

Seroconversion following COVID-19 vaccination: Can we optimize protective response in CD20-treated individuals?**David Baker^{1*}, Amy MacDougall², Angray S. Kang^{1,3}, Klaus Schmierer^{1,5}, Gavin Giovannoni^{1,5}, Ruth Dobson^{4,5}**

¹The Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom

²Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom

³Centre for Oral Immunobiology and Regenerative Medicine, Dental Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK.

⁴Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, Barts and The London School of Medicine & Dentistry, London, United Kingdom

⁵Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom

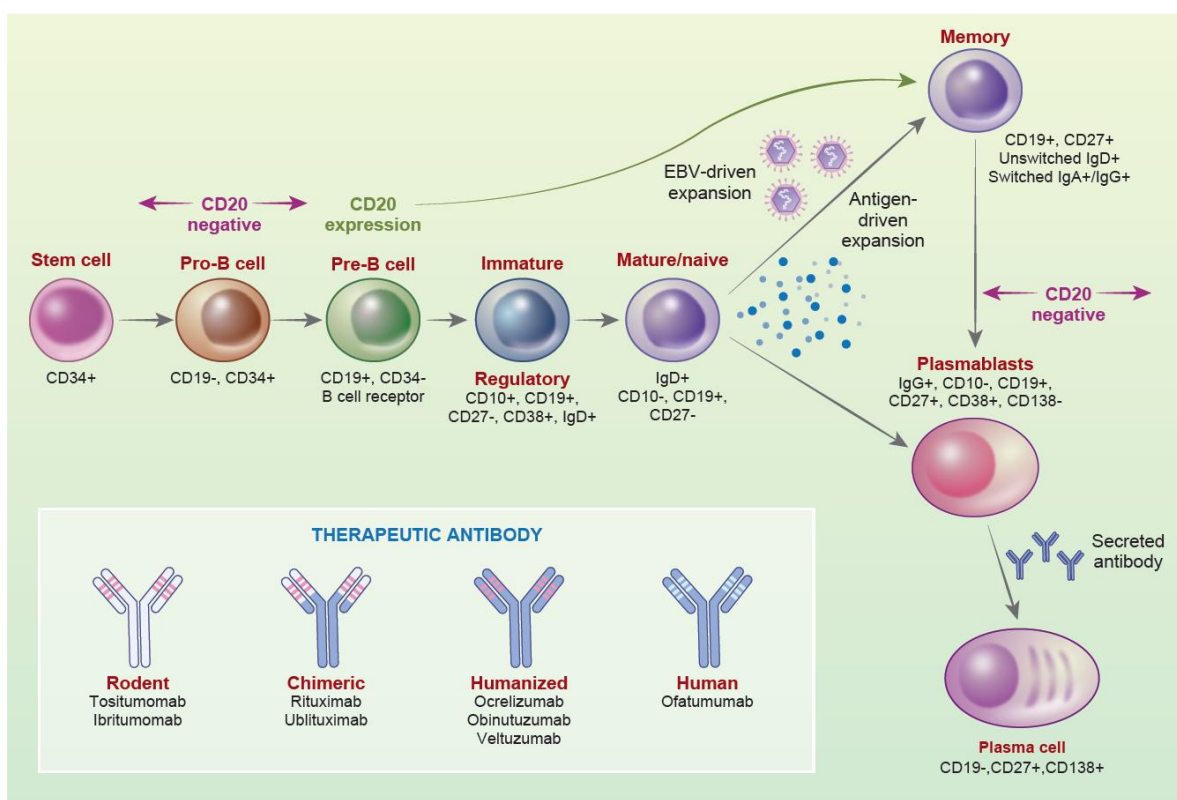
*Corresponding author: Professor David Baker, The Blizard Institute, Queen Mary University of London, 4 Newark Street, London, E1 2AT. Phone: +44 207 882 2485. Fax: +44 207 882 2410. Email: david.baker@qmul.ac.uk

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.

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 thrombocytopenic 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).

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-specific 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.

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,

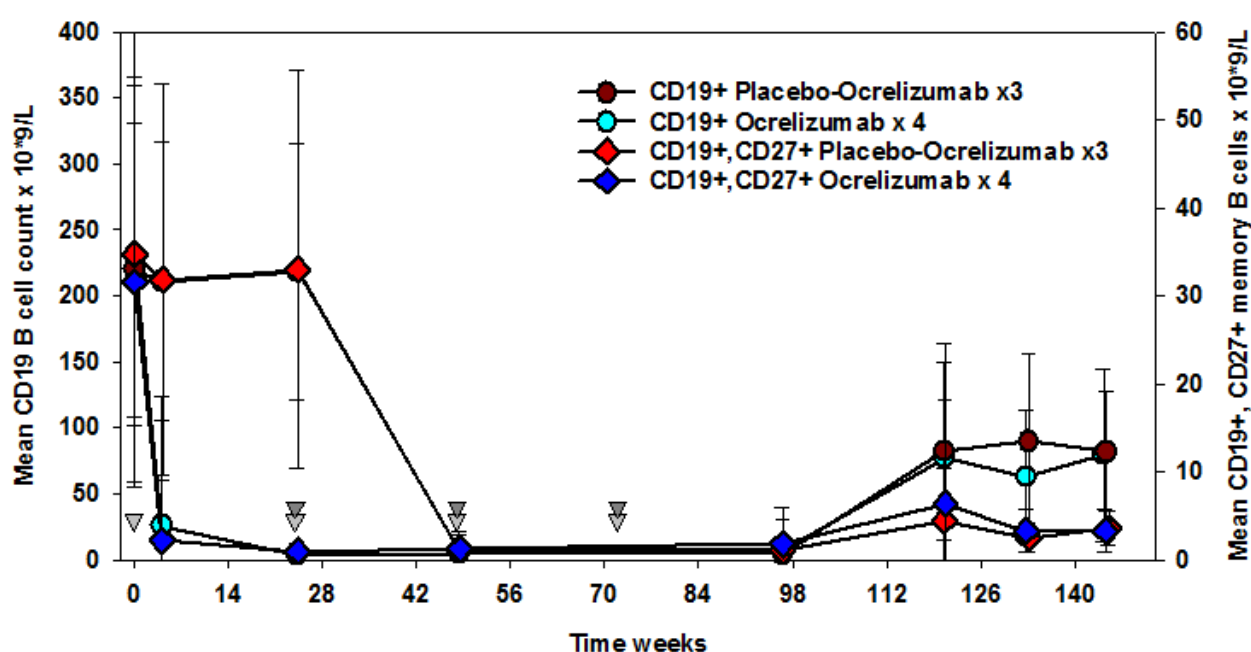
10] there is concern that disability and being immunocompromised may contribute to COVID-19 disease morbidity in the MS population [11-13]. CD20-depleting mAb have been reported to increase hospitalisation and more severe COVID-19 in many [13-19], but not all [20,21], studies in MS. As anti-CD20 therapies 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 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-depleting 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/ μ L, 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.

