Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

vaccination. Likewise, adverse effects to vaccination were mild in both studies. Taken together, the results of our and these 2 other studies strongly support the notion that patients with CVID must be included in COVID-19 vaccination programs because of the ability of mRNA vaccines to safely induce production of neutralizing antibodies in this category of patients.

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References

1. Bonilla FA, Barlan I, Chapel H, et al. International consensus document (ICON): common variable immunodeficiency disorders. *J Allergy Clin Immunol Pract*. 2016;4(1):38–59.
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324(8):782–793.
3. Hariyan T, Kinash M, Kovalenko R, Boyarchuk O. Evaluation of awareness about primary immunodeficiencies among physicians before and after implementation of the educational program: a longitudinal study. *PLoS One*. 2020;15:(5) e0233342.
4. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 vaccines. *JAMA*. 2021;325 (13):1318–1320.
5. Pisani G, Cristiano K, Simeoni M, et al. Detection of antibodies against SARS-CoV-2 both in plasma pools for fractionation and in commercial intravenous immunoglobulins produced from plasma collected in Italy during the pandemic [e-pub ahead of print]. Blood Transfus. doi:10.2450/2021.0055-21, accessed June 12, 2021.
6. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna vaccines. *Eur Rev Med Pharmacol Sci*. 2021;25 (3):1663–1669.
7. Gelfand EW, Ochs HD, Shearer WT. Controversies in IgG replacement therapy in patients with antibody deficiency diseases. *J Allergy Clin Immunol*. 2013;131 (4):1001–1005.
8. Lippi G, Henry BM, Plebani M. Anti-SARS-CoV-2 antibodies testing in recipients of COVID-19 vaccination: why, when, and how? *Diagnostics (Basel)*. 2021;11(6):941.
9. Squire J, Joshi A. Seroconversion after coronavirus disease 2019 vaccination in patients with immune deficiency [e-pub ahead of print]. Ann Allergy Asthma Immunol. doi:10.1016/j.anai.2021.05.015, accessed June 12, 2021.
10. Hagin D, Freund T, Navon M, et al. Immunogenicity of Pfizer-BioNTech COVID-19 vaccine in patients with inborn errors of immunity [e-pub ahead of print]. J Allergy Clin Immunol. doi:10.1016/j.jaci.2021.05.029, accessed June 12, 2021.

Specific antibody response of patients with common variable immunodeficiency to BNT162b2 coronavirus disease 2019 vaccination

On March 11, 2020, the World Health Organization declared that the coronavirus disease 2019 (COVID-19) was a pandemic.[1] Since then, the disease has reached a 1% to 3% estimated overall mortality rate.[2] COVID-19 severity ranges from asymptomatic to acute respiratory distress syndrome and possible death owing to multiorgan failure.[2] Therefore, to ameliorate the resultant poor health and social and economic consequences, prophylactic vaccines were developed. On December 11, 2020, the US Food and Drug Administration issued the first emergency use authorization of Pfizer-BioNTech (Pfizer Inc, New York City, New York) messenger RNA (mRNA) vaccine (BNT162b2) for COVID-19 prevention.[1] The vaccine was approved after a large randomized, placebo-controlled trial in approximately 44,000 participants aged 16 years or older and revealed that a 2-dose regimen of BNT162b2 conferred 95% protection against symptomatic COVID-19.[1] This novel lipid nanoparticle-formulated nucleoside-modified RNA vaccine encodes the full-length spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which contains the receptor binding domain (RBD) within the S1 subunit.[3] The RBD is a key functional component within the S1 subunit responsible for binding SARS-CoV-2 to angiotensin-converting enzyme 2 receptor, a critical initial step enabling SARS-CoV-2 to penetrate target cells.[4]

Among healthy adults, two 30 μg doses of BNT162b2 elicited robust antigen-specific CD8+ and T_H1-type CD4+ T-cell responses and strong specific antibody responses directed against RBD.[5] Nevertheless, it is unknown whether patients having primary immunodeficiency disorders of humoral immunity affecting B-cell differentiation and antibody production are able to produce effective specific antibody levels after the 2-dose BNT162b2 regimen. Common variable immunodeficiency (CVID) is an antibody deficiency with variable clinical manifestations; although patients mostly experience recurrent infections, there is an increased prevalence of autoimmune diseases and malignancy secondary to immune dysregulation.[6] A CVID diagnosis established after the fourth year of life requires a suggestive clinical history, a marked reduced total immunoglobulin G (IgG) serum concentration with low IgA or IgM, poor responses to vaccines (or absent isohemagglutinins), or low $IgD^-/CD27^+/CD19^+$ switched memory B (smB) cells, and no evidence of profound T-cell deficiency; in addition, other causes of secondary hypogammaglobulinemia must be excluded.[6]

