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CORONAVIRUS

Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs

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Life-threatening 'breakthrough' cases of critical COVID-19 are attributed to poor or waning antibody response to the SARS-CoV-2 vaccine in individuals already at risk. Pre-existing autoantibodies (auto-Abs) neutralizing type I IFNs underlie at least 15% of critical COVID-19 pneumonia cases in unvaccinated individuals; however, their contribution to hypoxemic breakthrough cases in vaccinated people remains unknown. Here, we studied a cohort of 48 individuals (age 20-86 years) who received 2 doses of an mRNA vaccine and developed a breakthrough infection with hypoxemic COVID-19 pneumonia 2 weeks to 4 months later. Antibody levels to the vaccine, neutralization of the virus, and auto-Abs to type I IFNs were measured in the plasma. Forty-two individuals had no known deficiency of B cell immunity and a normal antibody response to the vaccine. Among them, ten (24%) had auto-Abs neutralizing type I IFNs (aged 43-86 years). Eight of these ten patients had auto-Abs neutralizing both IFN- α 2 and IFN- ω , while two neutralized IFN- ω only. No patient neutralized IFN- β . Seven neutralized 10 ng/mL of type I IFNs, and three 100 pg/mL only. Seven patients neutralized SARS-CoV-2 D614G and the Delta variant (B.1.617.2) efficiently, while one patient neutralized Delta slightly less efficiently. Two of the three patients neutralizing only 100 pg/mL of type I IFNs neutralized both D614G and Delta less efficiently. Despite two mRNA vaccine inoculations and the presence of circulating antibodies capable of neutralizing SARS-CoV-2, auto-Abs neutralizing type I IFNs may underlie a significant proportion of hypoxemic COVID-19 pneumonia cases, highlighting the importance of this particularly vulnerable population.

INTRODUCTION

Since the start of the coronavirus disease 19 (COVID-19) pandemic (1), caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2), at least 6 million people have died from

COVID-19 (2). Although the majority of infected individuals recover, it remains important to identify factors that put patients at greater risk for severe disease. Age is the major epidemiological risk factor of death from pneumonia, the risk

doubling every five years of age from childhood onward (3–5). Patients with inborn errors (IE) of immunity affecting the production of, or response to type I IFNs, or both, are prone to critical COVID-19 pneumonia (6–8). These findings established the crucial role of type I IFNs in fending off SARS-CoV-2 (9). Moreover, auto-Abs neutralizing high concentrations (10 ng/mL in plasma diluted 1/10) of IFN- α 2 and/or IFN- ω were found in at least 10% of individuals with critical COVID-19 (10), an observation replicated in various regions of the world (11–21). Patients with autoimmune polyendocrine syndrome type I (APS-1) harbor these neutralizing auto-Abs from early childhood and are at high risk of life-threatening COVID-19 (20, 21). Moreover, at least 13.6% of unvaccinated patients with critical COVID-19 had auto-Abs neutralizing lower, more physiological concentrations (100 pg/mL in plasma diluted 1/10) of IFN- α 2 and/or IFN- ω , while auto-Abs neutralizing IFN- β were found in another 1% of patients (22). In more than 34,000 uninfected individuals aged 18 to 100 years, the prevalence of auto-Abs neutralizing 10 ng/mL (or 100 pg/mL) of IFN- α 2 or IFN- ω increased significantly with age, with 0.17% (1.1%) of individuals positive for these auto-Abs under 70 years old, and more than 1.4% (4.4%) positive over 70 years old, consistent with the higher risk of life-threatening COVID-19 in the elderly population (22). These auto-Abs thus precede infection and are strong determinants of critical disease, only second to age among common risk factors (23). The odds ratios (ORs) of critical disease are the highest in individuals with auto-Abs neutralizing 10 ng/mL of both IFN- α 2 and IFN- ω (OR = 67; p-value = 7.8×10^{-13}) (22, 23).

RNA vaccines are highly effective at protecting against severe COVID-19 pneumonia (24, 25). Despite their efficacy, ‘breakthrough’ cases, i.e., individuals diagnosed with SARS-CoV-2 infection despite being vaccinated with 2 doses, have been reported worldwide (26, 27). Most breakthrough cases are asymptomatic or mild (26), but in rare cases they are severe, critical, or even fatal (28, 29). It is thought that these severe or critical cases can result from a pathologically deficient (including inherited and acquired deficiencies of adaptive immunity) or a physiologically waning antibody response to the vaccine (especially in aging individuals). Incomplete protection from viral genotypes with vaccine-resilient mutations (such as Delta or Omicron), can also result in insufficient viral neutralization in vivo, in individuals otherwise at risk of hypoxemic pneumonia (for example, due to their age, sex, co-morbidity, rare or common genetic variant, or auto-Abs to type I IFNs) (30). In other words, breakthrough critical cases are thought to be due to a poor antibody response to the vaccine in at-risk individuals (31). Yet, the human genetic and immunological determinants of critical ‘breakthrough’ cases remain unclear, especially in patients with normal antibody response to the vaccine. Moreover, the biological and

clinical efficacy of RNA vaccines in patients with known genetic or immunological determinants of critical COVID-19 pneumonia, i.e., in patients with IE of, or auto-Abs to type I IFNs, is not clear. With the COVID Human Genetic Effort (CHGE, www.covidhge.com), we recruited and tested patients with breakthrough COVID-19 and hypoxemic pneumonia. We tested the double hypothesis that some of these breakthrough cases of severe or critical COVID-19 pneumonia may have a normal antibody response to the vaccine and may also harbor auto-Abs to type I IFNs.