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 \pm standard deviation n= maximum 46-47/group

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

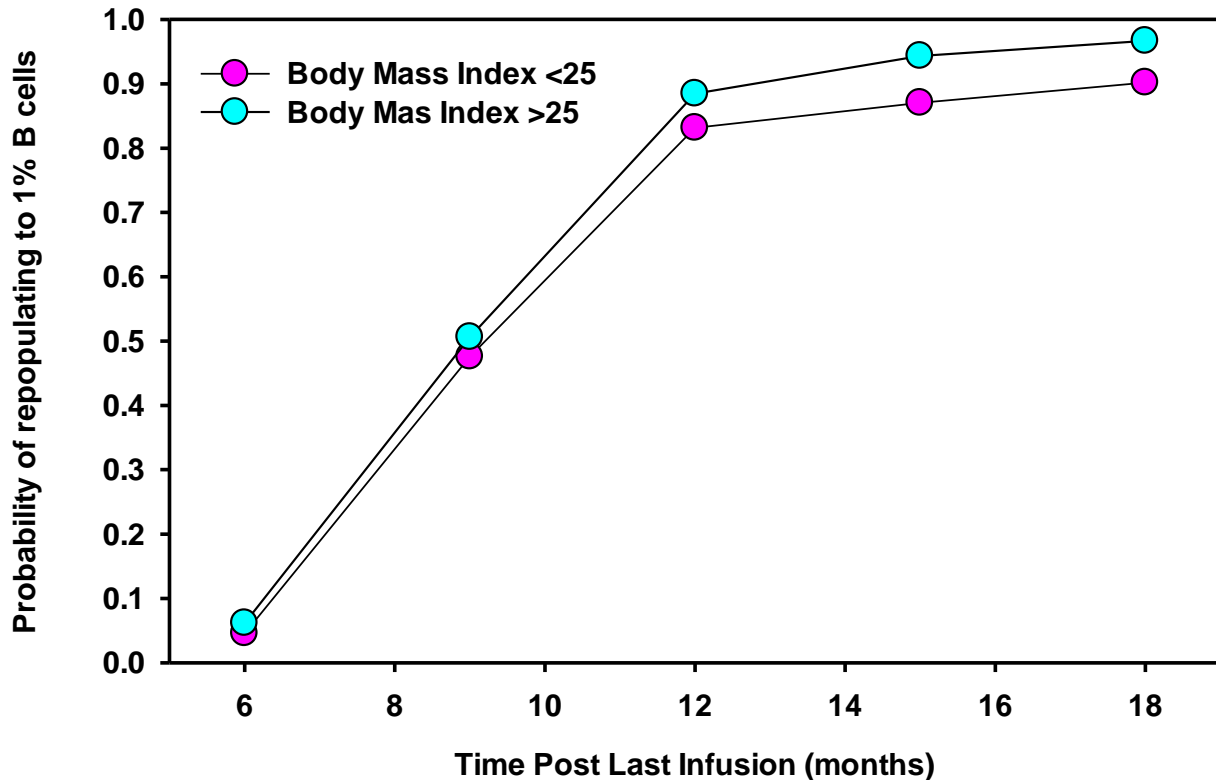
The inhibition of vaccine-induced antibody responses by continuous CD20 depletion [23,85,86] is not surprising, as B cells repopulate in a stereotyped behaviour following depletion with CD20-depleting mAb [5,6,23,87]. Immature/transitional/ regulatory B cells (**Figure 1**) rapidly repopulate the space 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/ μ l) [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/ μ l, 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.

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.

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.

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 PCR 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].

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.

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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, AK 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.

References

1. Cragg MS, Walshe CA, Ivanov AO, Glennie MJ. The biology of CD20 and its potential as a target for mAb therapy. *Curr Dir Autoimmun.* 2005;8:140-74.
2. Du et al. 2017. Du FH, Mills EA, Mao-Drayyer Y. Next generation anti-CD20 monoclonal antibodies in autoimmune disease treatment. *Auto Immun Highlights.* 2017 8:12
3. van der Meid KR, Elliott MR, Baran AM, Barr PM, Chu CC, Zent CS. Cellular Cytotoxicity of Next-Generation CD20 Monoclonal Antibodies. *Cancer Immunol Res.* 2018; 6:1150-1160.
4. Baker D, Marta M, Pryce G, Giovannoni G, Schmierer K. Memory B Cells are Major Targets for Effective Immunotherapy in Relapsing Multiple Sclerosis. *EBioMedicine.* 2017; 16:41-50.
5. Baker D, Pryce G, Amor S, Giovannoni G, Schmierer K. Learning from other autoimmunities to understand targeting of B cells to control multiple sclerosis. *Brain.* 2018; 141:2834-2847.
6. Baker D, Pryce G, James LK, Marta M, Schmierer K. The ocrelizumab phase II extension trial suggests the potential to improve the risk: Benefit balance in multiple sclerosis. *Mult Scler Relat Disord.* 2020a;44a:102279.
7. Jelcic I, Al Nimer F, Wang J, Lentsch V, Planas R, Jelcic I, Madjovski A, Ruhrmann S, Faigle W, Frauenknecht K, Pinilla C, Santos R, Hammer C, Ortiz Y, Opitz L, Grönlund H, Rogler G, Boyman O, Reynolds R, Lutterotti A, Khademi M, Olsson T, Piehl F, Sospedra M, Martin R. Memory B Cells Activate Brain-Homing, Autoreactive CD4+ T Cells in Multiple Sclerosis. *Cell.* 2018; 175:85-100.e23.
8. Sabatino JJ, Zamvil SS, Hauser SL. B-Cell Therapies in Multiple Sclerosis. *Cold Spring Harb Perspect Med.* 2019; 9:a032037.
9. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, Worrall D, Giguel F, Piechocka-Trocha A, Atyeo C, Fischinger S, Chan A, Flaherty KT, Hall K, Dougan M, Ryan ET, Gillespie E, Chishti R, Li Y, Jilg N, Hanidziar D, Baron RM, Baden L, Tsibris AM, Armstrong KA, Kuritzkes DR, Alter G, Walker BD, Yu X, Li JZ; Massachusetts Consortium for Pathogen Readiness. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun.* 2020; 11:5493.
10. Booth A, Reed AB, Ponzo S, Yassaee A, Aral M, Plans D, Labrique A, Mohan D. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. *PLoS One.* 2021;16(3):e0247461.
11. Sormani MP; Italian Study Group on COVID-19 infection in multiple sclerosis. An Italian programme for COVID-19 infection in multiple sclerosis. *Lancet Neurol.* 2020a;19:481-482.
12. Louapre C, Collongues N, Stankoff B, Giannesini C, Papeix C, Bensa C, Deschamps R, Créange A, Wahab A, Pelletier J, Heinzlef O, Labauge P, Guilloton L, Ahle G, Goudot M, Bigaut K, Laplaud DA, Vukusic S, Lubetzki C, De Sèze J; Covisep investigators, Derouiche F, Tourbah A, Mathey G, Théaudin M, Sellal F, Dugay MH, Zéphir H, Vermersch P, Durand-Dubief F, Françoise R,

