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Review Article

A Narrative Review on the Effect of Rituximab on Secondary Humoral Immune Response

Shayan Dasdar[1,2], Nika Kianfar[1,2], Hamidreza Mahmoudi[1], Maryam Daneshpazhooh[1*]

[1] *Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[2] *Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

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Abstract

Rituximab is a chimeric monoclonal antibody with binding specificity to CD20-positive B lymphocytes. Patients administered rituximab would not have adequate humoral response to the SARS-CoV-2 vaccine. Rituximab can also affect the durability of immunization. Plasma-secreting antibodies and memory B-cells are two major arms of long-term immunity. The role of memory B-cells becomes prominent by decreasing antibody titers over time. The activated memory B cells have CD20 protein on their surface. Investigating the effect of rituximab on other vaccines has demonstrated attenuated recall response. The evidence in this review suggests that we can also expect a deficit of recall response to SARS-CoV-2, making the rituximab-treated patients susceptible to reinfection with emerging variants. Therefore, it is better to consider other therapeutic options, use lower rituximab doses, and employ booster vaccines at shorter intervals.

Keywords: SARS-CoV-2; COVID-19; Rituximab; Vaccination

***Corresponding Author:** Maryam Daneshpazhooh
Cancer Immunology Project Interest Group (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran
E-mail: daneshpj@tums.ac.ir

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute illness caused by variants of severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2), which has been a catastrophic global pandemic since its emergence (1). During this pandemic, there has been an excessive concern for patients with immune-mediated inflammatory diseases (IMIDs) as a potentially highly susceptible population to SARS-CoV-2 infection (2-8).

Rituximab is a chimeric monoclonal antibody against membrane-embedded CD20 protein. The

CD20 markers are expressed in most stages of B cell maturation except on pro-B cells, plasmablasts, and plasma cells (9). The profound and long-lasting B-cell depletion following rituximab makes it a suitable option for hematologic malignancies and IMIDs of rheumatology, neurology, and dermatology (10, 11). However, rituximab could be associated with a risk of SARS-CoV-2 infection and feature more severe illness (12-20).

To date, vaccination has successfully reduced the spread of SARS-CoV-2. Nonetheless, numerous uncertainties exist regarding vaccine efficacy in patients receiving immunosuppressive/immunomodulating treatments, as they were excluded from initial trials (21-23). Production of vaccine-induced antibodies in rituximab-treated patients is markedly diminished until B cell reconstitution for approximately 6-12 months (24-26). However, previous antibody titers would not be affected as plasma cells do not have CD20 on their surface. Therefore, experts have suggested completing the vaccination series four weeks before the next injection or deferring vaccination 12 to 20 weeks after the infusion (27). The question that arises now is how rituximab would influence the durability of SARS-CoV-2 immunity, which is yet to be studied.

Long-lasting SARS-CoV-2 immunity is essential to overcome the current pandemic. Circulating antibodies and memory B cells form two major arms of prolonged protection against reinfection. It has been shown that secretion of SARS-CoV-2-related antibodies by plasma cells declines over time and hardly persists over a year (28-30). The role of memory cells becomes prominent when antibody titers are significantly reduced, and they are incapable of ceasing the infection. Memory B cells readily induce massive antibody responses, leading to viral elimination (31-33). They can also induce cross-reactivity response and protect against emerging variants (34).

Memory B cells are counted as CD20-presenting cells. There is a possibility that rituximab harms SARS-CoV-2 memory response, even in a fully immunized person. This study will briefly review previous experiences with rituximab in other vaccines and its potential effect on COVID-19.

Rituximab reduces memory B cells

Memory cells are driven from naïve B cells of the germinal center after primary exposure. This process is accompanied by CD27 expression, the characteristic surface marker of memory B cells (35, 36). The membrane-bound IgD further classifies memory B cells unswitched (IgM +/IgD+/CD27+), switched (IgG+ or IgA+/IgD–/CD27+), and smaller fraction of resting (IgM-/IgD-/CD27-) memory B cells (37). Following the recall response, unswitched memory cells form germinal center B cells, while switched memory cells rapidly differentiate into antibody-secreting cells. (38).

Rituximab induces a remarkable decrease in peripheral memory B cell counts, as they have CD20 markers on their surface (39-42). However, the effect of rituximab on various memory cells might be different (39, 43). A study on thrombotic thrombocytopenic purpura reported reconfiguration in the B cell population after rituximab administration. They indicated a significant decrease in the absolute number of all memory cells using immunophenotyping. Notably, this reduction was more prominent in unswitched memory cells (44). Another study evaluated B cells that persisted after rituximab treatment in patients with myasthenia gravis. Similarly, they observed that the memory cells population notably skewed toward switched cells in non-depleted clones (15% IgM, 27% IgG, and 55% IgA) compared to depleted ones (43% IgM, 25% IgG, and 26% IgA) (45).