RESULTS

Forty-two of 48 patients have normal antibody response to the vaccine

Forty-eight patients who suffered from hypoxemic COVID-19 pneumonia (severe or critical), despite having received 2 doses of mRNA vaccine, at least 2 weeks and up to 16 weeks (mean: 8 weeks) before infection were recruited from 6 countries (France, Greece, North Macedonia, Turkey, Ukraine, and United States of America). All COVID Human Genetic Effort (CHGE) patients whose samples were available were recruited; they had not been previously infected with SARS-CoV-2, as attested by the clinical information collected and/or a negative serology at the time of vaccination or performed at the onset of disease. These patients were aged 20 to 86 years (mean 53 years old) and included 34 men and 14 women. Five of them had a known deficiency of B cell immunity (immunosuppressive therapy in 3 individuals, and HIV infection in 1, and lymphoma with CAR-T cell treatment in one). We tested the 48 patients for their antibody response to SARS-CoV-2 mRNA vaccines. We found one of the 43 patients did not have a known B cell deficiency, but had an insufficient antibody response to the vaccine (defined as within 3 standard deviations from the mean of unvaccinated controls) (Arrow, Fig. 1A, S1A). The other patients had levels of antibody response to the vaccine similar to those of vaccinated controls (t-test, Supplementary Table 1). Of note, 3 of the 5 patients with a known B cell deficiency had a normal antibody response (above 3 standard deviations) (Fig. 1A). Overall, 42 patients had both no B cell deficiency and a normal antibody response to the vaccine, thus were further investigated.

Auto-Abs against type I IFNs in 10 of 42 patients with normal Ab response to the vaccine

We next tested all the samples from the 42 patients without known B cell deficiency and with a normal Ab response to the mRNA vaccine for IgG auto-Ab to type I IFN levels using a radioligand binding assay (RLBA). Seven of 42 patients tested had elevated titers of anti-IFN- α 2 auto-Abs in RLBA (Fig. 1B). We then tested all these samples for their neutralization activity against IFN- α 2, IFN- γ , and IFN- β at 10 ng/mL, 100 pg/mL, and 10 ng/mL respectively. We identified ten (24%) patients with IgG auto-Abs neutralizing IFN- α 2 and/or

IFN- ω , as did the APS-1 positive controls, while the healthy controls did not (Fig. 1C, D). Patients with neutralizing auto-Abs have lower luciferase induction (below threshold in dotted lines). All these patients had normal anti-SARS-CoV-2 Spike antibody response to the vaccine (Fig. S1D, E). In contrast, auto-Abs to type I IFN were not found in any of the 6 patients previously excluded because of a known B cell immunodeficiency (n=5) or an insufficient antibody response to the vaccine (n=1) (Fig. S1B, C). Of note, 8 of these 10 individuals (80%) had circulating auto-Abs neutralizing both IFN- α 2 and IFN- ω , while two neutralized IFN- ω only (20%), and none neutralized IFN- β (Fig. 1C-D and Table 2). In addition, plasma from 7 patients (diluted 1/10) neutralized a high concentration (10 ng/mL) of type I IFNs (70%), while 3 neutralized only the lower, more physiological, dose (100 pg/mL) of type I IFNs (including the 2 neutralizing IFN- ω only) (30%) (Fig. 1C, D and Table 2). Overall, auto-Abs neutralizing IFN- α 2 and/or IFN- ω were found at the onset of disease in 10 of 42 patients (24%) with breakthrough COVID-19 who suffered from hypoxemic pneumonia, despite having a normal antibody response to an mRNA vaccine.