- Androdias-Condemine G, Pique J, Codjia P, Tilikete C, Marcaud V, Lebrun-Frenay C, Cohen M, Ungureanu A, Maillart E, Beigneux Y, Roux T, Corvol JC, Bordet A, Mathieu Y, Le Breton F, Boulos DD, Gout O, Guéguen A, Moulignier A, Boudot M, Chardain A, Coulette S, Manchon E, Ayache SS, Moreau T, Garcia PY, Kumaran D, Castelnovo G, Thouvenot E, Taithe F, Poupart J, Kwiatkowski A, Defer G, Derache N, Branger P, Biotti D, Ciron J, Clerc C, Vaillant M, Magy L, Montcuquet A, Kerschen P, Coustans M, Guennoc AM, Brochet B, Ouallet JC, Ruet A, Dulau C, Wiertlewski S, Berger E, Buch D, Bourre B, Pallix-Guiot M, Maurousset A, Audoin B, Rico A, Maarouf A, Edan G, Papassin J, Videt D. Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. *JAMA Neurol.* 2020; 77:1079-1088.
13. Simpson-Yap et al. 2021. Simpson-Yap S, De Brouwer E, Kalincik T, Rijke N, Hillert JA, Walton C, Edan G, Moreau Y, Spelman T, Geys L, Parciak T, Gautrais C, Lazovski N, Pirmani A, Ardeshirdavanai A, Forsberg L, Glaser A, McBurney R, Schmidt H, Bergmann AB, Braune S, Stahmann A, Middleton R, Salter A, Fox RJ, van der Walt A, Butzkueven H, Alroughani R, Ozakbas S, Rojas JI, van der Mei I, Nag N, Ivanov R, Sciascia do Olival G, Dias AE, Magyari M, Brum D, Mendes MF, Alonso RN, Nicholas RS, Bauer J, Chertcoff AS, Zabalza A, Arrambide G, Fidao A, Comi G, Peeters L. Associations of Disease-Modifying Therapies With COVID-19 Severity in Multiple Sclerosis. *Neurology.* 2021 Oct 5:10.1212/WNL.0000000000012753.
 14. Reder et al. 2020 Reder AT, Centonze D, Naylor ML, Nagpal A, Rajbhandari R, Altincatal A, Kim M, Berdofe A, Radhakrishnan M, Jung E, Sandrock AW, Smirnakis K, Popescu C, de Moor C. COVID-19 in patients with multiple sclerosis: Associations with disease-modifying therapies. *CNS Drugs.* 2021; 35:317-330.
 15. Bsteh G, Assar H, Hegen H, Heschl B, Leutmezer F, Di Pauli F, Gradl C, Traxler G, Zulehner G, Rommer P, Wipfler P, Guger M, Enzinger C, Berger T; AUT-MuSC investigators. COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: Insights from a nation-wide Austrian registry. *PLoS One.* 2021; 16:e0255316
 16. Langer-Gould A, Smith JB, Li BH; KPSC MS Specialist Group. Multiple sclerosis, rituximab, and COVID-19. *Ann Clin Transl Neurol.* 2021; 8:938-943.
 17. Salter A, Fox RJ, Newsome SD, Halper J, Li DKB, Kanellis P, Costello K, Bebo B, Rammohan K, Cutter GR, Cross AH. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. *JAMA Neurol.* 2021; 78:699-708.
 18. Spellman et al. 2021Spelman T, Forsberg L, McKay K, Glaser A, Hillert J. Increased rate of hospitalisation for COVID-19 among rituximab-treated multiple sclerosis patients: A study of the Swedish multiple sclerosis registry. *Mult Scler.* 2021 Jul 2:13524585211026272.
 19. Sormani MP, Salvetti M, Labauge P, Schiavetti I, Zephir H, Carmisciano L, Bensa C, De Rossi N, Pelletier J, Cordioli C, Vukusic S, Moiola L, Kerschen P, Radaelli M, Théaudin M, Immovilli P, Casez O, Capobianco M, Ciron J, Trojano M, Stankoff B, Créange A, Tedeschi G, Clavelou P, Comi G, Thouvenot E, Battaglia MA, Moreau T, Patti F, De Sèze J, Louapre C; Musc-19; Covisep

study groups. DMTs and Covid-19 severity in MS: a pooled analysis from Italy and France. *Ann Clin Transl Neurol.* 2021a; 8:1738-1744

20. Hughes R, Whitley L, Fitovski K, Schneble HM, Muros E, Sauter A, Craveiro L, Dillon P, Bonati U, Jessop N, Pedotti R, Koendgen H. COVID-19 in ocrelizumab-treated people with multiple sclerosis. *Mult Scler Relat Disord.* 2021;49:102725
21. Pedotti R, Muros-Le Rouzic E, Raposo C, Schippling S, Jessop N. Understanding the impacts of COVID-19 pandemic in people with multiple sclerosis treated with ocrelizumab. *Mult Scler Rel Disord.* 2021; DOI:<https://doi.org/10.1016/j.msard.2021.103203>
22. Gadani SP, Reyes-Mantilla M, Jank L, Harris S, Douglas M, Smith MD, Calabresi PA, Mowry EM, Fitzgerald KC, Bhargava P. Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy. *EBiomedicine* 2021; 73: 103636.
23. Baker D, Roberts CAK, Pryce G, Kang AS, Marta M, Reyes S, Schmierer K, Giovannoni G, Amor S. COVID-19 vaccine-readiness for anti-CD20-depleting therapy in autoimmune diseases. *Clin Exp Immunol.* 2020b; 202:149-161.
24. Tallantyre EC, Vickaryous N, Anderson V, Asardag AN, Baker D, Bestwick J, Bramhall K, Chance R, Evangelou N, George K, Giovannoni G, Godkin A, Grant L, Harding KE, Hibbert A, Ingram G, Jones M, Kang AS, Loveless S, Moat SJ, Robertson NP, Schmierer K, Scurr MJ, Shah SN, Simmons J, Upcott M, Willis M, Jolles S, Dobson R. COVID-19 vaccine response in people with multiple sclerosis. *Ann Neurol.* doi: 10.1002/ana.26251.
25. Baker D, Amor S, Kang AS, Schmierer K, Giovannoni G. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. *Mult Scler Relat Disord.* 2020c; 43:102174.
26. Majdoubi A, Michalski C, O'Connell SE, Dada S, Narpala S, Gelinis J, Mehta D, Cheung C, Winkler DF, Basappa M, Liu AC, Görges M, Barakauskas VE, Irvine M, Mehalko J, Esposito D, Sekirov I, Jassem AN, Goldfarb DM, Pelech S, Douek DC, McDermott AB, Lavoie PM. A majority of uninfected adults show preexisting antibody reactivity against SARS-CoV-2. *JCI Insight.* 2021;22;6:e146316
27. Sharwani K, Sharma R, Krishnan M, Jones T, Mayora-Neto M, Cantoni D, Temperton NA, Dobson SL, Subramaniam K, McNamara PS, Cunliffe NA, Turtle L, Zhang Q. Detection of serum cross-reactive antibodies and memory response to SARS-CoV-2 in pre-pandemic and post-COVID-19 convalescent samples. *J Infect Dis.* 2021;:jiab333.
28. Gouma S, Weirick ME, Bolton MJ, Arevalo CP, Goodwin EC, Anderson EM, McAllister CM, Christensen SR, Dunbar D, Fiore D, Brock A, Weaver J, Millar J, Der Ohannessian S; UPenn COVID Processing Unit, Frank I, Rader DJ, Wherry EJ, Hensley SE. Sero-monitoring of health care workers reveals complex relationships between common coronavirus antibodies and SARS-CoV-2 severity. *JCI Insight.* 2021; 6: e150449

