Seroconversion following COVID-19 vaccination: Can we optimize protective response in CD20-treated individuals?

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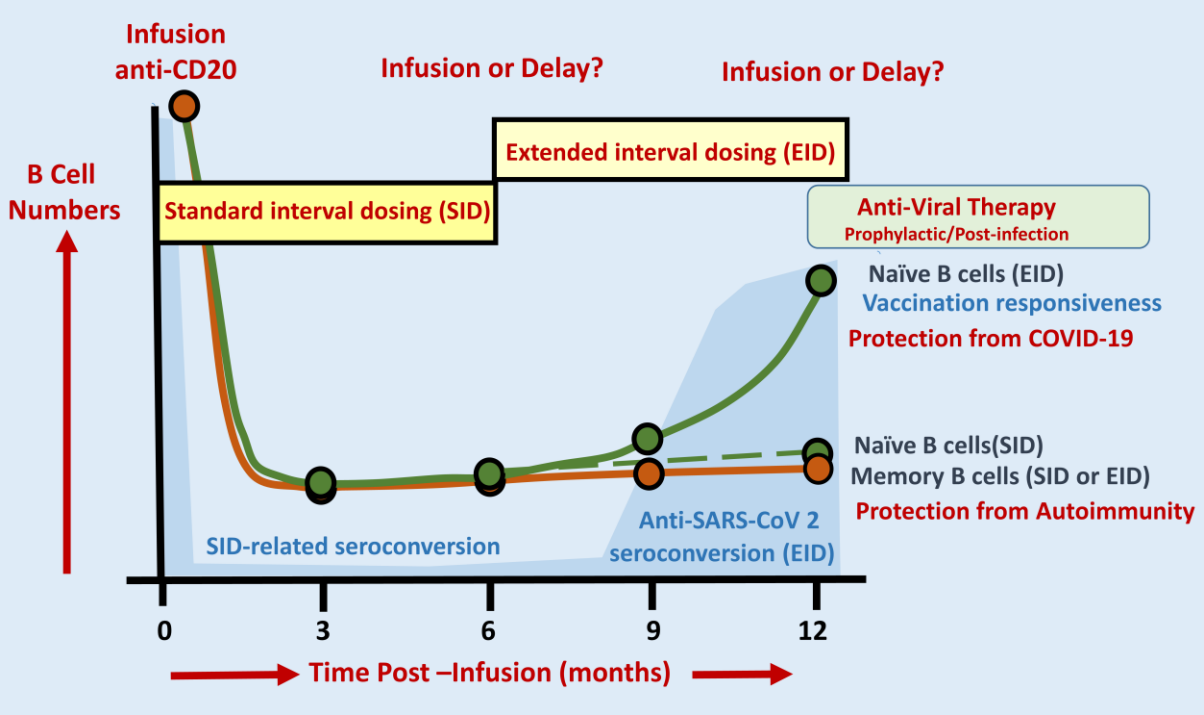
Abbreviations: Coronavirus disease 2019 COVID-19, Epstein Barr virus EBV, multiple sclerosis MS, polymerase chain reaction (PCR), severe acute respiratory syndrome corona virus two SARS-CoV-2,

ABSTRACT

Although there is an ever-increasing number of disease-modifying treatments for relapsing multiple sclerosis (MS), few appear to influence COVID-19 severity. There is concern about the use of anti-CD20-depleting monoclonal antibodies, due to the apparent increased risk of severe disease following SARS-CoV-2 infection and inhibition of protective anti-COVID-19 vaccine responses. These antibodies are given as maintenance infusions/injections and cause persistent depletion of CD20+ B cells, notably memory B cell populations that may be instrumental in the control of relapsing MS. However, they also continuously deplete immature and mature/naïve B cells that form the precursors for infection-protective antibody responses, thus blunting vaccine responses. Seroconversion and maintained SARS-CoV-2 neutralizing antibody levels provide protection from COVID-19. However, it is evident that poor-seroconversion occurs in the majority of individuals following initial and booster COVID-19 vaccinations, based on standard 6-monthly dosing intervals. Seroconversion may be optimized in the anti-CD20-treated population by vaccinating prior to treatment-onset or using extended/delayed interval dosing (3-6 month extension to dosing interval) in those established on therapy, with B cell monitoring until (1-3%) B cell repopulation occurs prior to vaccination. Some people will take more than a year to replete and therefore protection may depend on either the vaccine-induced T cell responses that typically occur or may require prophylactic, or rapid post-infection therapeutic, antibody or small molecule anti-viral treatment to optimise protection against COVID-19. Further studies are warranted to demonstrate the safety and efficacy of such approaches and whether or not immunity wanes prematurely as has been observed in the other populations.