Demographic, clinical, and virological features of the 10 patients with auto-Abs to type I IFNs

The patients with hypoxemic breakthrough COVID-19 pneumonia and auto-Abs neutralizing type I IFNs included three women and seven men. They were aged 43 to 86 years old (mean: 75 years old) (Table 1). All were of European ancestry, except one Cambodian, and they originated from France (n=3), Greece (n=5), and the USA (n=2). None of these individuals reported having previously suffered from other severe viral infections. All 10 patients were hospitalized during COVID-19 for oxygen supplementation, including 5 hospitalized in an intensive care unit (ICU) who received mechanical ventilation, and one who received nasal oxygen high flow therapy but was recused of ICU because of age (P8). All of them survived. All presented with bilateral COVID-19 pneumonia and had a positive SARS-CoV-2 RT-PCR in the respiratory tract. The SARS-CoV-2 variants involved were unknown but most likely to be Delta variant, given the epidemiology at the location and time of sampling (i.e., before October 2021 for all samples tested). They had been vaccinated 2 to 16 weeks prior to the diagnosis of COVID-19. Of note, one individual (P2) had at least two auto-immune conditions (myasthenia gravis and Hashimoto's thyroiditis), while another (P10) had APS-1. Myasthenia gravis and APS-1 are associated with auto-Abs to type I IFNs, which had however not been measured prior to COVID-19 in these two individuals. Finally, one individual (P1) belonged to a large family, whose members had all been fully vaccinated, and many were infected at the same time as he did (32). He was nevertheless the only one to suffer from critical disease, and also the only one to harbor neutralizing auto-Abs to type I

IFNs. None of the 10 patients died of COVID-19, while more than 20% of unvaccinated individuals who died of COVID-19 harbored neutralizing auto-Abs (22) and 5-10% of unvaccinated patients with these auto-Abs died of COVID-19 (23), suggesting that although insufficient to prevent hypoxemic pneumonia, vaccination may have protected these patients from a fatal outcome. Overall, auto-Abs to type I IFNs can underlie hypoxemic breakthrough COVID-19 infection in previously healthy individuals who developed normal antibody responses after SARS-CoV-2 mRNA vaccination.

Antibodies neutralizing SARS-CoV-2 in all 10 patients

To further test the hypothesis that the hypoxemic breakthrough cases were driven by the auto-Abs neutralizing type I IFNs and not by an insufficient antibody response to the vaccine, we assessed the neutralizing activity in all 10 patients' plasma against SARS-CoV-2. Although we did not collect blood samples prior to COVID-19 diagnosis, we collected them in the first 3 days of hospitalization. As we did not determine with which viral strain the patients had been infected, we performed the neutralization assay with pseudoviruses representing both the previously globally dominant D614G strain and the Delta variant (B.1.617.2), which was dominant when and where the patients were infected. We compared the patients' results with the neutralization titers of healthy vaccinated donors 2-8 weeks after the 2nd dose of the mRNA vaccine. All 10 individuals tested had a neutralization capacity, when compared with the healthy vaccinated controls, although it was slightly reduced for 2 individuals (P4 and P6) for the D614G strain and for 3 individuals (P1, P4 and P6) for the Delta variant (Fig. 2A, B, S1D, E). Although P1 neutralized 10 ng/mL of type I IFNs, P4 and P6 only neutralized low concentrations of type I IFNs. Specifically, P4 neutralized both IFN- α 2 and IFN- ω but only at 100 pg/mL, while P6 neutralized only IFN- ω at 100 pg/mL. This observation suggests that in patients whose auto-Abs neutralized only low concentrations of type I IFNs, sub-optimal antibody response to the vaccine may have also contributed to hypoxemic pneumonia. Overall, this suggested that hypoxemic COVID-19 pneumonia can occur in individuals with a normal antibody response to two doses of mRNA vaccine (42 of 48 patients tested). Moreover, in about 20% of the breakthrough cases (10 of 42 cases), hypoxemic pneumonia was probably due to auto-Abs neutralizing IFN- α 2 and/or IFN- ω (and typically at high concentration of both IFNs). Finally, 70% of the latter cases (7 of 10 cases), plasma neutralization of two viral strains was normal, while one had a lower neutralization against the delta strain, and the remaining 2 had a subnormal neutralization of both viral strains (D614G, and Delta).

DISCUSSION

The pathogenesis of life-threatening COVID-19 pneumonia involves two steps, with a deficiency of respiratory type I

IFN immunity in the first days of infection resulting in viral spread, which triggers excessive systemic and pulmonary inflammation (30, 33, 34). The vaccination of billions of individuals has efficiently reduced the number of critical cases. Nevertheless, breakthrough hypoxemic COVID-19 pneumonia can occur in previously healthy individuals who are vaccinated against SARS-CoV-2, which is assumed to be due to a poor antibody response to the vaccine (31). Our findings suggest that most breakthrough hypoxemic cases (42 of 48 tested) did not have a known B cell deficiency and also had a normal antibody response to the vaccine, although no samples were available before SARS-CoV-2 infection. Moreover, we showed that about 20% (10 of 42) of these breakthrough cases with normal antibody response to the vaccine also carried auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/mL for 7 patients and 100 pg/mL for 3 patients). In addition, the plasma of 7 of the 10 patients with auto-Abs to type I IFNs efficiently neutralized SARS-CoV-2 in vitro, while one had a lower neutralization against the delta strain, and plasma from the remaining 2 neutralized the two viral strains tested sub-optimally. Both patients had auto-Abs neutralizing only 100 pg/mL of type I IFNs. Plasma (diluted 1/10) from seven of the 10 individuals with these auto-Abs neutralized a high concentration (10 ng/mL) of both IFN- α 2 and IFN- ω , consistent with unvaccinated individuals carrying such auto-Abs being at the greatest risk of critical COVID-19 among individuals carrying any combinations of auto-Abs to type I IFNs (22, 23, 30). The proportion of individuals with hypoxemic COVID-19 due to neutralizing both IFN- α 2 and IFN- ω at the high dose (10 ng/mL) is even higher in the breakthrough cohort reported here (7 of 42, 16%) than in the previously described unvaccinated cohort (175 of 3,136, 7.1%) ($P = 0.015$) (22). Two of the 3 patients neutralizing only 100 pg/mL of type I IFNs, also had a slightly diminished neutralization capacity against SARS-CoV-2, suggesting in these individuals a combination of 2 factors: the presence of auto-Abs to low concentration of type I IFNs, and a suboptimal antibody response to the vaccine.