29. Jones BE, Brown-Augsburger PL, Corbett KS, Westendorf K, Davies J, Cujec TP, Wiethoff CM, Blackbourne JL, Heinz BA, Foster D, Higgs RE, Balasubramaniam D, Wang L, Zhang Y, Yang ES, Bidshahri R, Kraft L, Hwang Y, Žentelis S, Jepson KR, Goya R, Smith MA, Collins DW, Hinshaw SJ, Tycho SA, Pellacani D, Xiang P, Muthuraman K, Sobhanifar S, Piper MH, Triana FJ, Hendle J, Pustilnik A, Adams AC, Berens SJ, Baric RS, Martinez DR, Cross RW, Geisbert TW, Borisevich V, Abiona O, Belli HM, de Vries M, Mohamed A, Dittmann M, Samanovic MI, Mulligan MJ, Goldsmith JA, Hsieh CL, Johnson NV, Wrapp D, McLellan JS, Barnhart BC, Graham BS, Mascola JR, Hansen CL, Falconer E. The neutralizing antibody, LY-CoV555, protects against SARS-CoV-2 infection in nonhuman primates. *Sci Transl Med*. 2021;13:eabf1906.
30. Peter AS, Roth E, Schulz SR, Fraedrich K, Steinmetz T, Damm D, Hauke M, Richel E, Mueller-Schmucker S, Habenicht K, Eberlein V, Issmail L, Uhlig N, Dolles S, Grüner E, Peterhoff D, Ciesek S, Hoffmann M, Pöhlmann S, McKay PF, Shattock RJ, Wölfel R, Socher E, Wagner R, Eichler J, Sticht H, Schuh W, Neipel F, Ensser A, Mielenz D, Tenbusch M, Winkler TH, Grunwald T, Überla K, Jäck HM. A pair of non-competing neutralizing human monoclonal antibodies protecting from disease in a SARS-CoV-2 infection model. *Eur J Immunol*. 2021. doi: 10.1002/eji.202149374.
31. Corti D, Purcell LA, Snell G, Veessler D. Tackling COVID-19 with neutralizing monoclonal antibodies. *Cell*. 2021;184:3086.
32. O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, Bar KJ, Barnabas RV, Barouch DH, Cohen MS, Hurt CB, Burwen DR, Marovich MA, Hou P, Heirman I, Davis JD, Turner KC, Ramesh D, Mahmood A, Hooper AT, Hamilton JD, Kim Y, Purcell LA, Baum A, Kyratsous CA, Krainson J, Perez-Perez R, Mohseni R, Kowal B, DiCioccio AT, Stahl N, Lipsich L, Braunstein N, Herman G, Yancopoulos GD, Weinreich DM; Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *N Engl J Med*. 2021. doi: 10.1056/NEJMoa2109682
33. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B, Morris J, Crystal C, Igbinadolor A, Huhn G, Cardona J, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Dabora MC, Klekotka P, Shen L, Skovronsky DM; BLAZE-1 Investigators. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med*. 2021:NEJMoa2102685.
34. Kremer AE, Kremer AN, Willam C, Völkl S, Verhagen J, Achenbach S, van der Meijden ED, Lang V, Aigner M, Maier C, Tenbusch M, Korn K, Lutzny-Geier G, Spoerl S, Strauß R, Vetter M, Überla K, Neurath MF, Mackensen A, Schiffer M, Hackstein H. Successful treatment of COVID-19 infection with convalescent plasma in B-cell-depleted patients may promote cellular immunity. *Eur J Immunol*. 2021;51:2478-2484.
35. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:1205-1211.

36. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, Dold C, Fuskova M, Gilbert SC, Hirsch I, Humphries HE, Jepson B, Kelly EJ, Plested E, Shoemaker K, Thomas KM, Vekemans J, Villafana TL, Lambe T, Pollard AJ, Voysey M, the Oxford COVID Vaccine Trial Group. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med*. 2021. doi: 10.1038/s41591-021-01540-1.
37. Molodtsov I, Kegeles E, Mitin A, Mityaeva O, Musatova O, Panova A, Pashenkov M, Peshkova I, Almaqdad A, Asaad W, Budikhina A, Deryabin A, Dolzhikova I, Filimonova I, Gracheva A, Ivanova O, Kizilova A, Komogorova V, Komova A, Kompantseva N, Lagutkin D, Lomakin Y, Maleeva A, Maryukhnich E, Mohammad A, Murugin V, Murugina N, Navoikova A, Nikonova M, Ovchinnikova L, Pinegina N, Potashnikova D, Romanova E, Saidova A, Sakr N, Samoiloa A, Serdyuk Y, Shakirova N, Sharova N, Sheetikov S, Shemetova A, Shevkova L, Shpektor A, Trufanova A, Tvorogova A, Ukrainskaya V, Vinokurov A, Vorobyeva D, Ksenia Zornikova K, Efimov G, Khaitov M, Kofiadi I, Komissarov A, Logunov D, Naigovzina N, Rubtsov Y, Vasilyeva I, Volchkov P, Vasilieva E. A prospective study of the protective effect of SARS-CoV-2-specific antibodies and T cells in Moscow residents. *MedRxiv*. doi: <https://doi.org/10.1101/2021.08.19.21262278>
38. Israelow B, Mao T, Klein J, Song E, Menasche B, Omer SB, Iwasaki A. Adaptive immune determinants of viral clearance and protection in mouse models of SARS-CoV-2. *Science Immunol*. 2021. DOI: 10.1126/sciimmunol.abl4509
39. Vijenthira A, Gong I, Betschel SD, Cheung M, Hicks LK. Vaccine response following anti-CD20 therapy: a systematic review and meta-analysis of 905 patients. *Blood Adv*. 2021; 5:2624-2643.
40. Ollila et al. 2021], Ollila TA, Lu S, Masel R, Zayac A, Paiva K, Rogers RD, Olszewski AJ. Antibody Response to COVID-19 Vaccination in Adults With Hematologic Malignant Disease. *JAMA Oncol*. 2021 Aug 11:e214381.
41. Zabalza A, Cárdenas-Robledo S, Tagliani P, Arrambide G, Otero-Romero S, Carbonell-Mirabent P, Rodríguez-Barranco M, Rodríguez-Acevedo B, Restrepo Vera JL, Resina-Salles M, Midaglia L, Vidal-Jordana A, Río J, Galan I, Castillo J, Cobo-Calvo Á, Comabella M, Nos C, Sastre-Garriga J, Tintore M, Montalban X. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. *Eur J Neurol*. 2020. 28:3384-3395.
42. Bigaut et al. 2021; Bigaut K, Kremer L, Fleury M, Lanotte L, Collongues N, de Seze J. Impact of disease-modifying treatments on humoral response after COVID-19 vaccination: A mirror of the response after SARS-CoV-2 infection. *J.Rev Neurol*. 2021: S0035-3787(21)00569-5.
43. van Kempen ZLE, Strijbis EMM, Al MMCT, Steenhuis M, Uitdehaag BMJ, Rispens T, Killestein J. SARS-CoV-2 antibodies in adult patients with multiple sclerosis in the amsterdam MS cohort. *JAMA Neurol*. 2021. 78: 880-882.
44. Louapre C, Ibrahim M, Maillart E, Abdi B, Papeix C, Stankoff B, Dubessy AL, Bensa-Koscher C, Créange A, Chamekh Z, Lubetzki C, Marcelin AG, Corvol JC, Pourcher V; COVISEP and Bio-

