



## Commentary

# COVID-19 infection and vaccination in immunodeficiency

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## Summary

During the last 2 years and a half, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, causing about 6 million deaths. Clinical manifestations are highly variable, ranging from entirely asymptomatic infection to multiorgan failure and death. The outcome in immunocompromised patients is still a matter of debate, and so are the optimal strategies to prevent or treat the infection in these high-risk populations.

**Keywords:** immunodeficiency diseases, infection, vaccination, virus

Whereas vaccination is the safest and most effective tool to achieve a protective response in immunocompetent individuals, the ability of mRNA-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines to immunize patients with treatment-induced immunodeficiency or primary immunodeficiency has recently been questioned [1].

The topic is particularly relevant because of the high number of immunosuppressive or immunomodulatory treatment recipients, whose indications have hugely spread, now involving conditions ranging from cancers to immune-mediated diseases. In particular, patients with cancer [2], multiple sclerosis (MS) [3], and allogeneic stem cell transplantation [4] have all demonstrated a reduced ability to mount an immune response, potentially impairing the protection offered by vaccines.

In this context, the study of the immune response to SARS-CoV-2 infection and vaccination in rare inborn errors of immunity (IEIs) represents an excellent model for understanding the impact of the loss of a specific immune function to control COVID-19 and to respond to immunization [5, 6].

Both for IEIs and treatment-induced immunodeficiency, the impairment of a specific immune system pathway due to the immunosuppressive treatment or the genetic defect may have a differential effect on the efficacy of vaccination or the severity of infection.

For instance, therapeutic B-cell-targeting therapies, used to treat many hematological malignancies and autoimmune diseases, have been shown to affect the production of antibodies in response to SARS-CoV-2 vaccination while leaving unaltered the T-cell response [3]. This picture is similar to what

happens in patients with Bruton's agammaglobulinemia due to congenital B cells loss because of *Btk* mutations [5].

Although hematological and rheumatological indications, most recently anti-CD20 monoclonal antibodies have been used as a maintenance treatment to control MS. Here, Baker et al. [7] reviewed the recent findings on COVID-19 in patients with MS treated with anti-CD20 antibodies. CD20 is expressed at all stages of B-cell development except for the pro-B and plasma cells. Depleting B cells in MS can lead to a poor or absent antibody response [8] and loss of protective, cross-reactive immunity to cold-causing coronavirus. Anti-CD20 therapy is known to deplete peripheral B cells efficiently; these constitute only 2% of the total B-cell population in our body, but the effect of anti-CD20 treatment on B cells located in peripheral lymphoid tissues is less clear [9].

Considering the blunted response to vaccines in patients treated with anti-CD20 antibodies, such as rituximab and ocrelizumab, seroconversion following natural infection with SARS-CoV-2 is also expected to be inhibited. Following the treatment with anti-CD20, the timing of B-cell reappearance is variable. The majority of patients do not show disease reactivation 12–18 months after receiving rituximab and ocrelizumab, indicating that the pathogenic B-cell population is not regenerated in this timeframe. Moreover, only 5% of people treated with 3–4 cycles of ocrelizumab replenish the B-cell compartment 6 months after treatment. This indicates that anti-CD20 treatment recipients will unlikely to mount an effective COVID-19 vaccine antibody response within the 6-month dosing schedule. Fortunately, about 85–90% of patients exhibited CD19<sup>+</sup> B-cell level <1% 12 months

following ocrelizumab. Since anti-CD20 therapy impairs vaccine responses, a possible strategy may be to delay the anti-CD20 therapy after vaccination or offer an extended dosing interval with CD20-depleting antibodies infusions. Authors also suggest providing a prophylactic antiviral response through the use of small-molecule antiviral agents or the generation of a high-titer antibody response through the delivery of convalescent sera or monoclonal antibodies cocktails that can be optimized for activity against circulating variants.

Defining the best strategy to control COVID-19 in immunocompromised individuals is also necessary. In these cases, the persistence and replication of the virus can potentially lead to the development of new variants of concern. Consequently, surveys on the outcome and mechanism of control of SARS-CoV-2 infection in patients with different types of immunodeficiency may indicate the best clinical approach for this population.

In a large retrospective study from the UK, Shields et al. report morbidity and mortality from COVID-19 in a cohort of 310 individuals with primary immunodeficiency (PID) or secondary immunodeficiency (SID) from the UK [10]. Data provided were systematically collected by the United Kingdom Primary Immunodeficiency Network (UK PIN) and included the outcomes of SARS-CoV-2 infection in patients under the care of Clinical Immunology teams across the UK since March 2020. Data were analyzed according to the 2019 International Union of Immunological Societies (IUIS) classification of IEs. Further analysis was undertaken on three subgroups: 93 individuals with common variable immunodeficiency (CVID), 159 individuals with PID receiving immunoglobulin replacement therapy (IgRT), and 92 individuals with SID. Their findings indicate that individuals with PID and SID had higher inpatient mortality and died younger than the general population. Increasing age, low pre-SARS-CoV-2 infection lymphocyte count, and the presence of common comorbidities increased the risk of mortality in those patients. Lymphopenia has also been reported as a risk factor for poor prognosis in an independent cohort of patients with IEs [11]. Moreover, low pre-infection lymphocyte count has been related to the lack of anti-SARS-CoV-2-specific IgG and IgA response in CVID after immunization [12].