Nevertheless, as we were not able to identify and study auto-Ab positive individuals who were vaccinated and efficiently protected against severe infection, we cannot estimate the percentage of breakthrough cases with hypoxemic pneumonia in individuals with auto-Abs neutralizing type I IFNs infected with SARS-CoV-2. Until 70 years old, the proportion of individuals from the general population sampled prior to the pandemic that carry auto-Abs against both IFN- α 2 and IFN- ω is 0.02% and 0.03% for the neutralization of 10 ng/mL and 100 pg/mL, respectively, while it reaches 0.6% and 1.6% over 70 years old. As mRNA vaccines have high efficacy to prevent critical pneumonia, it is probable that most patients with auto-Abs against type I IFNs benefit from vaccination, although the protection might not be sufficient in individuals

neutralizing high concentrations of multiple type I IFNs. It is also not unreasonable to speculate that, despite an infection with a vaccine-covered viral variant and a normal antibody response to the vaccine, a small proportion of the patients with such auto-Abs might not be fully protected by the vaccine, especially if infected with a high viral inoculum. By inference from previous studies, the auto-Abs of the 8 patients neutralizing IFN- α 2 also probably neutralizes the 13 types of IFN- α (10, 20, 22, 35, 36). These findings suggest that a potent post-vaccine humoral immunity can be insufficient to fight SARS-CoV-2 infection, especially in patients with auto-Abs neutralizing both IFN- α 2 and IFN- ω , and even more so at high concentration.

Our results here suggest it may be beneficial to test for auto-Abs to type I IFN in vaccinated patients diagnosed with breakthrough COVID-19 pneumonia of varying severity. Testing uninfected people, including vaccinated individuals, may also be considered, especially in those over 70 years old given the high prevalence of auto-Abs to type I IFNs in this population (>4%) and their lower global type I IFN immunity (30, 36). One of the 10 patients suffered from APS-1 and thus most likely harbored these auto-Abs since early childhood (20, 21, 37), while another patient had myasthenia gravis, which is also commonly associated with these auto-Abs (38). Testing patients with conditions known to be associated with these auto-Abs may benefit these patients. All individuals with auto-Abs to IFNs might benefit not only from vaccine boosters but perhaps from recurrent vaccinations. Prospective studies assessing vaccine-induced immunity before infection in patients with auto-Abs to type I IFNs would be informative, for example in the setting of vaccine trials. Systematic screening at hospital admission for auto-Abs to type I IFNs would also be of help for the management of vaccinated or unvaccinated individuals with hypoxemic pneumonia. Indeed, monoclonal antibodies (mAbs) neutralizing the virus could also be administered promptly (39), as shown for an IRF9-deficient patient (40), especially in patients with the highest titers of auto-Abs to type I IFNs. Anti-viral compounds, such as remdesivir (41, 42) or molnupiravir (43), may also benefit these patients if administered early in the course of infection. Conversely, in ambulatory patients with these auto-Abs, early recombinant IFN- β therapy may also be considered, to prevent the development of hypoxemic pneumonia (44). In sum, our findings indicate that auto-Abs to type I IFNs is a susceptibility factor for a severe clinical course of COVID-19 even in vaccinated subjects with a breakthrough infection.

MATERIALS AND METHODS

Study Design

We enrolled 48 patients with proven hypoxemic COVID-19 pneumonia, 12 unvaccinated controls, and 11 vaccinated controls from 6 countries in this study. We collected plasma

or serum samples for all these individuals to test for the presence of IgG Abs against SARS-CoV-2 and auto-Abs to type I IFNs by immuno-assay. All individuals were recruited according to protocols approved by local Institutional Review Boards (IRBs).

