SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response

Treatment with rituximab (RTX), a monoclonal antibody targeting CD20, constitutes an important therapeutic strategy for patients with inflammatory rheumatic diseases. Some recent reports have already highlighted the risk of SARS-CoV-2 infection in patients treated with RTX.\(^1\)\(^-\)\(^4\) Besides the risk of a more severe disease course during B cell depleting therapy, a major concern relates to a risk of reduced immunogenicity of vaccination. Therefore, the question arises if patients should withhold or interrupt RTX therapy around COVID-19 vaccination or delay vaccination. To address this question, we have assessed antibody response and T cell mediated immune response to the BNT162b2 (Pfizer/BioNTech) vaccine in patients undergoing RTX treatment at the end of the treatment interval.

Five patients under regular and recent RTX treatment were selected for COVID-19 vaccination with BNT162b2 (Pfizer/BioNTech). A detailed description of the methods and the patient characteristics (online supplemental table S1) can be found in the online supplemental material. The last RTX infusion was administered between 4 and 12 months ago (online supplemental figure S1). At the time of the vaccination, peripheral CD19\(^+\) B cells could only be detected in two patients (online supplemental table S2). Antibodies against the SARS-CoV-2 nucleocapsid (NC) and the receptor-binding domain (RBD) of the spike protein were analysed 12–23 days following the second dose of BNT162b2. Sex-matched healthy individuals who had received two vaccinations with BNT162b2 (n=4) and unvaccinated healthy individuals (n=4) served as controls. No antibodies against the NC were detected in either group, implying no prior SARS-CoV-2 infection (data not shown). In three patients, no antibodies against the RBD were detected. Interestingly, in two patients with detectable CD19\(^+\) B cells, we determined a positive antibody response against the SARS-CoV-2 RBD, suggesting the development of a humoral immune response once peripheral B cells are repopulated (figure 1).

To determine a SARS-CoV-2 specific T cell reactivity, we measured interferon (IFN)-\(\gamma\) response to SARS-CoV-2 peptides in our patient cohort and control groups. All groups showed IFN-\(\gamma\)-secretion on non-specific T cell stimulation of heparinised whole blood with mitogen. After stimulation with two different SARS-CoV-2 specific antigen mixes, IFN-\(\gamma\) response could be detected in the vaccinated healthy control group as well as in the patient cohort, independent of the humoral immune response (online supplemental figure S2). Of note, lower levels of IFN-\(\gamma\) were detected in one patient who concomitantly received intermediate prednisone dose.

In the current report, we could demonstrate that B cell depleting therapy with RTX affects the humoral immune response to SARS-CoV-2 vaccination in B cell depleted patients. However, humoral immune response was observed in patients who had measurable peripheral B cells following RTX treatment. These data are in line with very recent reports showing that RTX treatment might affect the antibody response to SARS-CoV-2 vaccination.\(^3\)\(^\ 6\) However, we could here reveal a T cell mediated immune response even in B cell depleted patients. It will be important to understand if T cell immunity is important or possibly even sufficient to protect patients against infection with the virus on vaccination. Our data also indicate that RTX treatment may not have to preclude SARS-CoV-2 vaccination, since a cellular immune response will be mounted even in the absence of circulating B cells. Alternatively, in patients with stable disease delaying RTX treatment until after the second vaccination may be warranted and, therefore, vaccines with a short interval between first and second vaccination or those showing full protection after a single vaccination may be preferable. Importantly, in the presence of circulating B cells also a humoral immune response may be expected despite prior RTX therapy.

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REFERENCES