To the Editor,

We recently reported the presence of autoantibodies (auto-Abs) against at least 14 of the 17 type I interferons (IFNs) underlying life-threatening COVID-19 pneumonia in at least 10% of a large cohort of patients [1]. Patients with inborn errors of the TLR3- and IRF7-dependent production and amplification of type I IFNs are also prone to life-threatening COVID-19 pneumonia [2]. These findings suggest that the early administration of IFN-α2 or -β, the two clinically available human type I IFNs, might be beneficial to patients with inborn errors of, or auto-Abs against type I IFN infected with SARS-CoV-2. We recently reported the safety and apparent efficacy of early administration of a single subcutaneous injection of Peg-IFN-α2a in two unrelated patients with autosomal dominant deficiencies of TLR3 and IRF3, whose genetic disorders were diagnosed before SARS-CoV-2 infection [3]. Both patients were treated in the first 7 days of SARS-CoV-2 infection and recovered without developing severe COVID-19 pneumonia.

The administration of IFN-α2 would probably be ineffective in most patients with auto-Abs against type I IFNs, which typically neutralize high concentrations of IFN-ω and the 13 individual IFN-α, including IFN-α2 in particular, in vitro1. Plasmapheresis was recently reported to decrease the titers of blood auto-Abs in hospitalized patients with critical pneumonia [4]. However, this invasive procedure cannot be proposed in the outpatient setting, before the development of severe pneumonia. A more promising option is the early administration of IFN-β, as only 2% of patients with life-threatening COVID-19 and auto-Abs against type I IFNs have auto-Abs that neutralize IFN-β in the conditions in which other type I IFNs are neutralized.

In January 2021, we were contacted by a 24-year-old woman with incontinentia pigmenti (IP), a rare X-linked dominant disorder due to heterozygous loss-of-function variants of IKBKG [5]. We have shown that some of women with IP have auto-Abs against type I IFNs [1], including this patient, who has high titers of neutralizing auto-Abs against IFN-α2 and IFN-ω, but not IFN-β (Fig. 1). The only woman with IP previously reported to have been infected with SARS-CoV-2 suffered life-threatening COVID-19 pneumonia and displayed neutralizing auto-Abs against type I IFNs [1]. This led us to screen a cohort of women with IP preemptively for the presence of auto-Abs against type I IFNs, including IFN-β. We informed those with auto-Abs against type IFNs to contact us immediately in case of SARS-CoV-2 infection.
The patient had a classical history of IP, with the different stages of cutaneous lesions, vesicular and verrucous during the neonatal period (stages 1 and 2), hyperpigmented with a linear pattern on Blaschko lines in infancy until teenagerhood (stage 3). She also presented with patchy alopecia on vertex and dental agenesis leading to dental implants. No eyes or central nervous system involvement was observed in childhood, and the patient had a good psychomotor development. The common IP deletion of exons 4 to 10 on the \( \text{IKBKG} \) gene was found in the patient. Her mother was asymptomatic and did not carry the mutation. The diagnosis of a sporadic form of IP was retained.

She was working as a nurse in a public hospital in Paris, and had not been vaccinated when she was infected with SARS-CoV-2. She contacted us on the day she fell ill and was admitted to the internal medicine unit of Cochin Hospital for clinical management.

The patient had a high fever (39.5 °C) and reported headaches, dyspnea, complete anosmia and ageusia, cough, fatigue, and diffuse myalgia. She also reported pruritus along residual IP lesions stage 3 in axillary and inguinal folds. Her physical examination was normal. Oxygen saturation was also normal. PCR on a nasal swab collected at admission confirmed COVID-19, with a high viral load of SARS-CoV-2 (Ct: 14). A pulmonary CT-scan performed on the second day of symptoms revealed no signs of pneumonia or pulmonary embolism. C-reactive protein (CRP) levels were below the threshold of detection, and a complete blood count was normal (hemoglobin, 12.3 g/dL; platelets, 224,000/mm\(^3\); neutrophil count: 1490/mm\(^3\) and lymphocyte count, 1540/mm\(^3\)).