COVID-19 classification

The severity of COVID-19 was assessed for each patient as follows (6, 10): “critical COVID-19 pneumonia” was defined as pneumonia developing in patients with critical disease, whether pulmonary, with high-flow oxygen, mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, intubation), septic shock, or with damage to any other organ requiring admission to the intensive care unit. “Severe COVID-19” was defined as pneumonia developing in patients requiring low-flow oxygen (<6L/min). The controls were individuals infected with SARS-CoV-2 (as demonstrated by a positive PCR and/or serological test and/or displaying typical symptoms, such as anosmia/ageusia after exposure to a confirmed COVID-19 case) who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia.

Statistics

For comparison of groups in Fig. 1a, a two-sided *t* test was performed using a Python library (SciPy) for both Spike and RBD. Briefly, all groups were compared to the unvaccinated control group (n=12). In addition, the group of auto-Ab positive breakthrough cases were compared to the group of auto-Ab negative breakthrough cases.

Detection of anti-cytokine auto-Abs by a high throughput automated ELISA (Gyros)

Cytokines, recombinant human (rh)IFN- α 2 (Milteny Biotec, ref. number 130-108-984) or rhIFN- ω (Merck, ref. number SRP3061), were first biotinylated with EZ-Link Sulfo-NHS-LC-Biotin (Thermo Fisher Scientific, cat. number A39257), according to the manufacturer’s instructions, with a biotin-to-protein molar ratio of 1:12. The detection reagent contained a secondary antibody Alexa Fluor 647 goat anti-human IgG (Thermo Fisher Scientific, ref. number A21445) diluted in Rexas F (Gyros Protein Technologies, ref. number P0004825; 1/500 dilution of the 2 mg/mL stock to yield a final concentration of 4 μ g/mL). Buffer PBS-T 0.01% and Gyros Wash buffer (Gyros Protein Technologies, ref. number P0020087) were prepared according to the manufacturer’s instructions. Plasma or serum samples were then diluted 1/100 in PBS-T 0.01% and tested with the Bioaffy 1000 CD (Gyros Protein Technologies, ref. number P0004253), and the Gyrolab X-Pand (Gyros Protein Technologies, ref. number P0020520). Cleaning cycles were performed in 20% ethanol.

RLBA for anti-IFN- α 2 auto-Ab detection

A DNA plasmid containing full-length cDNA sequence with a Flag-Myc tag (OriGene, #RC221091) was verified by Sanger sequencing and used as template in T7-promoter-

based in vitro transcription/translation reactions (Promega, #L1170) using [S35]-methionine (PerkinElmer, #NEG709A). IFN- α 2 protein was column-purified using NAP-5 columns (GE Healthcare, #17-0853-01); incubated with 2.5 μ l of serum, 2.5 μ l of plasma, or 1 μ l of anti-myc-positive control antibody (Cell Signaling Technology, #2272); and immunoprecipitated with Sephadex protein A/G beads (4:1 ratio; Sigma-Aldrich, #GE17-5280-02 and #GE17-0618-05) in 96-well polyvinylidene difluoride filtration plates (Corning, #EK-680860). The radioactive counts [counts per minute (cpm)] of immunoprecipitated protein were quantified using a 96-well MicroBeta TriLux liquid scintillation plate reader (PerkinElmer). Antibody index for each sample was calculated as follows: (sample cpm value - mean blank cpm value)/(positive control antibody cpm value - mean blank cpm value). For the COVID-19 patient and CCP cohorts, a positive signal was defined as greater than 6 standard deviations above the mean of pre-COVID-19 blood bank non-inflammatory controls.

Functional evaluation of anti-cytokine auto-Abs by luciferase reporter assays

The blocking activity of anti-IFN- α 2 and anti-IFN- ω auto-Abs was determined with a reporter luciferase activity. Briefly, HEK293T cells were transfected with a plasmid containing the *Firefly* luciferase gene under the control of the human *ISRE* promoter in the pGL4.45 backbone, and a plasmid constitutively expressing *Renilla* luciferase for normalization (pRL-SV40). Cells were transfected in the presence of the X-tremeGene9 transfection reagent (Sigma-Aldrich, ref. number 6365779001) for 24 hours. Cells in Dulbecco’s modified Eagle medium (DMEM, Thermo Fisher Scientific) supplemented with 2% fetal calf serum (FCS) and 10% healthy control or patient serum/plasma (after inactivation at 56°C, for 20 min) were either left unstimulated or were stimulated with IFN- α 2 (Milteny Biotec, ref. number 130-108-984), IFN- ω (Merck, ref. number SRP3061), at 10 ng/mL or 100 pg/mL, or IFN- β (Milteny Biotec, ref. number: 130-107-888) at 10 ng/mL, for 16 hours at 37°C. Each sample was tested once for each cytokine and dose. Finally, cells were lysed for 20 min at room temperature and luciferase levels were measured with the Dual-Luciferase® Reporter 1000 assay system (Promega, ref. number E1980), according to the manufacturer’s protocol. Luminescence intensity was measured with a VICTOR-X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). *Firefly* luciferase activity values were normalized against *Renilla* luciferase activity values. These values were then normalized against the median induction level for non-neutralizing samples, and expressed as a percentage. Samples were considered neutralizing if luciferase induction, normalized against *Renilla* luciferase activity, was below 15% of the median values for controls tested the same day.

