

# Timing of COVID-19 Vaccine in the Setting of Anti-CD20 Therapy: A Primer for Nephrologists



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The corona virus disease 2019 (COVID-19) pandemic has continued to pose challenges to health care systems worldwide. This includes care of patients requiring immunosuppression, with significant disruption in health care delivery to these patients reported.<sup>1</sup> The use of immunosuppression has been associated with high risk of severe COVID-19 disease.<sup>2</sup> The rapid advent of safe and efficacious COVID-19 vaccines has been hailed as a landmark achievement of modern medicine. Administration of vaccine is likely to mitigate severe manifestations of COVID-19 in immunosuppressed patients; however, it is well known that anti-CD20 therapy is associated with

reduced immunological response to vaccines.<sup>3</sup> Anti-CD20 therapy has emerged as a promising targeted therapy for a number of immune mediated kidney diseases. Rituximab, a chimeric monoclonal antibody directed against the CD20 antigen expressed on B lymphocytes, is licensed for the treatment of antineutrophil cytoplasmic antibody-associated vasculitis. In addition, rituximab is widely used off-label for treatment of several glomerular diseases, including but not limited to idiopathic membranous nephropathy, minimal change disease, lupus nephritis, and mixed cryoglobulinemia. Last, in the transplant setting, rituximab is a major component of desensitization protocols and for treatment of allograft rejection. Obinutuzumab and ofatumumab are humanized anti-CD20 agents, currently in phase 2 clinical trial in systemic lupus erythematosus. We would be remiss not to mention that vaccine “rollout” has been slow in

this vulnerable population and should be prioritized. The purpose of this document is to review previous literature pertaining to established vaccine use in the setting of anti-CD20 treatment, along with providing recommendations for the timing of COVID-19 vaccine and measurement of response to administration. It is our hope that this review will serve as a primer for understanding the pathobiology of B-cell-depleting therapy and be helpful to practitioners and trainees in nephrology.

## The Effect of Anti-CD20 Inhibition on Vaccine Response

B lymphocytes or B cells are a central component of adaptive immunity and are a requisite for the secretion of antibodies against “non-self” antigens. B-cell-depleting therapies do not eliminate B-cell immunity completely. Anti-CD20 therapy results in depletion of circulating CD20-positive B cells in the periphery, but not hematopoietic stem cells in the bone marrow or antibody-producing long-lived plasma cells that lack CD20.<sup>4</sup> Therefore, humoral immunity to childhood vaccines, such as tetanus or meningitis, is preserved during therapy with anti-CD20 therapy.<sup>5</sup> Nevertheless, immune responses to vaccination during rituximab administration may be dampened. In addition, anti-CD-20 therapy is also associated with substantial T-cell depletion.<sup>6</sup> Moreover, CD20-positive memory B cells are not completely abrogated during anti-CD20 therapy but can rapidly expand and differentiate into antibody-producing cells when restimulated. Although it is known that anti-CD20 therapy impairs the humoral response to vaccination,

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**Table 1.** Studies assessing response to vaccines in various disease populations treated with rituximab

Study	Disease population	Number of patients	Mean age of the study cohort	Female, %	Mean treatment duration, wk	Humoral responses to vaccines, %					
						Seroconversion			Seroprotection		
						Influenza	23-valent Pneumococcal	Haemophilus influenzae	Tetanus	Hepatitis B	Measles
Kim <sup>8</sup>	NMOSD	16	39	81	85.7	37.5	–	–	37.5	75	87.5
Bingham <sup>55</sup>	RA	68	38	75	36	–	57	–	39.1	–	–
Nazi <sup>54</sup>	ITP	24	40	71	24	–	21	29	–	–	–
van Assen <sup>513</sup>	RA	23	55	70	NR	20	–	–	–	–	–
Richj <sup>510</sup>	Multiple	20	49	60	NR	40	–	–	–	–	–
Bühler <sup>514</sup>	Multiple	11	52	57	NR	–	–	–	98	–	–

ITP, immune thrombocytopenic purpura; NMOSD, neuromyelitis optica spectrum disorder; NR, not reported; RA, rheumatoid arthritis.

the interaction between CD20 depletion and immune response to vaccine is complex and remains poorly understood.

Vaccination is known to reduce rates of hospital admissions due to infections, emergency room visits, and the rate of invasive infectious diseases in patients with autoimmune disease.<sup>7</sup> However, it has been extensively demonstrated that anti-CD 20 therapy (both rituximab and ocrelizumab) is associated with impaired vaccine response. This was first demonstrated in patients with neuromyelitis optica on rituximab therapy, with reduction in protective antibody titer and seroconversion rate (37.5% vs. 75.0% healthy controls) post-H1N1 influenza A vaccination.<sup>8</sup> Similar blunting in immune response has been reported with respect to pneumococcus, haemophilus influenza B, hepatitis B, and tetanus toxoid in the context of anti-CD20 therapy.<sup>9–53</sup> In addition, antibody responses can be impaired up to 6 months after anti-CD20 therapy, with reduction in cellular immunity in parallel with depleted B-cell pools.<sup>54,55</sup> It has been proposed that vaccine response is blunted until B cells repopulate.<sup>51</sup> Repopulation kinetics varies among the anti-CD20 agents, ranging from 24 weeks to 35 weeks for rituximab, 40 weeks for ofatumumab, and 72 weeks for

ocrelizumab. Table 1 elucidates studies assessing response to vaccines in various disease populations being treated with rituximab.

