN-I activities

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

Serum samples carrying anti-IFN- $\alpha$  AAbs as detected by ELISA were assessed for their neutralisation capacity against 10<sup>2</sup> pg/mL IFN- $\alpha$  and IFN- $\omega$  and 10<sup>4</sup> pg/mL IFN- $\beta$  using a luciferase assay. 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 the analysis. The numbers and proportion of patients with severe or critical COVID-19 pneumonia are shown for each neutralising IFN-I subgroups. P values were calculated using the Fisher's exact test. anti-IFN- $\alpha$  AAbs, anti-interferon-alpha autoantibodies; IFN, interferon; n, number of patients; SLE, systemic lupus erythematosus.

with the observation that patients treated with IFN- $\alpha$  or IFN- $\beta$  are also prone to develop AAbs targeting these cytokines.<sup>44-46</sup> 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<sup>30</sup> 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<sup>47</sup> 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.<sup>48</sup> 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- $\alpha$ , was recently reported.<sup>49</sup> A total of seven deaths were attributed to infections (four pneumonia and three COVID-19) in anifrolumab-treated subjects, as compared with none in the group of patients receiving placebo.<sup>49</sup> The interpretation of these data should, however, take into account the large number of patients treated with anifrolumab, compared with 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



**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- $\alpha$  serum levels (right) according to anti-IFN- $\alpha$  AAb status. *Left and right*, columns represent the mean values of disease activity and IFN- $\alpha$  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- $\alpha$  AAb status. Red, neutralising aIFN- $\alpha$ +; blue, non-neutralising aIFN- $\alpha$ + (positivity ELISA threshold: 15 ng/mL); grey, aIFN- $\alpha$ -. 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- $\alpha$  AAbs. Pink solid circles and empty circles represent IFN-I-neutralising and IFN-I-non-neutralising aIFN- $\alpha$ + 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- $\alpha$  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- $\alpha$  AAbs, anti-interferon-alpha autoantibodies; SLE, systemic lupus erythematosus.

severe COVID-19. Our own study also dates back to the prevaccination 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- $\alpha$  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- $\alpha$  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 significant 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 3595 patients hospitalised with critical COVID-19 pneumonia.<sup>45 50–59</sup> Our study setup was not designed to estimate the prevalence of anti-IFN- $\alpha$  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 two out of the five patients with anti-IFN- $\alpha$  AAbs who developed a severe COVID-19 in the cohort.<sup>60</sup> Finally, although we report that the presence of neutralising anti-IFN- $\alpha$  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.<sup>61</sup> 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- $\alpha$  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.

#### Author affiliations

<sup>1</sup>Assistance Publique–Hôpitaux de Paris (AP-HP), Groupement Hospitalier Pitié–Salpêtrière, Centre de Référence pour le Lupus, le Syndrome des anti-phospholipides et autres maladies auto-immunes rares, Service de Médecine Interne 2, Institut E3M, Paris, France

<sup>2</sup>Sorbonne Université, Inserm, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), Paris, France

<sup>3</sup>Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Inserm U1163, Necker Hospital for Sick Children, Paris, France

<sup>4</sup>University of Paris Cité, Imagine Institute, Paris, France

<sup>5</sup>St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA

<sup>6</sup>Department of Pediatrics, Necker Hospital for Sick Children, Paris, France

<sup>7</sup>Université de Paris Cité, Assistance Publique–Hôpitaux de Paris, Hôpital Cochin, Service de Virologie, Paris, France

<sup>8</sup>INSERM U1016, CNRS UMR8104, Institut Cochin, Paris, France

<sup>9</sup>Sorbonne Université, Assistance Publique–Hôpitaux de Paris (AP-HP), Groupement Hospitalier Pitié–Salpêtrière, Centre de Référence pour le Lupus, le Syndrome des anti-phospholipides et autres maladies auto-immunes rares, Service de Médecine Interne 2, Paris, France

<sup>10</sup>Centre Hospitalier Universitaire de Dijon, Hôpital François-Mitterrand, service de médecine interne et maladies systémiques (médecine interne 2), Dijon, France

<sup>11</sup>Pasteur-TheraVectys Joint Lab, Institut Pasteur, Paris, France

<sup>12</sup>Département d'Immunologie, AP-HP, Groupement Hospitalier Pitié–Salpêtrière, Paris, France

<sup>13</sup>Service de Pharmacologie, Assistance Publique–Hôpitaux de Paris, Groupement Hospitalier Pitié–Salpêtrière, Paris, France

<sup>14</sup>Sorbonne Université, Service de dermatologie et allergologie, hôpital Tenon, AP-HP, Paris, France

<sup>15</sup>Howard Hughes Medical Institute, New York, NY, USA

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#### ORCID iDs

Alexis Mathian <http://orcid.org/0000-0002-7653-6528>

Paul Breillat <http://orcid.org/0000-0003-0475-1218>

Karim Dorgham <http://orcid.org/0000-0001-9539-3203>

Delphine Sterlin <http://orcid.org/0000-0002-5993-687X>

Guy Gorochov <http://orcid.org/0000-0003-2097-9677>

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