SARS-CoV-2 serological studies

Serum collection

Control serum was collected under informed consent from healthy recipients of BNT162b2 vaccine (vaccines based on the Wuhan spike protein -S protein- sequence), which were confirmed to have no prior SARS-CoV-2 infection by anti-SARS-CoV-2 nucleocapsid (N protein) IgG assay (45). All serum samples were heat inactivated at 56°C for 30 min prior to neutralization experiments.

Luminex Assay

Luminex immunoassays for SARS-CoV-2 serology studies were performed as previously described using proteins from the Wuhan strain of the virus (46). Briefly, whole N protein, trimeric Spike ectodomain (residues 1-1213) and receptor binding domain (residues 328-533, all generously provided by Dr. John Pak, Chan Zuckerberg Biohub) were each conjugated to a unique spectrally encoded bead using manufacturer instructions (Luminex Antibody Coupling Kit, #40-50016) with 5 µg of protein per 1 million beads. All beads were blocked overnight before use in PBST supplemented with 0.1% BSA and pooled on day of use. 2000-2500 beads per ID were pooled per replicate. Patient serum or plasma was incubated with beads at a final dilution of 1:250 for 1 hour, washed twice in PBST, stained with an anti-IgG (human) pre-conjugated to phycoerythrin (Thermo Scientific, #12-4998-82) for 30 min at 1:2000, then washed thrice in PBST. Primary incubations were done in PBST supplemented with 2% non-fat milk and secondary incubations were done in PBST. Beads were processed in duplicate in 96 well format and analyzed on a Luminex LX 200 cytometer. Median Fluorescence Intensity from each set of beads within each bead ID were retrieved directly from the LX200 after normalizing to the intra-assay negative controls (Bovine Serum Albumin (BSA) conjugated beads).

Pseudovirus production

SARS-CoV-2 pseudoviruses were generated using a previously described recombinant vesicular stomatitis virus expressing GFP in place of the VSV glycoprotein (rVSV★G-GFP) (47). The SARS-CoV-2 spike gene bearing the D614G mutation or the set of mutations in the B.1.617.2/Delta variant (T19R, T95I, G142D, ★157-158, L452R, T478K, P681R, D614G, D950N) were cloned in a CMV-driven expression vector and used to produce SARS-CoV-2 spike reporter pseudoviruses. Pseudoviruses were titered on Huh7.5.1 cells overexpressing ACE2 and Transmembrane protease, serine 2 (TMPRSS2) (gift of Andreas Puschnik) using GFP expression to measure the concentration of focus forming units (ffu).

Pseudovirus neutralization experiments

Huh7.5.1-ACE2-TMPRSS2 cells were seeded in 96-well plates at a density of 7000 cells/well one day prior to pseudovirus inoculation. Cells were verified to be free of mycoplasma contamination with the MycoAlert Mycoplasma detection kit (Lonza). Serum samples were diluted into complete culture media (DMEM with 10% FBS, 10mM HEPES, 1x

Pen-Strep-Glutamine) using the LabCyte Echo 525 liquid handler and 1500 ffu of SARS-CoV-2 pseudovirus was added to each well to reach final dilutions ranging from 1:20-1:10240, including no-serum and no-pseudovirus controls. Serum/pseudovirus mixtures were incubated at 37°C for 1h before being added directly to cells. Cells inoculated with serum/pseudovirus mixtures were incubated at 37°C and 5% CO₂ for 24h, resuspended using 10x TrypLE Select (Gibco), and cell fluorescence was measured with the BD Celesta flow cytometer. All neutralization assays were repeated for a total of three independent experiments with each experiment containing two technical replicates for each condition. Flow cytometry data was analyzed with FlowJo to determine the percentage of cells transduced with pseudovirus (GFP-positive). Percent neutralization for each serum dilution was calculated by normalizing GFP-positive cell percentage to no-serum control wells. Fifty percent neutralization titers (NT₅₀) were calculated from ten-point response curves generated in GraphPad Prism 7 using four-parameter logistic regression.