- coco-neuroscience study group. Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 in patients with multiple sclerosis or neuromyelitis optica spectrum disorders. *J Neurol Neurosurg Psychiatry*. 2021;jnnp-2021-326904.
45. Sormani MP, Schiavetti I, Landi D, Carmisciano L, De Rossi N, Cordioli C, Moiola L, Radaelli M, Immovilli P, Capobianco M, Brescia Morra V, Trojano M, Tedeschi G, Comi G, Battaglia MA, Patti F, Fragoso YD, Sen S, Siva A, Furlan R, Salvetti M. SARS-CoV-2 serology after COVID-19 in multiple sclerosis: An international cohort study. *Mult Scler*. 2021b; Jul 30:13524585211035318
 46. Klineova et al. 2021. Klineova S, Harel A, Straus Farber R, DeAngelis T, Zhang Y, Hentz R, Leung TM, Fong K, Smith T, Blanck R, Zhovtis-Ryerson L. Outcomes of COVID-19 infection in multiple sclerosis and related conditions: One-year pandemic experience of the multicenter New York COVID-19 Neuroimmunology Consortium (NYCNIC). *Mult Scler Relat Disord*. 2021;55:103153
 47. Garcia P, Anand S, Han J, Montez-Rath M, Sun S, Shang T, Parsonnet J, Chertow GM, Schiller B, Abra G. COVID19 vaccine type and humoral immune response in patients receiving dialysis. *Medrxiv* 2021; <https://doi.org/10.1101/2021.08.02.21261516>
 48. Ramesh S, Govindarajulu M, Parise RS, Neel L, Shankar T, Patel S, Lowery P, Smith F, Dhanasekaran M, Moore T. Emerging SARS-CoV-2 Variants: A Review of Its Mutations, Its Implications and Vaccine Efficacy. *Vaccines*. 2021;9:1195.
 49. Achiron A, Mandel M, Dreyer-Alster S, Harari G, Magalashvili D, Sonis P, Dolev M, Menascu S, Flechter S, Falb R, Gurevich M. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Disord*. 2021;14:17562864211012835.
 50. Apostolidis SA, Kakara M, Painter MM, Goel RR, Mathew D, Lenzi K, Rezk A, Patterson KR, Espinoza DA, Kadri JC, Markowitz DM, E Markowitz C, Mexhitaj I, Jacobs D, Babb A, Betts MR, Prak ETL, Weiskopf D, Grifoni A, Lundgreen KA, Gouma S, Sette A, Bates P, Hensley SE, Greenplate AR, Wherry EJ, Li R, Bar-Or A. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. *Nat Med*. 2021. doi: 10.1038/s41591-021-01507-2.
 51. Gallo A, Capuano R, Donnarumma G, Bisecco A, Grimaldi E, Conte M, d'Ambrosio A, Coppola N, Galdiero M, Tedeschi G. Preliminary evidence of blunted humoral response to SARS-CoV-2 mRNA vaccine in multiple sclerosis patients treated with ocrelizumab. *Neurol Sci*. 2021 Jun 15:1–4. doi: 10.1007/s10072-021-05397-7.
 52. Sormani MP, Inglese M, Schiavetti I, Carmisciano L, Laroni A, Lapucci C, Da Rin G, Serrati C, Gandoglia I, Tassinari T, Perego G, Bricchetto G, Gazzola P, Mannironi A, Stromillo ML, Cordioli C, Landi D, Clerico M, Signoriello E, Frau J, Ferrò MT, Sapio AD, Pasquali L, Ulivelli M, Marinelli F, Callari G, Iodice R, Liberatore G, Caleri F, Repice AM, Cordera S, Battaglia MA, Salvetti M, Franciotta D, Uccelli A; CovaXiMS study group on behalf of the Italian Covid-19 Alliance in MS.

Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *EBioMedicine*. 2021c Sep 19:103581. doi: 10.1016/j.ebiom.2021.103581

53. Schietzel S, Anderegg MA, Limacher A, Born A, Horn MP, Maurer B, Hirzel C, Sidler D, Moor MB. Humoral and cellular immune responses upon SARS-CoV-2 vaccines in patients with anti-CD20 therapies: A systematic review and meta-analysis of 1342 patients. *MedRxiv* 2021; doi: <https://doi.org/10.1101/2021.09.30.21264335>
54. König M, Lorentzen ÅR, Torgauten HM, Tran TT, Schikora-Rustad S, Vaage EB, Mygland Å, Wergeland S, Aarseth J, Aaberge IAS, Torkildsen Ø, Holmøy T, Berge T, Kjell-Morten M, Harbo HF, Andersen JT, Munthe LA, Søråas A, Celius EG, Vaage JT, Lund-Johansen F, Nygaard GO. Humoral immunity to SARS-CoV-2 mRNA vaccination in multiple sclerosis: the relevance of time since last rituximab infusion and first experience from sporadic revaccinations. *J Neurol Neurosurg Psychiatry*. 2021a Oct 20:jnnp-2021-327612.
55. Moor MB, Suter-Riniker F, Horn MP, Aeberli D, Amsler D, Möller B, Njue LM, Medri C, AngelilloScherrer A, Borradori L, Radonjic-Hoesli S, Jafari MS, Chan A, Hoepner R, Backer VUM, Mani LY, Iype JM, Hirzel C, Maurer B, Sidler D. Humoral and cellular responses to mRNA vaccines against SARS-CoV2 in patients with a history of CD20-B-cell depleting therapy. *Lancet Rheumatol*. 2021 :[https://doi.org/10.1016/S2665-9913\(21\)00251-4](https://doi.org/10.1016/S2665-9913(21)00251-4).
56. Mrak D, Tobudic S, Koblichke M, Graninger M, Radner H, Sieghart D, Hofer P, Perkmann T, Haslacher H, Thalhammer R, Winkler S, Blüml S, Stiasny K, Aberle JH, Smolen JS, Heinz LX, Aletaha D, Bonelli M. SARS-CoV-2 vaccination in rituximab-treated patients: B cells promote humoral immune responses in the presence of T-cell-mediated immunity. *Ann Rheum Dis*. 2021 Jul 20:annrheumdis-2021-220781. doi: 10.1136/annrheumdis-2021-220781.
57. Högelin AK, Ruffin N, Elisa P, Månberg A, Hober S, Gafvelin G, Grönlund H, Nilsson P, Khademi M, Olsson T, Piehl F, Al Nimer F. Humoral and cellular immunological memory against SARS-CoV-2 despite b-cell depleting treatment in multiple sclerosis. *iScience*. 2021 Sep 2:103078. doi: 10.1016/j.isci.2021.103078.
58. Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, Domingo-Vila C, Hayday TS, Graham C, Seow J, Abdul-Jawad S, Kamdar S, Harvey-Jones E, Graham R, Cooper J, Khan M, Vidler J, Kakkassery H, Sinha S, Davis R, Dupont L, Francos Quijorna I, O'Brien-Gore C, Lee PL, Eum J, Conde Poole M, Joseph M, Davies D, Wu Y, Swampillai A, North BV, Montes A, Harries M, Rigg A, Spicer J, Malim MH, Fields P, Patten P, Di Rosa F, Papa S, Tree T, Doores KJ, Hayday AC, Irshad S. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021; 22:765-778.
59. Madelon N, Lauper K, Breville G, Royo IS, Goldstein R, Andrey DO, Grifoni A, Sette A, Siegrist CA, Finckh A, Lalive PH, Didierlaurent AM, Eberhardt CS. Patients treated with anti-CD20 therapy can mount robust T cell responses to mRNA-based COVID-19 vaccines. *MedRxiv* 2021 doi: <https://doi.org/10.1101/2021.07.21.21260928>

