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After failing several treatments and given the severity of his symptoms, the patient was started on dupilumab monthly injections, and within 2 weeks, his rash resolved completely. The patient originally had good control of his symptoms with monthly dupilumab, propranolol 20-mg twice daily, and an antihistamine. However, in the summer of 2019, the patient had a flare-up of symptoms owing to hot weather and resumption of classes, so his propranolol was uptitrated to a maximum dose of 60-mg twice daily and his symptoms resolved completely. During this period, his POTS symptoms were not exacerbated. Unfortunately, in the spring of 2020, his dupilumab injections were temporarily paused owing to the coronavirus disease 2019 pandemic, and his symptoms recurred. The patient is soon to be restarted on therapy; once his symptoms resolve, the ultimate goal would be to space the dupilumab injections with the hopes of weaning it off.

The treatment options for AU are limited and not all patients will respond to the previously documented regimens, including propranolol and antihistamines. As illustrated by this case, dupilumab injections may be an adjuvant therapeutic option in AU. Dupilumab is a receptor antagonist that binds to the alpha subunit of the interleukin (IL)-4 receptor and modulates signaling of both the IL-4 and IL-13 pathways.[8] Therefore, a possible mechanism for dupilumab decreasing the severity of the rash in AU is by preventing the progression of the IL-4 pathway, thus preventing the increased expression of FcεR1 on B cells, mast cells, and basophils. By decreasing the production of FcεR1, there is an overall reduction in their cross-linkages with immunoglobulin E on the mast cell's surface, which decreases mast cell activation and histamine release. Although propranolol partially controlled his symptoms, dupilumab was necessary for complete resolution.

Brian Goodman, MD*
Sunit Jariwala, MD†
*Department of Medicine, Montefiore Medical Center
Bronx, New York
†Department of Allergy & Immunology, Montefiore Medical Center,
Bronx, New York
brgoodma@montefiore.org

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Non-neutralizing antibodies and limitations of serologic testing for severe acute respiratory syndrome coronavirus 2 in patients receiving immunoglobulin replacement products

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With the growing surges in coronavirus disease 2019 (COVID-19) cases caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the globe, there has been a growing concern regarding its implications among patients with primary immune deficiency disorders (PIDs). Common variable immunodeficiency is a common PID characterized by a failure in B cell differentiation with defective immunoglobulin production, making the patients uniquely susceptible to recurrent infections.[1] Although current evidence suggests a higher risk for more severe disease in patients with both primary and secondary immune deficiency states, the exact burden of COVID-19 in these disease states is unknown.[2,3]

There are multiple diagnostic strategies to identify COVID-19 infection. Reverse transcription–polymerase chain reaction (RT-PCR) or antigen-based testing is used to detect an active infection, whereas serologic tests are useful to detect past infections. A positive antibody test result is suggestive of infection at some time in the past, but whether these antibodies are protective against SARS-CoV-2 reinfection is unclear. A negative antibody result may indicate remote or no previous infection with SARS-CoV-2; however, individuals may receive negative results if samples are collected too soon after infection or if the individual is incapable of mounting a humoral immune response, particularly in PIDs or secondary immunosuppressed states. Immunity against SARS-CoV-2 is multifaceted and not solely dependent on the antibody response, with some studies reporting that innate and cell-mediated immunity may also play a substantial role in recovery and prevention of reinfection with SARS-CoV-2.[4,5] Neutralizing antibodies are those that inhibit the virus from infecting other cells and are generally thought to play a direct role in protective immunity. However, not all antibodies are neutralizing, and currently, the US Food and Drug Administration has yet to grant emergency use authorization to assays that are capable of distinguishing between neutralizing and non-neutralizing antibodies.

Here, we report a case of a 59-year-old woman, weighing 71 kg with common variable immunodeficiency, who presented for a yearly follow-up visit. She has been maintained on supplemental immunoglobulin G (IgG) therapy with 10% immune globulin injection (Gamunex -C, Grifols, Los Angeles, California) at a dose of 35 g every 3 weeks. Per the institutional guidelines, she underwent SARS-CoV-2 testing as a prerequisite for pulmonary function testing on May 20, 2020. The patient received a negative test result for SARS-CoV-2 by RT-PCR and a positive test result for IgG class antibodies against the SARS-COV-2 spike protein. She used to work in the local school system but had been mostly homebound over the previous 2 months because of the statewide "shelter-in-place" recommendations. Her potential exposure to SARS-CoV-2 might have been through her adult son, who was a health care worker and had received positive test results for SARS-CoV-2 by means of RT-PCR in March 2020. She reported very limited interactions with him and adherence to physical distancing and universal masking recommendations. It was unclear whether the SARS-CoV-2 antibodies were de novo production or exogenous from her intravenous immunoglobulin (IVIG) infusions.

Therefore, additional SARS-CoV-2 antibody levels were tested around her IVIG infusion to assess for a trend. We tested her again before her next IVIG infusion on June 5, 2020, and post-IVIG infusion on June 8, 2020.