SUPPLEMENTARY MATERIALS

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Materials and Methods

Fig. S1

Table S1

Data file S1

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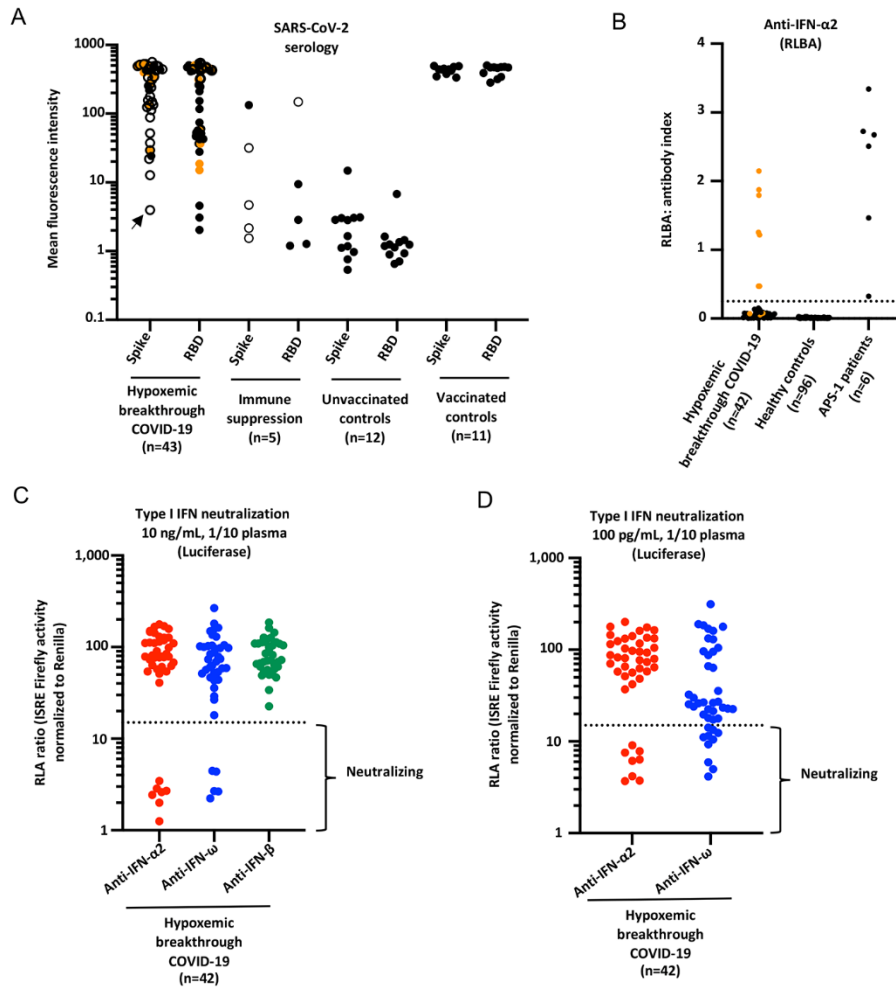


Fig. 1. Neutralizing auto-antibodies (Abs) against IFN- α 2 and IFN- ω in patients with hypoxemic breakthrough COVID-19 despite a normal serological response to SARS-CoV-2 mRNA vaccine. (A) SARS-CoV-2 serology against spike(S)-protein and receptor binding domain (RBD) in hypoxemic breakthrough COVID-19 (N=43), patients with immune suppression (n=5), unvaccinated controls (N=12), and vaccinated and uninfected healthy controls (n=11). Mean fluorescence intensity is shown. The orange dots correspond to the 10 individuals with auto-Abs neutralizing type I IFNs. Empty circles represent either Spike or RBD serology, to outline the highest value for one patient. The arrow represents the patient without B cell deficiency but with an insufficient Ab response to the virus. **(B)** Radioligand binding assay (RLBA) results for auto-Abs against IFN- α 2 in patients with hypoxemic breakthrough COVID-19 pneumonia without immune suppression or low Ab response to the vaccine (N=42), uninfected controls (N=96), and uninfected APS-1 patients (N=6). **(C)** Neutralization of 10 ng/mL IFN- α 2, IFN- ω or IFN- β in the presence of plasma 1/10 from patients with hypoxemic breakthrough COVID-19 pneumonia with a good Ab response to the vaccine (N=42). Relative luciferase activity is shown (ISRE dual luciferase activity, with normalization against *Renilla* luciferase activity) after stimulation with 10 ng/mL IFN- α 2 or IFN- ω in the presence of plasma 1/10. RLA: relative luciferase activity. **(D)** Neutralization of 100 pg/mL IFN- α 2 or IFN- ω in the presence of plasma 1/10 from patients with hypoxemic breakthrough COVID-19 pneumonia with a good Ab response to the vaccine (N=42).