60. Disanto et al. 2021 Disanto G, Sacco R, Bernasconi E, Martinetti G, Keller F, Gobbi C, Zecca C. Association of Disease-Modifying Treatment and Anti-CD20 Infusion Timing With Humoral Response to 2 SARS-CoV-2 Vaccines in Patients With Multiple Sclerosis. *JAMA Neurol.* 2021 Sep 23:e213609
61. Kornek B, Leutmezer F, Rommer PS, Koblichke, M, Schneider Lisa, Haslacher H, Thalhammer Renate, Zimprich F, Zulehner Gudrun, Bsteh G, Dal-Bianco A, Rinner W, Zebenholzer K, Wimmer I, Steinmaurer A, Graninger M, Mayer M, Roedl K, Berger T, Winkler S, Aberle J, Tobudic S. Distinct patterns of humoral and cellular immune responses following SARS-CoV-2 mRNA vaccination in patients with immune-mediated neurological disorders on anti-CD20 Therapy: A prospective cohort study. *SSRN 2021*: <http://dx.doi.org/10.2139/ssrn.3924204>
62. Stefanski AL, Rincon-Arevalo H, Schrezenmeier E, Karberg K, Szelinski F, Ritter J, Jahrsdörfer B, Schrezenmeier H, Ludwig C, Sattler A, Kotsch K, Chen Y, Claußnitzer A, Haibel H, Proft F, Guerra GM, Durek P, Heinrich F, Gomes F, Burmester GR, Radbruch A, Mashreghi MF, Lino AC, Dörner T et al. B cell numbers predict humoral and cellular response upon SARS-CoV-2 vaccination among patients treated with rituximab. *MedRxiv* doi: <https://doi.org/10.1101/2021.07.19.21260803>
63. Henriquez, S., Zerbit, J., Bruel, T., Ouedrani, A., Planas, D., Deschamps, P., Staropoli, I., Hadjadj, J., Varet, B., Suarez, F., Ermak, N., Bouscary, D., Willems, L., Fouquet, G., Decroocq, J., Franchi, P., Deau-Fischer, B., Terrier, B., Tamburini, J., Chatenoud, L., Schwartz, O., Vignon, M. Anti-CD38 therapy impairs SARS-CoV-2 vaccine response in multiple myeloma patients. *Medrxiv.* 10.1101/2021.08.08.21261769
64. Ghandili S, Schönlein M, Lütgehetmann M, Schulze Zur Wiesch J, Becher H, Bokemeyer C, Sinn M, Weisel KC, Leyboldt LB. Post-vaccination anti-SARS-CoV-2-antibody response in patients with multiple myeloma correlates with low CD19+ B-lymphocyte count and anti-CD38 treatment. *Cancers.* 2021; 13:3800.
65. Iannetta M, Landi D, Cola G, Malagnino V, Teti E, Fraboni D, Buccisano F, Grelli S, Coppola L, Campogiani L, Andreoni M, Marfia GA, Sarmati L. T-cell responses to SARS-CoV-2 in multiple sclerosis patients treated with ocrelizumab healed from COVID-19 with absent or low anti-spike antibody titers. *Mult Scler Relat Disord.* 2021; 55:103157.
66. Schwarz T, Otto C, Jones TC, Pache F, Schindler P, Niederschweiberer M, Schmidt F, Drosten C, Corman VM, Ruprecht K. A cohort of 222 anti-CD20 treated patients with multiple sclerosis followed through the COVID-19 pandemic: Attenuated humoral but robust cellular immune responses after vaccination and infection. *MedRXiv* 2021 <https://doi.org/10.1101/2021.10.11.21264694>
67. Brill L, Rechtman A, Zveik O, Haham N, Oiknine-Djian E, Wolf DG, Levin N, Raposo C, Vaknin-Dembinsky A. Humoral and T-Cell Response to SARS-CoV-2 Vaccination in Patients With Multiple Sclerosis Treated With Ocrelizumab. *JAMA Neurol.* 2021:e213599.

68. Baker D, Amor S, Kang AS, Schmierer K, Giovannoni G. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. *Mult Scler Relat Disord*. 2020c; 43:102174.
69. Huang A, Bange E, Han N, Wileyto EP, Kim J, Gouma S, Robinson J, Greenplate A, Porterfield F, Owoyemi O, Naik K, Zheng C, Galantino M, Weisman A, Ittner C, Kugler E, Baxter A, Weirick M, McAllister C, Babady NE, Kumar A, Widman A, Dewolf S, Boutemine S, Roberts C, Budzik K, Tollett S, Wright C, Perloff T, Sun L, Mathew D, Giles J, Oldridge D, Wu J, Alanio C, Adamski S, Vella L, Kerr S, Cohen J, Oyer R, Massa R, Maillard I, Maxwell K, Maslak P, Vonderheide R, Wolchok JD, Hensley S, Wherry E, Meyer N, DeMichele A, Vardhana S, Mamtani R, Oniyide O, Agyekum R, Dunn T, Jones T, Giannini H, Garfall A, Reilly J. CD8 T cells compensate for impaired humoral immunity in COVID-19 patients with hematologic cancer. *Res Sq*. 2021:rs.3.rs-162289. doi: 10.21203/rs.3.rs-162289/v1.
70. Oberhardt V, Luxenburger H, Kemming J, Schulien I, Ciminski K, Giese S, Csernalabics B, Lang-Meli J, Janowska I, Staniek J, Wild K, Basho K, Marinescu MS, Fuchs J, Topfstedt F, Janda A, Sogukpinar O, Hilger H, Stete K, Emmerich F, Bengsch B, Waller CF, Rieg S, Sagar, Boettler T, Zoldan K, Kochs G, Schwemmle M, Rizzi M, Thimme R, Neumann-Haefelin C, Hofmann M. Rapid and stable mobilization of CD8⁺ T cells by SARS-CoV-2 mRNA vaccine. *Nature*. 2021. doi: 10.1038/s41586-021-03841-4.
71. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, Chng MHY, Lin M, Tan N, Linster M, Chia WN, Chen MI, Wang LF, Ooi EE, Kalimuddin S, Tambyah PA, Low JG, Tan YJ, Bertoletti A. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature*. 2020; 584:457-462.
72. Grifoni A, Sidney J, Vita R, Peters B, Crotty S, Weiskopf D, Sette A. SARS-CoV-2 human T cell epitopes: Adaptive immune response against COVID-19. *Cell Host Microbe*. 2021;29:1076-1092
73. Wei J, Stoesser N, Matthews PC, Ayoubkhani D, Studley R, Bell I, Bell JI, Newton JN, Farrar J, Diamond I, Rourke E, Howarth A, Marsden BD, Hoosdally S, Jones EY, Stuart DI, Crook DW, Peto TEA, Pouwels KB, Eyre DW, Walker AS; COVID-19 Infection Survey team. Antibody responses to SARS-CoV-2 vaccines in 45,965 adults from the general population of the United Kingdom. *Nat Microbiol*. 2021; 6:1140-1149.
74. Shrotri et al. 2021; Shrotri M, Navaratnam AMD, Nguyen V, Byrne T, Geismar C, Fragaszy E, Beale S, Fong WLE, Patel P, Kovar J, Hayward AC, Aldridge RW; Virus Watch Collaborative. Spike-antibody waning after second dose of BNT162b2 or ChAdOx1. *Lancet*. 2021; 398:385-387
75. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, Mandelboim M, Gal Levin E, Rubin C, Indenbaum V, Tal I, Zavitan M, Zuckerman N, Bar-Chaim A, Kreiss Y, Regev-Yochay G. Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med*. 2021:NEJMoa2109072.

76. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman LS, Haas E, Milo R, Alroy-Preis, S, Ash N, Huppert A. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. *MedRxiv* 2021 doi:10.1101/2021.08.24.21262423
77. Cook C, Patel N, D'Silva K, Hsu TTY, DiIorio M, Prisco L, Martin L, Vanni KMM, Zaccardelli A, Todd DJ, Sparks J, Wallace Z. Clinical characteristics and outcomes of COVID-19 breakthrough infections among vaccinated patients with systemic autoimmune rheumatic diseases. *Ann Rheum Dis*. 2021 Sep 6:annrheumdis-2021-221326.
78. Di Fusco M, Moran MM, Cane A, Curcio D, Khan F, Malhotra D, Surinach A, Miles A, Swerdlow D, McLaughlin JM, Nguyen JL. Evaluation of COVID-19 vaccine breakthrough infections among immunocompromised patients fully vaccinated with BNT162b2. *MedRxiv* 2021. doi: <https://doi.org/10.1101/2021.10.12.21264707>.
79. Kearns P, Siebert S, Willicombe M, Gaskell C, Kirkham A, Pirrie S, Bowden S, Magwaro S, Hughes A, Lim Zixiang, Dimitriadis S, Murray SM, Marjot T, Win Zay, Irwin SL, Meacham G, Richter AG, Kelleher Peter, Satsangi J, Miller P, Rea D, Cook G, Turtle L, Klenerman P, Dunachie S, Basu Neil, de Silva TI, Thomas D, Barnes E, Goodyear CS, McInnes I, Examining the immunological effects of COVID-19 vaccination in patients with conditions potentially leading to diminished immune response capacity – The OCTAVE Trial. *SSRN*:2021. <http://dx.doi.org/10.2139/ssrn.3910058>
80. Shroff RT, Chalasani P, Wei R, Pennington D, Quirk G, Schoenle MV, Peyton KL, Uhrlaub JL, Ripperger TJ, Mladen Jergović M, Dalgai S, Wolf A, Whitmer R, Hammad H, Carrier A, Scott AJ, Nikolich-Žugich J, Worobey M, Sprissler R, Dake M, LaFleur BJ, Bhattacharya D. Immune responses to COVID-19 mRNA vaccines in patients with solid tumors on active, immunosuppressive cancer therapy. *MedRxiv* 2021; doi: <https://doi.org/10.1101/2021.05.13.21257129>
81. Re D, Seitz-Polski B, Carles M, Brglez V, Graça D, Benzaken S, Liguori S, Zahreddine K, Delforge M, Verrière B, Chamorey E, Jérôme B. Humoral and cellular responses after a third dose of BNT162b2 vaccine in patients treated for lymphoid malignancies *Medrxiv* 2021. doi: <https://doi.org/10.1101/2021.07.18.21260669>
82. Connolly CM, Teles M, Frey S, Boyarsky BJ, Alejo JL, Werbel WA, Albayda J, Christopher-Stine L, Garonzik-Wang J, Segev DL, Paik JJ. Booster-dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series. *Ann Rheum Dis*. 2021:annrheumdis-2021-221206. doi: [10.1136/annrheumdis-2021-221206](https://doi.org/10.1136/annrheumdis-2021-221206)
83. Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies *Cancer cell*. 2021 DOI: <https://doi.org/10.1016/j.ccell.2021.09.001>
84. König M, Torgauten HM, Overas MH, Chopra A, Lorentzen AR, Tran TT, Mjaaland S, Aaberge IS, Myhr KM, Wergeland S, Berge T, Harbo HF, Torkildsen OFG, Holmoy T, Celius EG, Munthe

