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LETTER TO EDITOR

Post-SARS-CoV-2 Vaccine Monitoring of Disease Flares in Autoinflammatory Diseases

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To the Editor:

SARS-CoV-2 infection is responsible for more than 800,000 deaths in the USA (https://coronavirus.jhu.edu/data/mortality). Patients with autoinflammatory diseases caused by innate immune dysregulation may be at higher risk of developing complications from SARS-CoV-2 infections or vaccinations. Furthermore, fear of disease complications with a SARS-CoV-2 infection and/or vaccination often leads to extensive measures to avoid exposure. The FDA-authorized vaccines (Pfizer-BioNTech/Comirnaty, Moderna, and Johnson & Johnson) are effective against severe disease, and reduce hospitalizations and death caused by COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html). The FDA authorized most vaccines for children older than twelve and the Pfizer vaccine for children older than five.

In our autoinflammatory diseases cohort, ten patients reported COVID infections between January and November 2021. All developed respiratory symptoms had a positive nasal swab ($n=6$) or a positive anti-N SARS-CoV-2 antibody titer ($n=4$) (Supplementary Table 1). One had IL-18-mediated disease, two had neonatal-onset multisystem inflammatory disease (NOMID), an IL-1-mediated disease, and seven had type I interferon–mediated diseases (IFNopathy); of those, two had SAVI (STING-associated vasculopathy with onset in infancy), four had CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) or PRAAS (proteasome-associated autoinflammatory syndrome), and one had SAMD9L-associated autoinflammatory disease (SAAD). The patient with SAAD and interstitial lung disease was treated with the JAK inhibitor, baricitinib, developed severe pneumonia and a systemic inflammatory response syndrome, and required mechanical ventilation for 8 days; he received glucocorticosteroids and one dose of tocilizumab with appropriate response and was discharged. All other patients ($n=9$) had mild disease and did not require hospitalization.

As the vaccines became available, patients and providers reached out with two main questions: would the vaccine trigger a flare of the autoinflammatory condition, and does vaccination lead to protective antibody responses given that patients are on immunomodulatory treatments.

Patients with autoinflammatory diseases can develop disease flares following routine vaccinations [1, 2]. We, therefore, offered to monitor post-vaccine responses in patients enrolled in our natural history protocol (NCT02974595) who asked for guidance. Thirty patients received SARS-CoV-2 vaccines (NOMID ($n=12$), CANDLE/PRAAS ($n=5$), SAVI ($n=6$), *TREX1* mutation interferonopathy ($n=1$) and SAAD ($n=1$), and IL-18-mediated diseases ($n=5$)). Of the thirty patients, nineteen received Pfizer (63%), ten received Moderna (33%), and one (3%) the Johnson & Johnson vaccine (Fig. 1a). At the time of vaccination, their autoinflammatory disease was either stable ($n=6$, 20%) or in remission ($n=24$, 80%).

Post-vaccination signs and symptoms and symptoms of possible disease flares were recorded for all thirty patients. In twelve patients and two healthy controls, we monitored clinical biomarker changes (CBC and acute phase reactants); in seven patients and three healthy controls, we also monitored type I Interferon (IFN) response gene signature changes [3] at baseline and post-mRNA-based COVID vaccine on days two, four, and six after the vaccines or until the scores returned to baseline (Supplementary Table 2).

Overall, the patients tolerated the SARS-CoV-2 vaccines well. No patient developed disease flares requiring hospitalization. The most common symptoms following vaccination were arm pain ($n=18$), body ache ($n=7$), and headaches ($n=5$) that patients managed by taking as-needed