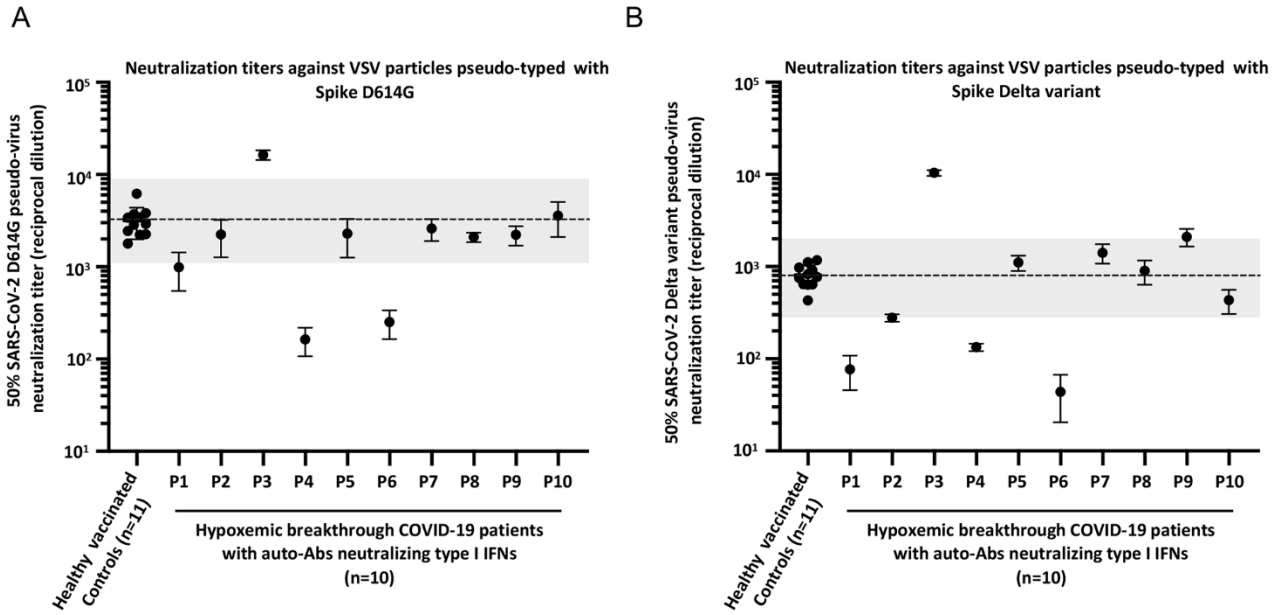


Fig. 2. Neutralization titers against SARS-CoV-2 in the patients with auto-Abs against type I IFNs. Neutralization titers against SARS-CoV-2 for healthy vaccinated donors 2-8 weeks after the second dose of mRNA vaccine (n=11), and patients with hypoxemic breakthrough COVID-19 pneumonia and auto-Abs to type I IFNs (n=10). The dashed line shows the geometric mean of healthy donor titers, the box shows interquartile range, and the shaded region is the full range. **(A)** Neutralization assay performed with pseudoviruses representing the D614G strain, and **(B)** the Delta variant (B.1.617.2).

Table 1. Clinical and demographic information of the 10 patients with hypoxemic breakthrough COVID-19 infection and auto-Abs neutralizing type I IFNs. HTN: hypertension, AF: atrial fibrillation. APS-1: auto-immune polyendocrine syndrome type 1.

Patient	Origin	Residence	Sex	Age	Comorbidities	Vaccine source	Doses number	Time of disease post vaccination (weeks)	ICU	Classification	Outcome
P1	American	USA	M	80	Diabetes, asthma	Pfizer	2	2	Yes	Critical	Alive
P2	Greek	Greece	F	82	HTN, myasthenia gravis, hashimoto, dyslipidemia	Pfizer	2	4	Yes	Critical	Alive
P3	Greek	Greece	M	73	HTN, diabetes, dyslipidemia, glaucome	Pfizer	2	2	Yes	Critical	Alive
P4	Greek	Greece	M	86	HTN, diabetes, dyslipidemia, AF, benign prostate hyperplasia, parkinson	Pfizer	2	12	Yes	Critical	Alive
P5	Greek	Greece	M	73	Diabetes, coronary heart disease	Pfizer	2	3	No	Severe	Alive
P6	Greek	Greece	F	77	HTN, diabetes, dyslipidemia	Pfizer	2	16	No	Severe	Alive
P7	Cambodian	France	M	71	HTN	Pfizer	2	15	Yes	Critical	Alive
P8	French	France	F	86	NA	Pfizer	2	6	No	Critical	Alive
P9	American	USA	M	80	NA	Pfizer	2	2	No	Critical	Alive
P10	French	France	M	43	APS-1	Pfizer	2	2	No	Severe	Alive

Table 2. Auto-Abs neutralized in the 10 patients. 1: neutralizing. 0: non-neutralizing.

Patient	anti-IFN- α 2 auto-Abs (10 ng/mL)	anti-IFN- β auto-Abs (10 ng/mL)	anti-IFN- ω , auto-Abs (10 ng/mL)	anti-IFN- α 2 auto-Abs (100 pg/mL)	anti-IFN- ω , auto-Abs (100 pg/mL)
P1	1	0	1	1	1
P2	1	0	0	1	1
P3	1	0	0	1	1
P4	0	0	0	0	1
P5	1	0	1	1	1
P6	0	0	0	1	1
P7	0	0	0	0	1
P8	1	0	1	1	1
P9	1	0	1	1	1
P10	1	0	1	1	1

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