- LA, Vaage JT, Lund-Johansen F, Nygaard GO. Efficacy and safety of a third SARS-CoV-2 vaccination in multiple sclerosis vaccine non-responders. *MedRxiv*. 2021b1. <https://doi.org/10.1101/2021.10.15.21264977>
85. Vijenthira A, Gong I, Betschel SD, Cheung M, Hicks LK. Vaccine response following anti-CD20 therapy: a systematic review and meta-analysis of 905 patients. *Blood Adv*. 2021; 5:2624-2643.
86. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis*. 2021; 80:1357-1359.
87. Palanichamy A, Jahn S, Nickles D, Derstine M, Abounasr A, Hauser SL, Baranzini SE, Leppert D, von Büdingen HC. Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. *J Immunol*. 2014; 193:580-586.
88. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. *Arthritis Rheum*. 2006; 54:613-20.
89. Bar-Or A, Wiendl H, Montalban X, Alvarez E, Davydovskaya M, Delgado SR, Evdoshenko EP, Giedraitiene N, Gross-Paju K, Haldre S, Herrman CE, Izquierdo G, Karelis G, Leutmezer F, Mares M, Meca-Lallana JE, Mickeviciene D, Nicholas J, Robertson DS, Sazonov DV, Sharlin K, Sundaram B, Totolyan N, Vachova M, Valis M, Bagger M, Häring DA, Ludwig I, Willi R, Zalesak M, Su W, Merschhemke M, Fox EJ. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase-2 study. *Mult Scler*. 2021 Oct 4:13524585211044479. doi: 10.1177/13524585211044479.
90. Kesimpta®. Summary of medical product characteristics/Label. European medicines Agency 2021 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125326s070lbl.pdf (Assessed 24 October 2021)
91. Gibiansky E, Petry C, Mercier F, Günther A, Herman A, Kappos L, Hauser S, Yamamoto Y, Wang Q, Model F, Kletzl H. Ocrelizumab in relapsing and primary progressive multiple sclerosis: Pharmacokinetic and pharmacodynamic analyses of OPERA I, OPERA II and ORATORIO. *Br J Clin Pharmacol*. 2021; 87: 2511-2520
92. Genovese MC, Kaine JL, Lowenstein MB, Del Giudice J, Baldassare A, Schechtman J, Fudman E, Kohen M, Gujrathi S, Trapp RG, Sweiss NJ, Spaniolo G, Dummer W; ACTION Study Group. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum*. 2008; 58:2652-2661.
93. Ellwardt L, Bittner S, Zipp F. Monitoring B-cell repopulation after depletion therapy in neurologic patients. *Neurol Neuroimmunol Neuroinflamm*. 2018; 5:e463.

94. Ellrichmann G, Bolz J, Peschke M, Duscha A, Hellwig K, Lee DH, Linker RA, Gold R, Haghikia A. Peripheral CD19⁺ B-cell counts and infusion intervals as a surrogate for long-term B-cell depleting therapy in multiple sclerosis and neuromyelitis optica/neuromyelitis optica spectrum disorders. *J Neurol*. 2019; 266:57-67.
95. Signoriello E, Bonavita S, Di Pietro A, Abbadessa G, Rossi F, Miele G, Casertano S, Lus G. BMI influences CD20 kinetics in multiple sclerosis patients treated with ocrelizumab. *Mult Scler Relat Disord*. 2020; 43:102186.
96. Nakou M, Katsikas G, Sidiropoulos P, et al. Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells correlates with clinical response. *Arthritis Res Ther*. 2009;11:R131.
97. Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH, Waubant E, Gazda S, Fox RJ, Panzara M, Sarkar N, Agarwal S, Smith CH. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Ann Neurol*. 2008; 63:395-400.
98. Sahi NK, Abidi SMA, Salim O, Abraham R, Kalra S, Al-Araji A. Clinical impact of ocrelizumab extended interval dosing during the COVID-19 pandemic and associations with CD19+B-cell repopulation. *Mult Scler Relat Disord*. 2021 Sep 27;56:103287
99. Maarouf A, Rico A, Boutiere C, Perriguet M, Demortiere S, Pelletier J, Audoin B; Under the aegis of OFSEP. Extending rituximab dosing intervals in patients with MS during the COVID-19 pandemic and beyond? *Neurol Neuroimmunol Neuroinflamm*. 2020; 7:e825.
100. Rolfes L, Pawlitzki M, Pfeuffer S, Nelke C, Lux A, Pul R, Kleinschnitz C, Kleinschnitz K, Rogall R, Pape K, Bittner S, Zipp F, Warnke C, Goeraci Y, Schroeter M, Ingwersen J, Aktas O, Klotz L, Ruck T, Wiendl H, Meuth SG. Ocrelizumab Extended Interval Dosing in Multiple Sclerosis in Times of COVID-19. *Neurol Neuroimmunol Neuroinflamm*. 2021; 8:e1035.
101. Tazza F, Lapucci C, Cellerino M, Boffa G, Novi G, Poire I, Mancuso E, Bruschi N, Sbragia E, Laroni A, Capello E, Inglese M. Personalizing ocrelizumab treatment in Multiple Sclerosis: What can we learn from Sars-Cov2 pandemic? *J Neurol Sci*. 2021; 427:117501.
102. Chertcoff A, Bauer J, Silva BA, Aldecoa M, Eizaguirre MB, Rodriguez R, Chereque A, Rodríguez Heudebert ML, Milanesi V, Morales L, Castellón M, Mejía Pineda S, Ferrandina F, Henestroza P, Ruiz Peraza M, Vallecillo Rivas F, Cedeño Lopez L, Herrera L, Sosa M, Cruchet Muñoz V, Barahona AS, Ramírez Gudiño LM, Carballido S, Walton C, Peeters LM, Rijke N, Garcea O, Carrá A, Alonso R. Changes on the health care of people with multiple sclerosis from Latin America during the COVID-19 pandemic. *Mult Scler Relat Disord*. 2021; 54:103120.
103. van Lierop ZY, Toorop AA, van Ballegoij WJ, Olde Dubbelink TB, Strijbis EM, de Jong BA, van Oosten BW, Moraal B, Teunissen CE, Uitdehaag BM, Killestein J, Kempen ZLV. Personalized B-cell tailored dosing of ocrelizumab in patients with multiple sclerosis during the COVID-19 pandemic. *Mult Scler*. 2021 Jul 9:13524585211028833.