Keywords: Autoimmunity; CD20 B cells; COVID-19 vaccination; immunotherapy, multiple sclerosis

Graphical Abstract



Therapeutic B cell targeting antibodies are used in the treatment of autoimmune diseases; most recently as a maintenance treatment for the control of multiple sclerosis. Membrane-spanning 4A1 (CD20) protein is a cell membrane molecule that is involved in the development and differentiation of B cells and is thought to represent a type of calcium channel [1]. It is expressed throughout B cell development except in early (stem cells and pro/pre B cells) and late (plasmablasts and plasma cells) stages (Figure 1) [1]. B cells can be targeted by an increasing number and variety of CD20-depleting monoclonal antibodies (mAb) including: *murine* (*Tositumomab* and *ibritumomab* used as radioactive isotope targeting vehicles for lymphoma); *chimeric* (*rituximab* used in lymphoma, leukaemia, rheumatoid arthritis, vasculitis, pemphigus vulgaris and used off-label in many other autoimmune diseases including multiple sclerosis (MS) and *ublituximab* for MS; *humanised* (*ocrelizumab* for MS; *obinutuzumab* for B cell lymphomas and leukaemia; *veltuzumab* for idiopathic thrombocytopaenic purpura and pemphigus) and *human* (*ofatumumab* used intravenously from chronic lymphocytic leukemia and subcutaneously for MS) antibodies (Figure 1) [2]. These cause complement-dependent killing, antibody-dependent cellular cytotoxicity and apoptosis of CD20 expressing B cells [3]. In autoimmune disease, efficacy may relate to either the direct long-term depletion of memory B cells (Figure 2) and development of regulatory B cells within the regenerating CD19 population [4-6] or indirectly through blockade of T cell activity to inhibit autoimmunity [7,8] (Figure 1).

CD20-depletion is a risk factor for severe symptomatic COVID-19. Coronavirus disease 2019 (COVID-19) has been a devastating global pandemic, killing millions of people. Although the major drivers of disease severity relate to age, sex, comorbidities, socioeconomic factors and viral load [9, 10] there is concern that disability and being immunocompromised may contribute to COVID-19 disease morbidity in the MS population [11-13]. CD20-depleting mAb have been reported to increase hospitalisation and more severe COVID-19 in many [13-19], but not all [20,21], studies in MS. As anti-CD20 therapies appear to limit antibody responses [22-24], this apparent increased risk from COVID-19 infection [13] may relate to the inability to form, or loss of, a protective, cross-reactive immunity to cold-causing coronavirus responses [25-28]. The ability of specific antibody responses to inhibit severe acute respiratory syndrome corona virus two (SARS-CoV-2) infection in animal models [29,30] and humans [31-34] highlights the importance of the B cell response for protection. A sufficiently high neutralizing titre may limit symptomatic SARS-CoV-2 infection [35,36] more than a T cell response [37]. However, a B cell response is not absolutely necessary, as the SARS-CoV-2 virus can be eliminated by the innate-immune and T cell response before the formation of an effective IgG response, and recovery can occur in the relative absence of B cells [23,25]. However, the full spectrum of innate, T and B cell immunity will provide the best protection [38].