We observed retrospectively the ability of patients with CVID to produce SARS-CoV-2 spike-specific IgG in response to the 2-dose BNT162b2 regimen as part of the national vaccination program of Israel. Furthermore, we looked for a correlation with CVID subgroups based on flow cytometry B-cell immunophenotyping.[7] All patients diagnosed as having CVID (n = 17) were treated with intravenous immunoglobulin (IVIG) every 4 weeks at Lin, Zvulun, and Carmel Medical Centers belonging to Clalit Health Services in Haifa, Israel. Revised European Society for Immunodeficiencies registry criteria[6] were used for CVID diagnosis. Between December 23, 2020, and

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Table 1
Cohort Characteristics[a] (n = 15) and Serologic Results

Group	Sex	Age (y)	Flow cytometry results	Second vaccination/ serology interval (d)	SARS-CoV-2 S1 IgG (AU/mL)
B−	M[b]	51	B% = 1	29	<21
	F	30	B% = 0	14	<21
B+/smB+	M	50	B% = 4, smB% = 9	14	307.3
	M	72	B% = 3, smB% = 14	34	300.4
	M	22	B% = 9, smB% = 3	18	4924.9
	M	81	B% = 2, smB% = 10	41	58
	F	28	B% = 9, smB% = 11	15	9780.3
	M	61	B% = 11, smB% = 7	28	2178.3
B+/smB−	F[c]	44	B% = 8, smB% = 0	61	205.7
	F	62	B% = 20, smB% = 0	36	84.6
	F	48	B% = 8, smB% = 2	55	625.8
	F	40	B% = 17, smB% = 0	18	109.9
	M	54	B% = 6, smB% = 2	48	828.7
	F	38	B% = 4, smB% = 1	25	<21
	F	66	B% = 5, smB% = 0	30	<21

Abbreviations: B%, percentage of total circulating $CD19^+$ B cells as fraction of lymphocytes; smB%, percentage of $IgD^-/CD27^+/CD19^+$ switch memory B cells as fraction of total circulating $CD19^+$ B cells; F, female; IgG, immunoglobulin G; M, male; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Phenotypes are not listed because no correlation was found between a specific phenotype and vaccination response; there are no comorbidities that might have affected patients' BNT162b2 response.
[b]Receiving 10 mg prednisone for inflammatory bowel disease.
[c]Receiving 40 mg prednisone for autoimmune hemolytic anemia.

March 6, 2021, all patients with CVID were vaccinated with the 2-dose BNT162b2 regimen. Blood samples were taken at least 14 days after the second dose, before receiving IVIG to measure SARS-CoV-2 S1 IgG levels and obtain and updated flow cytometry analysis. Day 14 was chosen because mRNA vaccine-induced B-cell responses typically peak 2 weeks after the second dose and SARS-COV-2 neutralizing titers seem to follow this pattern.[5] SARS-CoV-2 S1 IgG values more than 50 AU/mL were considered protective by the Abbott Architect SARS-CoV-2 S1 IgG assay (manufacturer's data: sensitivity, 98.1% [95% confidence interval, 89.9%-99.7%]; specificity, 99.6% [95% confidence interval, 99.2%-99.8%]) performed by the serology laboratory of Clalit Health Services. There were 2 patients who were excluded: COVID-19 was detected on prevaccination polymerase chain reaction testing in one patient, whereas the second was receiving ongoing immunosuppressive medication (rituximab). The remaining 15 patients were divided into the following 3 groups, based on their results: group B−, total circulating $CD19^+$ B cells less than or equal to 1%; group B+/smB+, total circulating $CD19^+$ B cells greater than 1% and smB cells greater than 2%; and group B+/smB−, total circulating $CD19^+$ B cells greater than 1% and smB cells less than or equal to 2%.[7]