104. Barun B, Gabelić T, Adamec I, Babić A, Lalić H, Batinić D, Krbot Skorić M, Habek M. Influence of delaying ocrelizumab dosing in multiple sclerosis due to COVID-19 pandemics on clinical and laboratory effectiveness. *Mult Scler Relat Disord*. 2021;48:102704.
105. Schulz, E., Hodl, I., Forstner, P., Hatzl, S., Sareban, N., Moritz, M., Fessler, J., Dreo, B., Uhl, B., Url, C., Grisold, A., Khalil, M., Kleinhapfl, B., Enzinger, C., Stradner, M. H., Greinix, H., Schlenke, P., Steinmetz, Association of Naive B Cells with Humoral Response to SARS-CoV-2 Vaccination. *MedRxiv* DOI.10.1101/2021.08.11.21261898
106. Gurion R, Rozovski U, Itchaki G, Gafter-Gvili A, Leibovitch C, Raanani P, Ben-Zvi H, Szwarcwort M, Taylor-Abigadol M, Dann EJ, Horesh N, Inbar T, Tzoran I, Lavi N, Fineman R, Ringelstein-Harlev S, Horowitz NA. Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD20 antibodies. *Haematologica*. 2021 Jul 29. doi: 10.3324/haematol.2021.279216.
107. Famulare M. Seroconversion after COVID-19 vaccination in patients using B-cell depleting therapies to manage multiple sclerosis increases with time between treatment and vaccination. *GitHub v0.2* 03 June 2021. https://github.com/famulare/covid-vax-response-vs_time_since_bcdt
108. Baker D, MacDougall A, Kang AS, Schmierer K, Giovannoni G, Dobson R. CD19 B cell repopulation after ocrelizumab, alemtuzumab and cladribine: Implications for SARS-CoV-2 vaccinations in multiple sclerosis. *MedRxiv* 2021 doi: <https://doi.org/10.1101/2021.09.26.21264023>
109. Kletzl H, Gibiansky E, Petry C, Mercier F, Guenther A, Wang Q, Model F, Kappos L, Hauser S Pharmacokinetics, Pharmacodynamics and Exposure-Response Analyses of Ocrelizumab in Patients With Multiple Sclerosis (N4.001). *Neurology* 2019; 92 (Supl 15) N4.001
110. Kim SH, Hyun JW, Kim HJ. Individualized B cell-targeting therapy for neuromyelitis optica spectrum disorder. *Neurochem Int*. 2019;130:104347.
111. Novi et al. 2020. Novi G, Bovis F, Fabbri S, Tazza F, Gazzola P, Maietta I, Currò D, Bruschi N, Roccatagliata L, Boffa G, Lapucci C, Pesce G, Cellerino M, Solaro C, Laroni A, Capello E, Mancardi G, Sormani M, Inglese M, Uccelli A. Tailoring B cell depletion therapy in MS according to memory B cell monitoring. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e845.
112. Yavuz S, Komsuoğlu Çelikyurt FI. Antiviral treatment of COVID-19: An update. *Turk J Med Sci*. 2021. doi: 10.3906/sag-2106-250.
113. Mahase E. Covid-19: Molnupiravir reduces risk of hospital admission or death by 50% in patients at risk, MSD reports. *BMJ*. 2021 Oct 4;375:n2422.
114. Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. *Viruses*. 2021 7;13:628

115. Drouin AC, Theberge MW, Liu SY, Smither AR, Flaherty SM, Zeller M, Geba GP, Reynaud P, Rothwell WB, Luk AP, Tian D, Boisen ML, Branco LM, Andersen KG, Robinson JE, Garry RF, Fusco DN. Successful Clearance of 300 Day SARS-CoV-2 Infection in a Subject with B-Cell Depletion Associated Prolonged (B-DEAP) COVID by REGEN-COV Anti-Spike Monoclonal Antibody Cocktail. *Viruses*. 2021;13:1202.
116. Dong J, Zost SJ, Greaney AJ, Starr TN, Dingens AS, Chen EC, Chen RE, Case JB, Sutton RE, Gilchuk P, Rodriguez J, Armstrong E, Gainza C, Nargi RS, Binshtein E, Xie X, Zhang X, Shi PY, Logue J, Weston S, McGrath ME, Frieman MB, Brady T, Tuffy KM, Bright H, Loo YM, McTamney PM, Esser MT, Carnahan RH, Diamond MS, Bloom JD, Crowe JE Jr. Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail. *Nat Microbiol*. 2021;6:1233-1244.
117. Astrazeneca.com 2021. <https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html> (accessed 1 September 2021)
118. Luitel P, Vais D, Gidron A. Successful Treatment of Persistent Coronavirus Disease 2019 Infection in a Patient With Hypogammaglobulinemia With REGN-COV2: A Case Report. *Open Forum Infect Dis*. 2021; 8:ofab335.
119. Lazarevic I, Pravica V, Miljanovic D, Cupic M. Immune Evasion of SARS-CoV-2 Emerging Variants: What Have We Learnt So Far? *Viruses*. 2021;13:1192.
120. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, Planchais C, Porrot F, Robillard N, Puech J, Prot M, Gallais F, Gantner P, Velay A, Le Guen J, Kassis-Chikhani N, Edriss D, Belec L, Seve A, Courtellemont L, Péré H, Hocqueloux L, Fafi-Kremer S, Prazuck T, Mouquet H, Bruel T, Simon-Lorière E, Rey FA, Schwartz O. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature*. 2021;596:276-280.
121. Avanzato VA, Matson MJ, Seifert SN, Pryce R, Williamson BN, Anzick SL, Barbian K, Judson SD, Fischer ER, Martens C, Bowden TA, de Wit E, Riedo FX, Munster VJ. Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with *Cancer Cell*. 2020;183:1901-1912.e9.
122. Pan D, Mudalige NL, Sze S, Koeckerling D, Oyefeso O, Barker J, Williams CM, Tang JW, Pareek M. The new UK SARS-CoV-2 variant and lockdown – causes and consequences. *Clin Med*. 2021; 21: e295-e299.
123. Corey L, Beyrer C, Cohen MS, Michael NL, Bedford T, Rolland M. SARS-CoV-2 variants in patients with immunosuppression. *N Engl J Med*. 2021;385:562-566
124. Gibson EG, Pender M, Angerbauer M, Cook C, Jones B, Spivak AM, Spivak ES, Swaminathan S. Prolonged SARS-CoV-2 Illness in a Patient Receiving Ocrelizumab for Multiple Sclerosis. *Open Forum Infect Dis*. 2021; 8:ofab176.
125. Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, Hosmillo M, Rees-Spear C, Mlcochova P, Lumb IU, Roberts DJ, Chandra A, Temperton N; CITIID-NIHR BioResource COVID-

19 Collaboration; COVID-19 Genomics UK (COG-UK) Consortium, Sharrocks K, Blane E, Modis Y, Leigh KE, Briggs JAG, van Gils MJ, Smith KGC, Bradley JR, Smith C, Doffinger R, Ceron-Gutierrez L, Barcenas-Morales G, Pollock DD, Goldstein RA, Smielewska A, Skittrall JP, Gouliouris T, Goodfellow IG, Gkrania-Klotsas E, Illingworth CJR, McCoy LE, Gupta RK. SARS-CoV-2 evolution during treatment of chronic infection. *Nature*. 2021; 592:277-282.

126. Giovannoni G, Hawkes CH, Lechner-Scott J, Levy M, Yeh EA, Baker D. COVID-19 vaccines and multiple sclerosis disease-modifying therapies. *Mult Scler Relat Disord*. 2021;53:103155. doi: 10.1016/j.msard.2021.103155