CD20-depletion is also a risk factor for poor serological response to infection and vaccination. Given the blunted antibody response to other vaccines [23,39,40], it is not surprising that CD20-depeleting antibodies, notably rituximab and ocrelizumab, have been repeatedly and consistently shown to induce poor seroconversion following natural infection with SARS-CoV-2 [41-46]. Likewise, although RNA vaccines produce higher antibody titres and result in greater proportional seroconversion than adenoviral vector vaccines [24,35,47,48], seroconversion in CD20-depleted, COVID-19 vaccinated individuals is universally poor [22,24,49-55]. It is evident that it is possible to generate a COVID-19 vaccine response in the absence of detectable peripheral B cells [55-57], indicating that the generation of the vaccine-related antibody response likely occurs within lymphoid tissues, which are seemingly not completely purged of B cells [5], rather than the peripheral blood. However, baseline B cell number within the blood has potential biomarker activity for predicting seroconversion following vaccination [58-61]. People with 1-3% CD19/>10 cells/μL, often, but not always, generate COVID-19-related IgG responses following vaccination [50,56,60-62] related to repopulation of naïve B cells. Depletion with CD38-specific antibodies, as used in myeloma, can also be associated with poor seroconversion [63,64] supporting a role for CD20+ naïve B, although CD38 is also found on CD20-, plasmablasts and plasma cells (Figure 1).

Despite a consistently blunted antibody response in those treated with anti-CD20 mAb, it is increasingly clear that T cell responses are often generated following both natural infection and COVID-19 vaccination [22,41,50,53,57,65-67]. CD4 responses may not only facilitate antibody responses, but can also provide help for other defence mechanisms against the SARS-CoV-2 virus that are augmented by vaccination [50,57,65-68]. CD8-responses may even be augmented in antibody-deficient individuals in MS and elsewhere [50,59,69], perhaps consistent with mobilization of CD8 T cells by vaccination [70]. Such viral spike-protein directed CD8 responses from vaccination [Ramesh et al. 2021], may complement protective CD8 responses to other viral proteins, such as the nucleocapsid protein that are generated following natural infection with SARS-CoV-2 or in some instances with other coronaviruses [68, 71,72].

However, given the importance of neutralizing antibody responses following vaccination [37,38] Molodtsov et al. 2021; Israelow et al. 2021], and the finding that protective antibody titres subside over time [35] [Khoury et al 2021], COVID-19 breakthrough can and will occur. This is already seen in vaccinated, healthy individuals [73-76] [Wei et al. 2021; Shrotri et al. 2021; Bergwerk et al. 2021; Goldberg et al. 2021] and is being seen in immunosuppressed individuals [77, 78] [Cook et al. 2021; Di Fusco et al. 2021]. As CD20-treated individuals produce lower titre antibody responses than untreated controls [24,49,79] [Tallantyre et al. 2021; Achiron et al. 2021; Kearns et al. 2021], they

are potentially in need of effective third cycle/booster vaccinations. Whilst boosters increase seroconversion in some immunocompromised people [80,81] [Shroff et al. 2021; Re et al. 2021], it is likely that CD20-depletion will still inhibit this response in the majority of people, as is currently being seen [81-84] [Re et al. 2021; Connolly et al. 2021; Greenberger et al. 2021; Konig et al. 2021b] There is thus a potential need for pilot studies to help optimise COVID-19 vaccination in the anti-CD20 treated population before mass use of a potentially futile strategy.

Long-term memory B cell depletion may support safe treatment breaks for vaccination.

The inhibition of vaccine-induced antibody responses by continuous CD20 depletion [23,85,86] is not surprising, as B cells repopulate in a stereotyped behaviour following depletion with CD20-depleting mAb [5,6,23,87]. Immature/transitional/ regulatory B cells (**Figure 1**) rapidly repopulate the space created by B cell depletion and generate a novel mature/naïve B cell pool containing cells that can respond to new antigenic stimuli to potentially generate vaccine responses [5,23,87]. Following 600mg 24QW doses of ocrelizumab, it takes on average 62-72 weeks (range 27-175 weeks) for CD19 cells to return to the lower limit of normal (80 cells/µl) [6,23]. Repopulation following 500mg/1000mg 24QW rituximab administration is more rapid [87,88]. Depletion of CD19+ cells following 20mg subcutaneous ofatumumab injections is rapid and sustained during treatment [89]. Following treatment cessation, it takes a median of about 25 weeks for CD19+ cells to repopulate to 40 cells/µl, which is faster than found with repeated doses of ocrelizumab [90,91]. The degree of depletion and speed of repopulation induced by ocrelizumab may depend on both the dose used *in vivo* and the individual, most notably related to body mass index, where larger people may repopulate quicker [92-95].