Shields et al. demonstrate an increased mortality risk from COVID-19 in individuals with PID with hypogammaglobulinemia receiving IgRT. In this group, the median age of death was 57 years, compared to the national UK average of 83 years. Although cardiovascular disease and diabetes, univariate analysis revealed that chronic lung and hepatic diseases are risk factors for mortality in PID, confirming data from other cohorts [13].

In this cohort, only 10 patients received anti-SARS-CoV-2 antibody-based therapies either as a monotherapy or combined, with a possible impact on the recorded overall survival rates.

As stated before, as fragile patients may have a more prolonged or severe infection, it is essential to define their immune response to COVID-19 and to identify reliable clinical correlates of exposure and immunity. The Committee of Experts on Primary Immunodeficiency of the IUIS has included vaccination both as a diagnostic tool (to assess the specific antibody response to protein and polysaccharide antigens) and as a means of prevention [14]. As for other infections/immunizations, the response to COVID-19 or the efficacy of vaccination relied on the detection of specific antibodies against

SARS-CoV-2 antigens. In the general population, the level of neutralizing antibodies is significantly positively correlated to protection, and mRNA vaccination generated robust humoral and cellular immune memory to SARS-CoV-2 for at least 6 months following mRNA vaccination [15].

However, the antibody response may wane over time or may not be detectable in patients with antibody deficiency [16], necessitating an examination of the role of cell-mediated immunity.

Several distinct assays have been developed and optimized to quantify and characterize T cells. Most methods use a functional response to a specific antigen as the read-out, including the induction of proliferation (i.e. fluorescent dye), the analysis by flow cytometry of activation-induced markers (CD25, CD134, and CD154), and the production of cytokines that can be measured by intracellular staining (flow cytometry), by ELISA or by ELISpot.

Due to the low number of cells, cell proliferation assays are widely used to monitor antigen-specific CD4<sup>+</sup> T-cell response. The analysis of the incorporation of <sup>3</sup>H-thymidine during DNA synthesis remains the most commonly used method. Under the same experimental conditions, <sup>3</sup>H-thymidine incorporation and dye-based proliferation assay were compared to detect the antigen-specific T-cell responses to influenza vaccine peptides [17]. The results show a strong correlation between the <sup>3</sup>H-thymidine and dye-based proliferation assays.

In the paper published here by Awuah et al. [18], the authors develop a functional <sup>3</sup>H-thymidine incorporation assay to assess the T-cell response to SARS-CoV-2 in a cohort of PID after vaccination or infection. The study cohort included 18 healthy controls (8 pre-vaccination, 6 post-vaccination, and 4 post-infection); 12 patients with PID (8 post-vaccination and 4 post-infection); and 8 with combined immune deficiencies with predominantly T-cell disorders (1 post-vaccination, 4 post-infection, and 3 unknown). The PID group can be further divided into CVID and patients with absent B cells X-linked agammaglobulinemia (XLA).

Authors detected that T-cell proliferation post-exposure and post-vaccination was comparatively low in CVID patients, indicating that although T-cell numbers may be normal, they may also have significant impairment in T-cell function. XLA patients always have a negative serological response to COVID-19 but were able to mount a robust T-cell response post-infection. In the third group, patients with T-cell disorders, the authors did not detect any proliferation responses to SARS-CoV-2 antigens, which were near-equivalent to the background. Their results are in line with results obtained in a CVID and XLA group in which specific T cells were analyzed by IFN- $\gamma$  ELISpot. Specific T-cell responses were evident in all healthy donors (HD) and defective in 30% of CVID, whereas all patients with XLA responded by specific T cells [5]. The impaired antigen-specific T-cell responses in CVID patients and those with T-cell disorders raise a concern about the effectiveness of vaccination in these patients.

In those patients in whom the T-cell defect makes this test impracticable but in whom B-cell function, it might be helpful to assess by flow cytometry or ELISpot the presence of SARS-CoV-2-specific memory B cells [5, 6, 15, 19]. We previously showed that while HD produced specific antibodies and generated memory B cells with high binding capacity that significantly increased after immunization. These responses are severely compromised in CVID patients and absent XLA and after immunization with mRNA vaccine. Through flow

cytometry, we could demonstrate that the few COVID patients that produce anti-spike IgG developed atypical memory B cells and plasmablasts with low binding capacity for the spike protein, and these responses are short-lived and should be re-assessed over time.

The analysis of cellular response would make it possible to assess the response to vaccination in the long term by compensating for the decline in antibodies. As a whole, tools to quantify the post-exposure and post-vaccination immune response in patients with immunodeficiency may identify patients who will benefit from pre-exposure prophylaxis by neutralizing monoclonal antibodies [20] or from immunization with inactivated vaccines [21].

In conclusion, after 2 years of research and development, much progress has been made and has allowed us to understand the biology of the SARS-CoV-2 virus. Thanks to the global vaccination strategy, most infections are mild or asymptomatic in the general population. However, we must still identify frail patients' best vaccination and treatment policies. Translational research studies will help us to create therapeutic and prophylactic interventions rationally designed and targeted to the type of immune defect and immunotherapy. Only in this way will we be able to improve the protection of the high-risk populations.

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## Data availability

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## Author contributions

E.P.M. and F.P. wrote and revised the manuscript.

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