



T cells as the hoped-for savior for SARS-CoV-2 vaccination during CD20-depleting antibody therapy?

Commentary for: “Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy.”

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A range of measures has been rolled out to suppress and mitigate coronavirus infectious disease 2019 (COVID-19), a multi-organ disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In this regard, an unprecedented worldwide scientific effort has yielded the approval of several vaccines against SARS-CoV-2. These vaccines utilize either mRNA or adenovirus vector-based technology, with high efficacy in phase 3 pivotal trials regardless of the mode of action [1]. People living with multiple sclerosis (pwMS) on B cell depleting therapies are less likely to mount an antibody response against SARS-CoV-2 after symptomatic infection [3]. Whether this observation is responsible for the increased probability of suffering a more severe COVID-19 course on B cell depleting therapies remains to be determined [4]. A significant hurdle would be posed by the impaired development of a protective B cell response when on treatment with specific immunomodulatory or immunosuppressive medication. The questionable disease-modifying drugs (DMD) include the B cell/CD20-depleting monoclonal antibodies ocrelizumab and rituximab, and fingolimod, an oral sphingosine-1-phosphate (S1P) receptor modulator [2]. Understanding protective T cell responses, which are an additional line of defense against viruses, in the context of COVID-19 and specifically in pwMS on immunotherapies is crucial but still in its infancy.

In this article of *EBioMedicine*, Gadani and colleagues studied both humoral and T cell responses in 101 pwMS, a mean of 6.8 weeks

apart from the terminal vaccination [5]. Thirty-eight patients were on CD20-depleting therapies and the average time from the last infusion, which is given at 6-month intervals, was 165 days. The study corroborates a low rate of SARS-CoV-2 spike S1 glycoprotein specific IgG on CD20 depleting therapy (56%) and discloses that a 30-day increase in time from the last infusion is associated with 1.45 increased odds of a positive humoral immune response to vaccination. This finding underscores a favorable time frame for immunization with mRNA vaccines in pwMS on ocrelizumab and rituximab at least 4-months apart from the last infusion [2]. This observation is also in line with recent data from pwMS demonstrating markedly reduced antibody and memory B cell responses on CD20-depleting antibody treatment [6]. Notably, these authors also found that antigen-specific CD4 and CD8 T cell responses after vaccination remain intact with a skewing towards augmented induction of CD8 T cell and preserved type 1 helper T cell priming. In contrast, a study mainly comprising patients with autoimmune diseases (e.g. ANCA-associated vasculitis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus) and a mean time of 1.1 years since the last CD20 antibody use demonstrated a blunted immune response for both humoral and T cell responses after SARS-CoV-2 vaccination [7]. This discrepancy may be explained by peculiarities within the immunological traits of MS pathogenesis, the use of additional immunotherapies and/or the time elapsed since B cell depletion. The current study adds to the hypothesis that an attenuated development of S1-IgG on CD20 depleting antibody therapy may be counterbalanced by T-cell responses, as detected in 97% of patients. Provided there is an exaggerated T cell response after SARS-CoV-2 vaccination in the absence of circulating B cells, the next logical question is to root the underlying immunological mechanisms. A potential option is a more extensive antigen-driven CD8 T cell activation without antibody-mediated antigen clearance. Further, disinhibition of CD8 T cell responses by CD20-depletion related lack of regulatory B cells can be envisioned [6]. The interferon (IFN)- γ release findings, which revealed qualitative differences in the T cell response, seem to support these lines of evidence. Patients on B cell depleting treatment had a significantly higher rate of IFN- γ spot forming units than other

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treated and untreated study participants. The next steps for unraveling the mysteries of virus-specific immune responses in B cell-depleted patients should include the comparison of T cell responses in COVID-19 survivors vs. post-vaccination.

How virus-specific T cell responses adapt to SARS-CoV-2 mutations is another issue. Whether B and T cell responses differ between different vaccine technologies and concerning the mode of action of the DMD, needs to be clarified [10]. Some methodological limitations need to be acknowledged. The manner in which T cell responses are measured differs and differences in the applied methodology need to be considered. These include the preanalytical protocol, the type of blood sample, the stimulants used, time of incubation/stimulation, and most importantly, the measures of read-out. IFN- γ levels can be measured by ELISA, various options of flow-cytometry-based assays, and advanced methods such assays for the quantification of activation-induced markers. The latter provide a broader view of the total antigen-specific T cell response by defining antigen-specificity on the basis of upregulation of T cell receptor stimulation-induced surface markers rather than the production of cytokine. This needs to be borne in mind when comparing and interpreting future studies.

Let's focus on the question of whether and how these observations can be translated into clinical practice. We still do not know the value of virus-specific T cell responses in the absence of antibodies for protection against and clearance of SARS-CoV-2. At the current stage, we are just aware that SARS-CoV-2 infection induces CD4 and CD8 T cell immunity and that the magnitude of the T cell response is associated with both decreased COVID-19 severity and improved survival in patients with hematologic malignancies receiving B cell depleting therapies [8,9]. Can we now soothe our COVID-19 related concerns against B cell depleting therapies in the absence of a humoral immune response following SARS-CoV-2 vaccination? Whether T cells are the hoped-for saviors for these indispensable DMDs remains to be elucidated.

Statement

No medical writer or editor was involved in the preparation of this manuscript.

Contributors

Both authors contributed to conceptualization, formal analysis, investigation, methodology, writing – original draft, and writing review & editing.

Declaration of Competing Interest

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