Table 1 provides the cohort characteristics and their serologic results. Patients ranged from the age of 22 to 81 years (average, 49.8 years). Blood serology samples were taken 14 to 61 days after the second dose (average, day 31). In addition, 4 patients (26.67%) did not produce SARS-CoV-2 S1 IgG after both BNT162b2 doses, whereas 11 (73.33%) had protective titers ranging from 58 AU/mL to 9780.3 AU/mL (average, 1764.00; median, 307.3). Note that although the 2 patients in group B− had negative serology result, all 6 patients in group B+/smB+ had seropositive result. For group B+/smB−, 5 of 7 patients were seropositive. Interestingly, the 2 patients with negative serology had a total peripheral $CD19^+$ B-cell percentage below the lower limit for the normal range (6%-19%),[7] whereas that of the 5 seropositive patients was within the normal range. It has been found that patients with CVID with nearly absent total $CD19^+$ B cells (≤1%) have severe defects of early B-cell differentiation, whereas severely reduced smB cells (≤2%) indicate defective germinal center (GC) development.[7] Our results suggest that patients with both $CD19^+$ B% cells lower than the normal range (6%-19%) and reduced smB cells (≤2%) have prominent GC generation impairment. In line with this idea, the GC has been found to play a pivotal role on protective antibody generation for SARS-CoV-2 mRNA vaccines and that GC responses are strongly correlated with neutralizing antibody production.[8]

A possible study limitation may be that patients acquired protective antibodies from the IVIG. Nevertheless, all patients with CVID were on PRIVIGEN (CSL Behring, Bern, Switzerland; manufacture date: January 14, 2020). Hence, IVIG-stimulated cross-reactive antibodies cannot explain the wide differences between protective antibody levels after vaccination. The presence of considerable protective COVID-19 antibody levels in these products is doubtful. In addition, although 2 patients were receiving steroids, their serologic results (Table 1) indicate that steroid use was not responsible for the lack of response to BNT162b2 vaccination.

In conclusion, vaccination of patients with CVID with the 2-dose BNT162b2 regimen is important, because most of them will produce specific SARS-CoV-2 S1 antibodies in good titers. Nevertheless, our data indicate that total peripheral $CD19^+$ B cells below the normal range (6%-19%) together with smB cells (≤2%) or total peripheral $CD19^+$ B cells (≤1%) may predict unresponsiveness to BNT162b2. Our data require further validation in larger populations with CVID and subsequent research to detect the rate of postvaccination antibody decay compared with that of the general population.

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References

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 383(27):2603–2615.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 323(13):1239–1242.
3. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature. 586(7830):589–593.
4. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 181(2):281–292. e6.
5. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T_H1 T cell responses. Nature. 586(7830):594–599.
6. Baloh C, Reddy A, Henson M, Prince K, Buckley R, Lugar P. 30-year review of pediatric- and adult-onset CVID: clinical correlates and prognostic indicators. J Clin Immunol. 39(7):678–687.
7. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 111(1):77–85.
8. Lederer K, Castaño D, Gómez Atria D, et al. SARS-CoV-2 mRNA vaccines foster potent antigen-specific germinal center responses associated with neutralizing antibody generation. Immunity. 53(6):1281–1295. e5.

Hereditary alpha tryptasemia in identical twins

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Elevated serum tryptase level supports the diagnoses of anaphylactic reactions and mast cell (MC) disorders, and is a marker of increased MC burden, activation, and degranulation.[1] Recently, Lyons et al[2] described hereditary alpha tryptasemia (HAT) as an autosomal dominant condition characterized by an increased copy number of the *TPSAB1* gene, encoding for alpha tryptase, and mild-to-moderate elevated basal serum tryptase levels. Patients with HAT were described to present with urticaria, dysautonomia, and gastrointestinal symptoms. However, some of the individuals studied had HAT and elevated tryptase levels but did not have any symptoms. In an independent study, 5% of an unselected British birth cohort of 423 patients were found to have HAT.[3] Family members with the same increased copy number of the *TSAB1* gene were found to be either asymptomatic or with symptoms reported in HAT, such as urticaria and flushing. One of the hypotheses to explain the variable clinical presentation found in HAT is that the interaction of *TSAB1* copy number with other genes, yet to be characterized, is necessary to promote the disease.