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Table 1
Commercial Immunoglobulin G Products and Severe Acute Respiratory Syndrome Coronavirus 2 Antibodies

Sample ID	Index value (1:1 dilution)	SARS-CoV-2 IgG antibody result[a]	Index value (1:101 dilution)	SARS-CoV-2 IgG antibody result	Neutralization antibody results
PRIVIGEN 6709	7.33	Positive	1.00	Indeterminate	Negative
PRIVIGEN 0054	7.81	Positive	1.06	Indeterminate	Negative
HIZENTRA 8411	3.07	Positive	1.62	Positive	Negative
HIZENTRA 0624	1.62	Positive	0.38	Negative	Negative
GAMUNEX 0013	7.22	Positive	1.38	Positive	Negative
GAMMAGARD 39AB	8.48	Positive	1.68	Positive	Negative
GAMUNEX 0362	N/A	N/A	N/A	N/A	Negative

Abbreviations: ID, identification; IgG, immunoglobulin G; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Positive indicates values greater than 1.10. Indeterminate indicates values between 0.8 and 1.1. Negative indicates values less than 0.8.

Her serial SARS-CoV-2 antibody levels exhibited initial positive results at an index value of 1.13 (May 20, 2020, positive is $\geq$ 1.1 index) and then intermediate results (index values, 0.8-1.0) on June 5, 2020, and June 8, 2020, with no changes in her titers post-IVIG infusion on June 5, 2020, likely indicating the natural trajectory of waning immunity after natural infection or variability of the lot for SARS-CoV-2 antibody concentrations.

To further assess whether her seropositivity was a result of the IVIG infusions she received, we tested 6 samples from different commercially available IgG products (Privigen [CSL Behring, King of Prussia, Pennsylvania], Hizentra [CSL Behring, King of Prussia, Pennsylvania], Gamunex-C, and Gammagard Liquid [Takeda, Lexington, Massachusetts]) for SARS-CoV-2 IgG antibodies. All 6 samples were positive when tested undiluted using the Euroimmun SARS-CoV-2 IgG enzyme-linked immunosorbent assay (Euroimmun, Lübeck, Germany). At a 1-to-101 dilution (the recommended dilution by the manufacturer for testing serum), 4 commercial IgG preparations were still positive, 2 were negative, and 1 indeterminate. We further sought to assess whether these antibodies were neutralizing and found that none of the IVIG products were positive for neutralizing antibodies (Table 1).

The IVIG solutions were pooled from 3000 to 10,000 donors, which contributed to a wide range of antibody specificities against various infectious agents. These included but were not limited to bacterial and viral pathogens, including those causing respiratory coronavirus infections that are ubiquitous, reflecting the cumulative exposure of the donor population to the environment.[6] The lead time for IVIG preparation is typically 6 to 9 months after donor collection pooling. Recently, antibodies against several antigens of common human beta coronaviruses in IVIG preparations have exhibited positive cross-reactivity with SARS-CoV-2 antigens.[7]

Cohorts representing the general population have exhibited low seroprevalence even in COVID-19 hotspots, suggesting that these antibodies may not be long lasting or individuals have not yet seroconverted. A recent cohort study of 175 patients with clinically mild COVID-19 infection reported robust induction of SARS-CoV-2–specific neutralizing antibodies in 94% of patients within 2 weeks of symptom onset. Of note, 10 of these patients recovered without developing detectable neutralizing antibodies, suggesting that other components of the serologic response and cellular immune response may play a role in convalescence.[8]

The positive SARS-CoV-2 IgG antibody results with negative neutralizing antibodies found in commercial IgG preparations may signify cross-reacting antibodies or false reactivity owing to the presence of these antibodies in the IVIG or subcutaneous immunoglobulin samples or the differences in the analytical sensitivity between the assays.

Future studies should seek to explore whether patients receiving commercial IVIG therapy have a lower incidence of SARS-CoV-2 infections or milder disease courses when infected. In addition, the potential to use commercial IVIG in patients as a prophylactic or therapeutic strategy has been explored on a clinical trial basis.[9]

In summary, the utility of SARS-CoV-2 antibody testing in patients with humoral immunodeficiency on IgG replacement therapy is unclear—our case highlighting the caveats of serologic testing for COVID-19. Our survey of several commercially available IgG products for SARS-CoV-2 antibodies reported the presence of cross-reacting antibodies, which may be non-neutralizing in nature.

Deepti Vellaichamy Manian, MD[*]
Chelsee Jensen, PharmD[†]
Elitza S. Theel, RPh, PhD[‡]
John R. Mills, PhD[‡]
Avni Joshi, MD, MS[*]
[*]*Division of Allergic Diseases*
Department of Medicine
Mayo Clinic
Rochester, Minnesota
[†]*Mayo Clinic*
Rochester, Minnesota
[‡]*Department of Laboratory Medicine and Pathology*
Mayo Clinic
Rochester, Minnesota
Joshi.avni@mayo.edu

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