In contrast to peripheral blood, lymphoid tissues, including the spleen, lymph nodes, and bone marrow, are more resistant reservoirs for memory B cells against rituximab (46-48). Comparison between the B cells of the peripheral blood and spleen in patients with idiopathic thrombocytopenic purpura who underwent splenectomy months after rituximab indicated that memory B cells resided more in the spleen (46). Similar results were also obtained about the B cells in lymph nodes in patients with rheumatoid arthritis (47).

Some probable intrinsic factors influence memory B cell depletion post-rituximab, including CD20 level on the surface, expression of B cell activating factor and its receptor, frequency of somatic hypermutation, and transmembrane activator and CAML interactor expression (45, 47, 49). According to animal studies, higher rituximab doses could act as an extrinsic factor in removing resistance B cells in solid tissues (50-52).

Rituximab attenuates the recall response

In a non-human model, the primates previously immunized against a specific antigen were half administered monoclonal anti-CD20 IgG. They were rechallenged with the antigen 48 hours later. They found that the subjects in the treated group could not mount a memory response (53). Another study examined the recall response in patients with lymphoma before and after rituximab infusion using different antigens of tetanus toxoid and poliomyelitis. Similarly, they found that secondary immunity significantly declined after rituximab (54).

Several studies compared the recall response to tetanus toxoid between rituximab-treated patients and healthy controls. They consistently reported impaired secondary response in rituximab-treated patients (55-57). It should be noted that some of the patients with impaired humoral response had almost recovered B lymphocyte counts, highlighting the critical role of memory B cells in the recall response.

Experiments with the influenza vaccine provided conflicting results. In a study on non-Hodgkin's lymphoma, humoral response to the trivalent seasonal vaccine was significantly decreased in rituximab-treated patients compared to their matched controls. They noted that post-vaccination antibody titers were correlated to residual memory cells (58). This failure of response to the seasonal vaccine was also observed in rituximab-treated rheumatology patients (59).

In contrast, other studies have reported the opposite result. Sustained recall response to influenza antigens was detected in patients after chemotherapy combined with rituximab (60). Similarly, patients with autoimmune blistering diseases retained their ability to mount recall responses even in the absence of memory cells (61). Some believed that the resided memory cells in solid organs were responsible for this adequate recall response.

It is not easy to draw a definite conclusion due to the great differences in the contexts and methods of these studies. However, it seems that memory B cell depletion following rituximab could attenuate the secondary immune response. This weakness in recall response might be negligible in some patients to harm the protective immunity.

Rituximab effect on SARS-CoV-2 humoral memory

Based on the evidence provided, it can be reasonably assumed that rituximab would compromise memory B cell response caused by SARS-CoV-2 infection or vaccination. A recent study has evaluated humoral immune responses in multiple sclerosis patients with anti-CD20 therapy after SARS-CoV-2 mRNA vaccination. As expected, they documented a prominent decrease in generating spike-specific and receptor-binding domain memory B cells (62). Now, the main question is how the impairment in secondary immune response would affect the COVID-19 course.

An animal study rechallenged three cynomolgus macaques recovered from infection to measure the quality and magnitude of recall immunity against subsequent SARS-CoV-2 infection. According to their observations, memory response successfully prevented reinfection (63). In a human study, the post-vaccination antibody level strongly depended on preexisting memory B cells (32). Some studies have also suggested that higher memory cell counts could be associated with better outcomes in infected patients. Evaluating the peripheral blood samples of non-hospitalized COVID-19 individuals indicated that memory B cell counts were significantly correlated to the duration of symptoms (62). Another study stated that lower IgM memory cells increased disease severity and mortality risk (64, 65). Notably, It was shown that vaccinated individuals infected with the delta variant had lower memory B cell counts compared to noninfected ones (34). Therefore, decreasing memory B cells following rituximab can potentially increase the risk of SARS-CoV-2 reinfection and complications (66-68). Importantly, this effect can also occur in those who receive rituximab after vaccination, as they would not have a complete secondary humoral immunity against SARS-CoV-2.

As long as this pandemic continues, clinicians would better consider other feasible and admissible treatment options. As mentioned earlier, higher doses of rituximab are associated with a greater decrease in protective memory B cells. Thus, another solution can be employing lower doses of rituximab that, according to the ample evidence, could have a favorable response in autoimmune

diseases (69-73). Some studies have shown a tied correlation between the number of memory B cells before and after rituximab treatment (43, 74). Therefore, with vaccination in a short interval before rituximab infusion, more SARS-CoV-2 activated memory cells are supposed to remain. Finally, repeated vaccination at early B cell reconstitution could also be beneficial (56, 75).

Conclusion

Based on the evidence above, rituximab could reduce SARS-CoV-2-activated memory B cells and consequently impair humoral recall response. At this moment, it is impossible to provide a definite opinion on the extent of this defect and its contribution to the outcome of the COVID-19 infection. Notwithstanding, the proposed theory is of utmost importance and needs to be further examined in subsequent studies. In due time, clinicians should use rituximab with more caution.

Conflict of interests

There is no conflict of interests.

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