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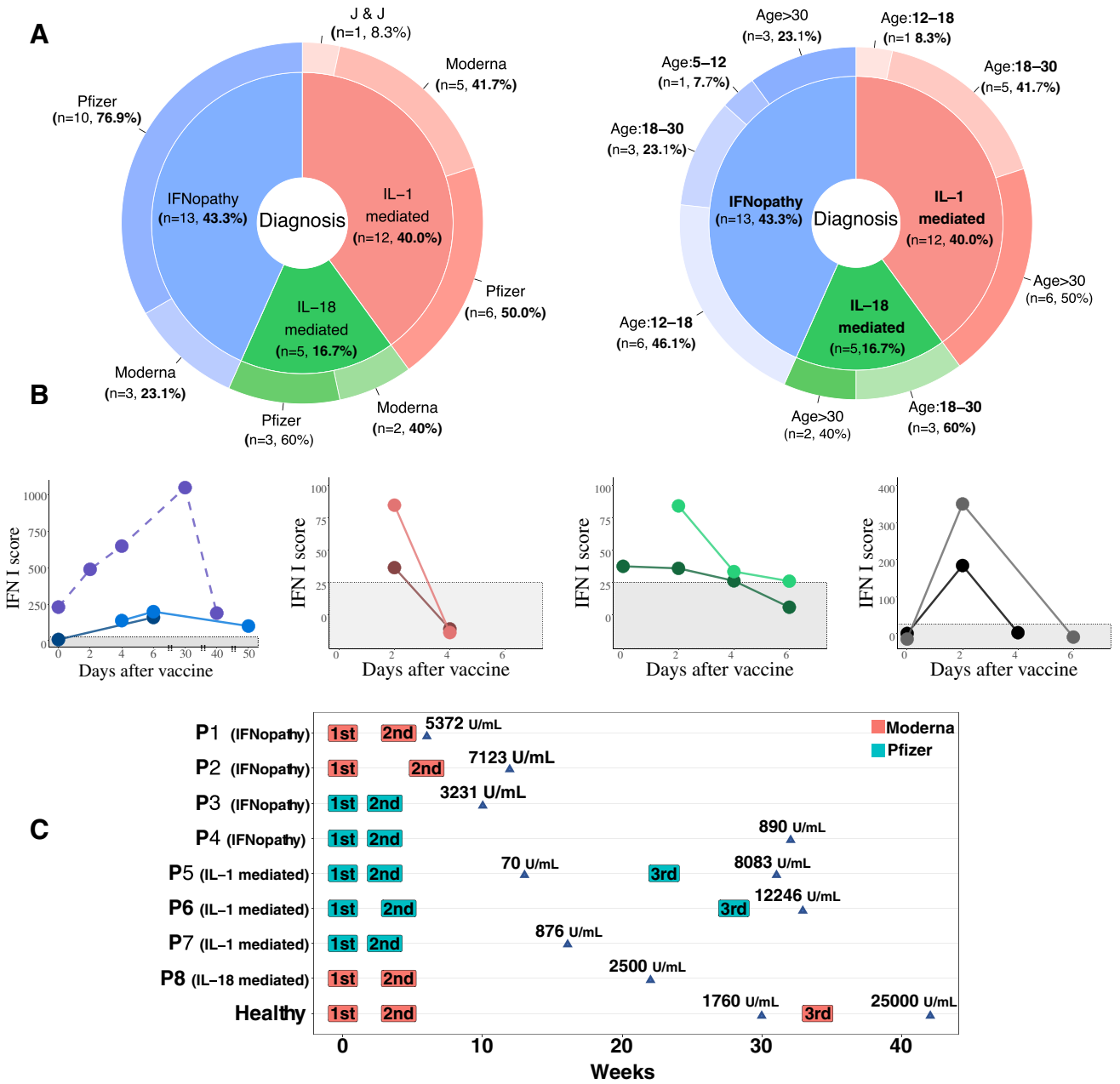

Fig. 1 **a** Thirty patients in our cohort received the COVID-19 vaccines. The cohort comprises the IL-1-mediated diseases ($n=12$, red), IL-18-mediated disease ($n=5$, green), and interferonopathies ($n=13$, blue). All but one received mRNA-based vaccines (Pfizer = 19, Moderna = 10, Johnson and Johnson = 1). **b** Interferon scores were obtained in seven patients with the first vaccine dose (dark shade circles), and representative observations were depicted on four patients (IL-1-mediated disease, NOMID, red circles ($n=1$), IL-18-mediated disease, green circles ($n=1$), and interferonopathies blue and purple circles ($n=2$) and in one healthy control (black circles). For three patients and the healthy control, the IFN score is also shown for the second vaccine dose (lighter shade). The normal IFN score is < 25.2 (gray-shaded area in each graph). The y-axis is adjusted to visualize the change in score. (Data on all patients and controls is described in the text). **c** Post-vaccine anti-S antibody levels (Diagnostics Roche) were assessed in eight patients and one healthy control. Two patients (patient 5 and patient 7) had antibody titers below 1000 U/mL. Patient 5 with NOMID (IL-1-mediated disease) and inflammatory bowel disease is on combination treatment with the IL-1 blocker anakinra and the TNF-a blocker, infliximab

Tylenol or non-steroidal anti-inflammatory drugs (NSAIDs). Two patients with NOMID reported worsening of chronic headaches following the second dose of mRNA-based vaccination. Both had elevated C-reactive protein (CRP) and neutrophil counts following the vaccine. In both cases, we increased the dose of IL-1 inhibitor treatment by 0.5 mg/kg per day, and the headache improved to baseline after 10 to 14 days post-vaccination.