In contrast, the memory B cell pool, which potentially harbours important pathogenic response cells, repopulates very slowly over many months [4,5,96] (Figure 2). This may provide durability of protection against autoimmunity [4,5]. The majority of people do not show disease reactivation within twelve to eighteen months following treatment cessation following rituximab and ocrelizumab treatment [6,97,98] Following the development of the COVID-19 pandemic, concerns about the influence of immunosuppression led to treatment interruption [68]. Delays of 1-3 and even 6 months were not generally associated with disease breakthrough [98-104].

Is it possible to optimise vaccine response through treatment delay? There is increasing evidence that antibody responses relate to the degree of B cell depletion and repopulation [56, 62,105,106]. However, B cell repletion to 1% CD19+ lymphocytes occurred in less than 5% of people at 6 months following 3 to 4 cycles of ocrelizumab (Figure 3). Therefore, a large population of people established on treatment are unlikely to be able to mount an effective COVID-19 vaccine antibody response

within the 6month dosing schedule [53,107]. However, about 85%-90% of people exhibited a 1% CD19+ B cell level at 12 months following ocrelizumab [108]. It was evident that even at 18 months post-infusion some people had not repleted to 1% B cells (Figure 3). A higher BMI (>25) may exhibit a small influence on B cell depletion and repopulation (Figure 3) [95,109] [Signoriello et al. 2019; Kletzl et al. 2019]. This could argue for a more personalised dosing regime as is currently employed with off-label rituximab in MS and a number of other autoimmune diseases, allowing >6 monthly extended dosing intervals based on B cell repletion [6,110,111]. It is evident that people are willing to accept delays in ocrelizumab and rituximab treatment [98-104], therefore, offering an extended dosing interval with CD20-depleting mAb infusions is feasible and may safely allow better seroconversion responses for the majority of people [53; 98,108]. Given the novelty of monthly ofatumumab injections, vaccination prior to treatment onset should be feasible for most people. How this agent will influence future COVID-19 related and other vaccinations, and the safety of treatment delays, is currently unknown. Therefore, is not possible to offer evidence-based advice to assist patient choice for this treatment.

Generating a protective antibody response. An alternative solution to extended dosing or boosters may be to provide a prophylactic anti-viral response through the use of small molecule anti-viral agents, such as Molnupiravir, which are in development [112-114], or the generation of a high-titre antibody response through the delivery of convalescent sera or mAb cocktails that can be optimised for activity against circulating variants [114-117]. Intravenous or subcutaneous SARS-CoV-2 mAb cocktails such as casirivimab/imdevimab and bamlanivimab/etesevimab [32,33], against different parts of the SARS-CoV-2 Spike protein may offer the potential to provide prophylactic treatment in people who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination [32, 114]. These have shown some protection in CD20-depleted individuals [115,118]. However, their benefit will depend on efficacy against SARS-CoV-2 variants of concern circulating with the population at the time of use [119,120]. Some of these agents have standard antibody half-lives and require frequent administration, perhaps limiting their long-term use [114]. However, they have potential for targeted prophylaxis, such as following exposure to household infection [32]. Long-acting antibodies that are Fc-manipulated to substantially increase serum half-lives, such as a tixagevimab/cilgavimab cocktail [116, 117], may offer more widespread benefit (Table 1).

However, a concern is that untreated, immunosuppressed individuals may harbour prolonged SARS-CoV-2 infection that could allow serial mutations to develop, impacting on infectivity and immune escape [121-124]. This view is tempered by the alternative possibility that evolution of the virus selected by the presence of convalescent sera/mAb cocktails could drive the selection of viral escape

mutants [125]. Whilst mAb cocktails have been developed to limit this risk [32,33, 114], this remains a potential problem.