As this patient was in the early stages of infection (day 6 after first symptom), with no radiological signs of pneumonia, biological signs of inflammation, or need for oxygen supplementation, she was prescribed three intramuscular injections of 44 μg of IFN-β1a (AVONEX), every 48 h. She developed flu-like symptoms following the first injection, which was resolved with oral paracetamol. She was discharged the following day, and the last two injections were performed by a nurse, at the patient’s home. Anosmia and ageusia were resolved within 48 h and the patient’s cough disappeared after the second injection. Ten days after the onset of symptoms, the patient was asymptomatic, except mild asthenia, with negative PCR results, and positive serological results for SARS-CoV-2 (IgG index: 6.1). She remained asymptomatic 4 weeks later.

The rationale for administering IFN-β in this patient was based on (i) her high titers of pre-existing blood auto-Abs neutralizing most individual type I IFNs, including the 13 individual IFN-α and IFN-ω; (ii) the reported development of life-threatening COVID-19 pneumonia in all known patients with these auto-Abs (i.e., the complete penetrance of critical pneumonia upon viral infection in the absence of medical intervention) [1]; (iii) the high mortality (36%) of COVID-19 in patients with auto-Abs against type I IFNs [1]; (iv) the susceptibility of control cells to SARS-CoV-2 when infected in the presence of plasma from patients with auto-Abs against type I IFNs, despite the administration of exogenous IFN-α2 [2]; (v) the known safety profile of three intramuscular injections of IFN-β1a (AVONEX).

The patient’s symptoms and signs were resolved rapidly, and she mounted an antibody response to SARS-CoV-2. Auto-Abs against type I IFNs, including IFN-β, will be monitored. Our findings suggest that three intramuscular injections of IFN-β1a in patients with auto-Abs against type I IFNs at an early stage of SARS-CoV-2 infection are both safe and effective. We will follow her clinical and antibody responses to
SARS-CoV-2. This patient is the only known individual with neutralizing auto-Abs against type I IFNs not to have developed life-threatening pneumonia on infection with SARS-CoV-2 [1]. This observation suggests that patients with auto-Abs against IFN-α and/or IFN-ω, but not against IFN-β, could benefit from early treatment with three intramuscular injections of IFN-β, or a single subcutaneous injection of Peg-IFN-β, or inhaled IFN-β [5]. Moreover, IFN-β could also be considered in specific groups, in which the prevalence of auto-Abs is high, such as men over the age of 65 years [1]. This approach might also be of benefit in selected patients with adverse reactions to yellow fever virus live attenuated vaccine due to the production of these auto-Abs, provided that the antibodies concerned do not neutralize IFN-β [6].

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Author Contribution PB discovered the autoantibodies in the patient and performed the experiments. PB, RL, SH, CB, and TAS treated the patient. JLC supervised the study. PB, RL, and JLC wrote the manuscript. All authors edited the manuscript.

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Data Availability All data and materials can be obtained by contacting the corresponding authors.

Declarations

Ethical Approval Written informed consent was obtained from the patient in the country in which they were followed, in accordance with local regulations, and the study was approved by the institutional review boards of The Rockefeller University and Institut National de la Santé et de la Recherche Médicale. Experiments were conducted in the USA and France, in accordance with local regulations and with the approval of the institutional review boards of The Rockefeller University and Institut National de la Santé et de la Recherche Médicale, respectively.

Conflict to Publish The patient consents to publish the case report.

Conflict of Interest J.L. Casanova reported a patent to application number 63/055,155, filed July 22, 2020 pending. No other disclosures were reported.

References

1. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science. 2020;370:eabd4585.
2. Zhang Q, Bastard P, Liu Z, le Pen J, Moncada-Velez M, Chen J, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science. 2020;370:eabd4570.
3. Levy R, Bastard P, Lanternier F, Lecuit M, Zhang SY, Casanova JL. IFN-alpha2a therapy in two patients with inborn errors of TLR3 and IRF3 infected with SARS-CoV-2. J Clin Immunol. 2021;41:26–7.
4. De Prost, N., Bastard, P., Arrestier, R. et al. Plasma exchange to rescue patients with autoantibodies against type I interferons and life-threatening COVID-19 pneumonia. J Clin Immunol. 2021;41: 536–544. https://doi.org/10.1007/s10875-021-00994-9.
5. Monk PD, Marsden RJ, Tear VJ, Brooks J, Batten TN, Mankowski M, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2021;9:196–206.
6. Bastard P, Michailidis E, Hoffmann HH, Chbhii M, le Voyer T, Rosain J, et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. J Exp Med. 2021:218:e20202486.

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