### Existing Non-COVID-19 Vaccine Administration Recommendations

The European League Against Rheumatism provided updated guidelines for vaccinations in the setting of anti-CD20 therapy in 2019.<sup>56</sup> In light of the increasingly documented reduction in response to vaccines in the setting of B-cell–depleting therapy, the European League Against Rheumatism recommends the following:

1. Vaccines should be ideally administered before the planned immunosuppression.
2. In case of nonimmunized patients on B-cell–depleting therapy, vaccination should be provided at the following time window: at least 6 months after the administration and 4 weeks before the next course of B-cell–depleting therapy, based on the state of clinical practice.
3. In cases when this time window for immunization is not possible, vaccination may be considered under B-cell–depleting therapy, taking into consideration a potential sub-optimal response to vaccine.

### Existing COVID-19 Vaccine Administration Recommendations

A COVID-19 vaccine guidance clinical summary released by the American College of Rheumatology issued the following recommendations after a moderate consensus among the North American task force panel:

1. Initiate the vaccine series 4 weeks before next scheduled rituximab cycle.
2. After vaccination, the guidance states to delay rituximab 2 to 4 weeks after the second vaccine dose, if disease activity allows.

### Vaccine Readiness and Timing of COVID-19 Vaccine

The generation of neutralizing antibodies are likely central to protection against coronaviruses, as has been shown previously with severe acute respiratory distress syndrome and

Middle East respiratory syndrome.<sup>57,58</sup> This humoral response is likely to be dampened as a consequence of anti-CD20 therapy, as has been demonstrated extensively by vaccine response studies discussed previously. Therefore, appropriate timing of vaccine in relation to anti-CD20 therapy is of paramount importance to gain maximum efficacy of vaccine and mitigate risk of infection along with associated complications.

Based on available data on rituximab B-cell repopulation kinetics and previous vaccine studies, the following are recommendations for timing of COVID-19 vaccine:

1. Administer complete vaccine series 12 weeks before anti-CD20 therapy, because better responses are achieved when similar timeline was used between previous types of vaccination and rituximab administration.<sup>S9,S10</sup> This approach is particularly feasible in patients with membranous nephropathy who are at mild to moderate risk of progression and patients with anti-neutrophil cytoplasmic antibody–associated vasculitis who receive rituximab for remission maintenance.
2. Individualized risk assessment with respect to comorbidities and infection, along with risk of disease relapse, must be undertaken in deciding delaying anti-CD20 therapy to aid in vaccine administration.
3. Delaying anti-CD20 therapy in a patient with active disease or high risk of relapse in favor of receiving vaccine is not advisable. Accentuated measures of physical distancing and use of personal protective equipment can be helpful in mitigating risk of COVID-19 in patients with autoimmune disease.<sup>1</sup>
4. Delaying administration of the vaccine 6 months after anti-CD20 therapy has been deemed to be ideal to maximize efficacy of vaccines in general and likely to be applicable to COVID-19 vaccine.<sup>S2</sup>
5. Measurement of B-cell populations could be undertaken 3 months after rituximab treatment for guiding vaccine administration, because any evidence of repopulation may be a “window” for vaccine administration and ensuing desired immune response (with need for assessing for concomitant risk for incipient disease relapse). It has been demonstrated that B-cell repopulation kinetics post anti-CD20 therapy can vary in individuals and disease processes.<sup>S11,S12</sup>
6. As vaccine response may be attenuated or occur at lower rates after anti-CD20 therapy, vaccine response can be quantified with titers also taking into consideration development of emerging virus variants. This may guide the decision to revaccinate individuals after B-cell reconstitution.
7. Centers of excellence should establish protocols to measure humoral response to vaccine and correlate this with demographics, treatment-related factors, and immune profile of these patients.

### Conclusion

There is a paucity of data to guide timing of vaccine in the patients receiving anti-CD20 therapy, and current recommendations are being extrapolated from prior vaccine studies and knowledge of B-cell repopulation kinetics. Therefore, a pressing need exists for studies that can elucidate seroconversion to the COVID-19 vaccine in the setting of anti-CD20 therapy, along with defining parameters for assessing durable response. This is even more pertinent given well-established risk of severe COVID-19 in patients on immunosuppression and ongoing vaccine shortage worldwide.

### DISCLOSURES

DG reports being consultant to ChemoCentryx and Aurinia. All the other authors declared no competing interests.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References

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