Conclusions. At initial vaccine roll-out, the priority was to vaccinate all people with MS in the timeliest manner possible, to provide some immunity against COVID-19 [126]. However, recent data enables us to take a more considered approach on the best way to balance protecting people taking CD20-depleting antibodies, whilst maintaining effective disease control. Although blunted, many people make some form of response; a simple approach would be to determine whether boosters can augment this, as suggested by early evidence [78,84]. A growing body of evidence appears to show that inactivated and adenoviral-based vaccines generate lower titre antibody responses and potentially weaker protection than RNA vaccines [24,35,48], thus booster injections should ideally focus on RNA vaccines, where mRNA-1273 appears to give the highest titre response [35,52]. In some places, it may be feasible to offer whole inactivated virus vaccines and whilst they may not offer comparable protection from infection to RNA vaccines [48], they expose the immune response, notably the T cell compartment to additional viral antigens, such as the nucleocapsid protein, that could contribute to more effective protection against severe COVID-19 [72]. Furthermore, delaying treatment for a short period, perhaps by 3 to 6 months, to facilitate 1-3% B cell repletion, and the development of the most effective booster programme possible may be a justifiable risk and could be offered to the immunosuppressed individual to make an informed choice. This could be facilitated by monitoring B cell repletion and disease activity using imaging. It remains to be seen whether anti-CD20-depleted, but vaccinated individuals remain at any additional risk of severe COVID-19 compared to the general population, and if so, measures discussed here may be warranted. Optimization studies are therefore urgently required so that they can inform on vaccine boosters for immunosuppressed people.

Data Availability: Clinical trial data (NCT00676715/WA21493) is available from Roche/Genentech under contract via the www.vivli.org clinical research data sharing platform.

Human Studies Ethics: Clinical trial data (NCT00676715) was collected with ethical approval with informed consent [6,127].

Funding: This rearch received no specific funding

Acknowledgments: This publication is in part based on research using data from data contributors Roche that has been made available through Vivli, Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication. Data analysis, interpretation and conclusions made are independent from Roche. We thank Alison Schroeer for assistance with production of figures.

Author contribution: Concept: DB, ASK, KS, GG, RD; Data Extraction: DB AM; Statistical analysis AM; Figure design: DB; ASK; Initial Draft DB, ASK, RB; Manuscript:DB, AM, ASK, KS, GG, RD

Conflicts of Interest: DB, KS, GG and RD, have received compensation for consultancy/educational activity from Novartis, or Roche/Genentech who manufacture COVID-19 and MS drugs discussed in this study. These were not involved in the content or the decision to publish. However, Roche received the manuscript to review prior to submission, consistent with the legal agreement required to access the Roche trial data via the Vivli Inc. platform. AM, ASK have nothing relevant to declare. Although considered irrelevant DB, KS, GG, RD have received compensation for consultancy/educational activity from all companies manufacturing licensed disease modifying agents in the MS space.

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Table 1. *Prophylactic inhibition of COVID-19 infection*

Demographic		Treatment		Protection
Baseline subgroup	Onset of case	AZD7442	placebo	Relative Risk Reduction
All participants	All cases	23/749	17/372	33% (-26-65) reduction
PCR-negative	All cases	6/715	11/358	73% (27-90) reduction
PCR-negative	7 days	1/170	6/352	92% (32-99) reduction

Participants (adults >18 years old) with a potential exposure to an affected individual were 1:2 randomised to saline placebo (n=372) or a single set of intramuscular 300mg tixagevimab/cilgavimab ((AZD7442) n=749) in a double blind, randomised trial (STORMCHASER. NCT04625972). Whilst the primary endpoint, triggered after 35 infection events, of illness occurring up to day 183 post-potential contact, was not met, unplanned post-hoc analysis of individuals who were confirmed viral polymerase chain reaction (PCR) test negative at the start of the trial and did not develop disease for 7 days after infusion, to avoid analysis of people infected before infusion, showed marked prophylactic protection [117].

Figure Legends

Figure 1. *B cell lineage and CD20-specific antibodies*. A simplified schematic of the B cell lineage related to CD20 antigen expression and the CD20-speicifc antibodies. Epstein Barr Virus (EBV) can generate memory B cells in the potential absence of antigen and co-stimulation or they can be antigen expanded.

Figure 2. *Deletion and repopulation of B cells following ocrelizumab infusion in multiple sclerosis.* Individuals received 600mg ocrelizumab Q24W for 4 cycles or placebo followed by three 600mg ocrelizumab cycles [6]. The raw data was extracted from the phase II ocrelizumab extension study supplied via the www.vivli.org portal using R software. The results represent the mean ± standard deviation n= maximum 46-47/group.