Post-vaccine, all twelve patients assessed increased their CRP consistent with a temporary increase in the systemic inflammatory response (Supplementary Fig. 1). Of those, five (four out of five NOMID patients and one out of three patients with an IL-18-mediated disease) had responses exceeding the upper limit of normal (CRP > 5 mg/L). This was similar to inflammatory responses in two healthy controls. We measured the interferon-response gene signature in seven patients to assess whether patients with interferonopathies and a genetic predisposition of increased IFN signaling mount an increased or prolonged IFN response post-vaccine. An increased type I IFN signature (normal value < 25.2) [3] was seen within 2 to 3 days post-mRNA-based vaccine in all seven patients assessed (IL-1-mediated disease ($n = 1$), IL-18-mediated disease ($n = 2$), and IFNopathy ($n = 4$)). The rise in the IFN signature was also observed in three healthy controls. It peaked on day two post-vaccine and normalized by day four. The heightened IFN-response gene signature had returned to baseline in four of seven patients (NOMID ($n = 1$), interferonopathies ($n = 2$), IL-18-mediated ($n = 1$)). Two interferonopathy patients, one with CANDLE and one with SAVI, who both had elevated IFN scores at baseline, showed rises in the IFN score that peaked later, on days six and thirty, and returned to baseline after 50 and 40 days, respectively (Fig. 1b). The IFN score also remained mildly elevated in a patient with an IL-18-mediated disease. The IFN score increases were higher with the second vaccine dose (assessed in three patients and one healthy control), but the response patterns were similar to those observed after the first dose (Fig. 2b, lighter-shaded circles). One patient with mild SAVI and one with an IL-18-mediated disease had normal IFN scores at baseline; both had an increase in the IFN score after their first vaccine dose, which dropped to normal levels by day four (Fig. 1b). Among all three patients with IL-18-mediated macrophage activation syndrome (MAS), the ferritin level was moderately increased shortly following the vaccine in one patient but decreased to baseline within a few days.

Lastly, to address the protective antibody titer development post-vaccine, we measured blood anti-S SARS-CoV-2 antibody levels in 8 patients. Overall, antibody titers tended to be higher after the Moderna vaccine. One patient with NOMID and inflammatory bowel disease on anakinra (300 mg daily) and infliximab (300 mg every 6 weeks) had the lowest level of anti-S antibody of only 70 U/mL, 72 days after two doses of an mRNA-based vaccine. After receiving the booster, his antibody level increased to 8083 U/mL. One patient with SAVI, one with CANDLE, and one with heterozygous *TREX1* mutation interferonopathy, all on treatment with baricitinib, had anti-S-antibody levels of 7123 U/mL, 5271 U/mL, and 3231 U/mL, respectively. One patient with NOMID had an anti-S antibody level of 12,246 U/mL after receiving the booster (Fig. 1c).

In summary, we advise patients with autoinflammatory diseases to follow general guidelines for disease prevention and encourage them to receive the COVID-19 vaccines. Our observations suggest a measured and individualized approach to monitoring and managing post-vaccine increases in inflammatory markers. Health care providers should monitor the patients carefully for signs of autoinflammatory disease flares post-vaccination and adjust the anti-inflammatory therapies if flares occur. Monitoring the IFN signature post-vaccine, particularly in patients with interferonopathies who can mount high IFN responses post-vaccine, may assist in choosing a time point when the IFN response gene signature has returned to baseline levels for administration of repeat vaccines and booster doses. Administration of the Pfizer vaccine, which contains less mRNA than Moderna, may trigger a lower IFN response and may be preferable in patients with IFNopathies and high baseline IFN scores. Given the variability of the immune response to various COVID vaccines, health care providers may consider measuring post-vaccine antibody responses, especially in patients on combination immune modulators, and consider administering the booster dose to ensure appropriate protection.

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Author Contribution SA and RGM provided patient care and designed the patient review.

EVG contributed to data collection and analysis.

AR and ADJ ran the NanoString assay and measured the IFN scores.

SA wrote the first draft, analyzed, and graphed the data.

All authors reviewed and edited the manuscript.

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Data Availability The authors confirm that the data supporting the findings of this study are available within the supplementary materials.

Declarations

RGM has received grant support from Lilly. All patients were enrolled under the IRB-approved natural history protocol (NCT02974595). All patients consented to participate in clinical research.

Conflict of Interest The other authors have no conflict of interest to report.

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