Other studies support the influence of nongenetic comorbidities and environmental factors in the manifestations of the disease.[4,5] In one study, the proportion of patients with HAT seems to be increased in certain MC-associated conditions: 17% (8/47) of patients with idiopathic anaphylaxis and 12% (10/82) of patients with systemic mastocytosis were reported to have HAT.[4] Giannetti et al[5] studied a cohort of 101 patients with MC activation symptoms and confirmed to have HAT. These patients were predominantly of female sex with a mean age of 51 years, suggesting an association of sex hormones and menopause with occurrence of symptoms.

Twin studies add strength to family studies to reveal the contribution of genetics in disease manifestations.[6] We report identical twins with HAT and different clinical presentations. Twin A is a 16-year-old boy who developed frequent episodes of urticaria when he started a program of physical fitness training. Warm weather and exercise were triggers for these episodes, which presented within 15 minutes of physical activity and were well controlled with second-generation H_1 antihistamine medications, resulting in resolution of itching and hives within an hour. No other triggers were reported, and there were no wheezing or other associated symptoms. Diagnostic testing, performed after 10 months from the start of symptoms, included serum tryptase level, which was 27.0 ng/mL (normal, <11.4 ng/mL). This finding prompted a concern for systemic mastocytosis. In the absence of additional clinical or laboratory findings, a decision was made for genetic testing to rule out HAT. Results revealed 4 copies of the *TSAB1* gene, and he was diagnosed as having HAT. He was instructed to take cetirizine 10 mg daily. Urticaria continued to occur if he missed to take this medication before exercise. Twin B was considered healthy, although he complained of occasional episodes of unusual extreme fatigue only after substantial physical activity, such as playing a soccer game. He had needed additional sleep time and would have missed a school day to rest, with full recovery. No other associated skin, respiratory, or gastrointestinal symptoms were reported. These episodes had started at age 14 years, and he had stopped playing competitive soccer owing to fatigue. Cardiology evaluation, including electrocardiogram and echocardiogram, was reported without significant findings. Daily oral sodium cromolyn but not H_1 or H_2 antihistamine medication was effective to reduce the occurrence of fatigue. He had seasonal allergic rhinitis, occasional frontal headaches, and history of frequent sinusitis and sinus surgery. Rhinorrhea and nasal congestion occurred during spring and fall seasons. His headaches were associated with nasal congestion, localized to frontal and retro-orbital areas. These symptoms improved with taking 10 mg levocetirizine daily, nasal fluticasone, and nasal saline washes. Skin allergy prick testing was reactive for mold, weed pollen, grass pollen, and tree pollen. His serum tryptase level was 31.9 ng/mL, and, as expected, he also had 4 copies of the *TSAB1* gene. Other than reportedly mild allergic rhinitis in childhood, the twin siblings did not have other medical problems until adolescence. They did not present with episodes of severe allergic reactions, anaphylaxis, gastrointestinal symptoms, or dysautonomia. The twins have been followed for 3 years, and the tryptase levels have remained at similar levels, ranging from 23 to 32 ng/mL. Additional investigations for systemic mastocytosis have been agreed to be performed, conditional to the development of new symptoms or changes in laboratory test results that might suggest disease progression. This clinical decision followed the recommended approach by Robey et al,[3] Giannetti et al,[5] and Carrigan et al,[7] regarding the usefulness of the *TSAB1* gene copy number test for patients presenting with elevated serum tryptase and low suspicion for systemic mastocytosis.

Extra copies of the *TSAB1* gene determine an increase of baseline serum tryptase levels and might be associated with severity but not the occurrence of specific symptoms of allergic conditions or MC activation syndrome. The twins shared the elevated basal serum tryptase and exercise as one of the triggers for symptoms; however, their clinical manifestations were different. The mechanisms explaining the role of the elevated tryptase in HAT are being investigated. Alpha tryptase forms heterotetramers with beta tryptase to activate other molecules and enzymes, such as the protease-activated receptor 2 (PAR2).[8] This enzyme is present in several types of immune cells and is involved in diverse biological functions, including coagulation, cytokine release, and smooth muscle cell relaxation and vasodilation.

Based on the clinical presentation of the identical twins, we believe that factors other than genetics, such as exposure to environmental factors, allergic sensitization, hormonal changes, and other stressors,

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