Figure 3. *CD19 B cell repletion after repeated ocrelizumab infusions.* Individuals received 600mg ocrelizumab Q24W for 3 or 4 cycles followed an 18 month treatment-free period [6]. The data was extracted the raw data from the phase II ocrelizumab extension study (NCT00676715) supplied via the Vilvi Inc.portal using R software. Data was stratified according to baseline Body Mass Index. The results represent the approximate time from the last infusion and probability of repopulating to 1% CD19 B lymphocytes.

Figure1

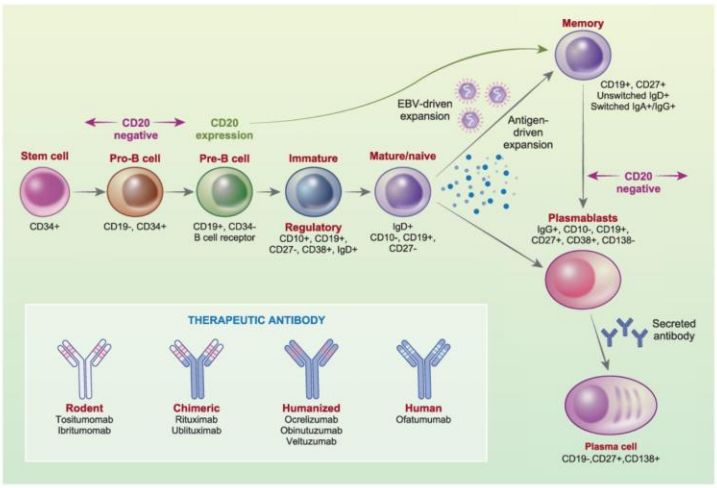

Figure 2

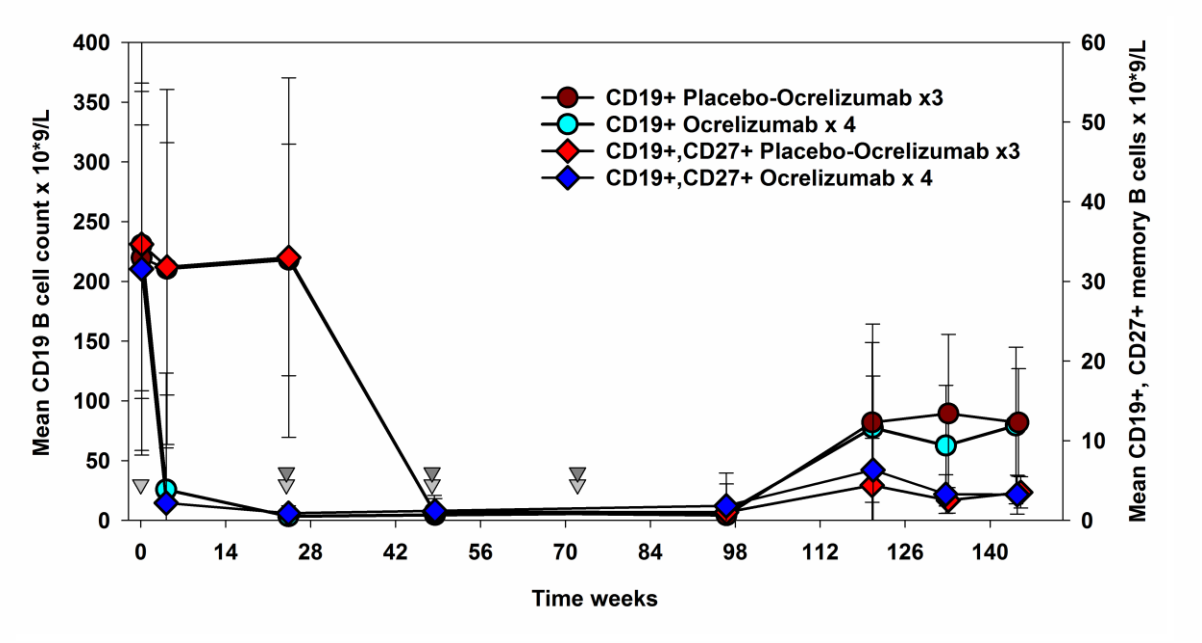

Figure 3