Correspondence

Impaired memory B-cell response to the Pfizer-BioNTech COVID-19 vaccine in patients with common variable immunodeficiency

To the Editor:

The recent article by Hagin et al reports that most patients with inborn errors of immunity (IEI) generate humoral and cellular immune responses to the Pfizer-BioNTech COVID-19 vaccine. Neutralizing anti–receptor-binding domain (RBD) antibodies, RBD-specific B cells of the IgG and IgA isotype, and T cells producing IL-2 and IFN-γ were detected in most vaccinated patients.

Hagin et al conclude that patients with IEI should be vaccinated because most of them are able to generate protective responses. Although we completely agree on the necessity of vaccinating patients with IEI, it is also indispensable to correctly evaluate the establishment and duration of protective immunity in this group of patients.

We conducted a similar study in a cohort of 33 patients with common variable immunodeficiency (CVID). We evaluated the level of SARS-CoV-2–specific serum antibodies and frequency of memory B cells (MBCs) following administration of the Pfizer-BioNTech vaccine. Only 33% of our patients with CVID showed an antibody response, compared with 85.7% of the patients (12 of 14) reported by Hagin et al (see Fig 2, A in Hagin et al). Hagin et al also measured RBD-specific MBCs, which play a fundamental role in long-term protection when serum antibody levels decline. In Fig E2 of Hagin et al (available in the Online Repository at www.jacionline.org), the gating strategy to identify RBD-specific IgG and IgA B cells and the percentage thereof are shown. Hagin et al conclude that RBD-binding B cells are detected in healthy vaccinated donors and patients with CVID.

We have different results showing that healthy vaccinated donors generate RBD-specific MBCs after 2 vaccine doses, whereas patients with CVID are unable to do so (Fig 1).

Our different results might be explained by the difficulty of correctly quantifying cells present at low frequency in the sample analyzed. Flow cytometry can effectively and accurately manage extremely rare event analyses down to $10^{-5}$. In cases of rare event analysis, the nonspecific cell events can often outnumber the relevant cell frequency, making the count totally unreliable. Introduction of the concepts of limit of detection and limit of quantification is necessary to properly evaluate the results.

FIG 1. Detection of RBD-binding MBCs in healthy vaccinated donors (HVs) (left plots) and patients with CVID (right plots). MBCs, contained in the CD19 gate, were identified as CD24+CD27+. MBCs binding RBDs were detected by RBD-biotin labeled with streptavidin–fluorescein isothiocyanate. The numbers shown correspond to the RBD+ events divided by the total number of acquired live cells. HVs 1, 2, and 3 have the requisites to reach the limit of quantification (LOQ), and the percentages can be considered reliable. HV 4 is just under the limit of LOQ, but the number of events is sufficient for the limit of detection. None of the samples from patients with CVID had sufficient RBD+ events to reach either the limit of detection or the LOQ. Thus, frequencies are not reported.
quantification in rare event analysis has been a remarkable advancement to ensure robust and reliable measurements of rare events. Only when the limit of quantification is achieved can the frequency be considered reliable. The numbers of relevant events (RBD-specific B cells in this case) should be a defined percentage of the total acquired events.

RBD cells are a fraction of the MBCs generated by vaccination. B cells acquire increased specificity and affinity thanks to the mechanisms of somatic mutation and selection in the germinal centers. These mechanisms are severely impaired in patients with CVID.

Beyond the technicalities, an inaccurate evaluation of the number of specific MBCs may lead to the conclusion that patients are protected and will be able to react to a SARS-CoV-2 encounter thanks to their MBCs. In contrast, when serum titers decline, patients with CVID will be unable to produce new specific antibodies because they lack the right MBCs. Administration of mAbs may prevent severe disease and emergence of new viral variants in these cases.

Ane Fernandez Salinas, BDe,b Eva Piano Mortari, PhDb Sara Terreri, PhDb Cinzia Milito, PhDa Salvatore Zaffina, MDc,d Carlo Federico Perno, MDf Franco Locatelli, MDg,h Isabella Quinti, MDa,b Rita Carsetti, MDa,i

From the Department of Molecular Medicine and the Dipartimento Materno-Infantile e Scienze Urologiche, Sapienza University of Rome, Rome, Italy, and the Diagnostic Immunology Research Unit, Multimodal Medicine Research Area, the Occupational Medicine/Health Technology Assessment and Safety Research Unit, Clinical-Tecnological Innovations Research Area, the Health Directorate, the Multimodal Medicine Research Area, the Microbiology and Diagnostic Immunology Unit, the Department Onco-Haematology, and Cell and Gene Therapy, and the Diagnostic Immunology Clinical Unit, Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy. E-mail: rita.carsetti@opbg.net.

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